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Publication Date
2011

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA
RIVERSIDE

From Ions to Intrinsic Connectivity Networks: the Neuroscience That Bio-Sociology Needs to Know

A Dissertation submitted in partial satisfaction
of the requirements for the degree of

Doctor of Philosophy

in

Sociology

by

Richard Evan Niemeyer

August 2011

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ABSTRACT OF THE DISSERTATION

From Ions to Intrinsic Connectivity Networks: the Neuroscience That Bio-Sociology Needs to Know

by

Richard Evan Niemeyer

Doctor of Philosophy, Graduate Program in Sociology
University of California, Riverside, August 2011
Dr. Jonathan H. Turner, Chairperson

In 1995 sociologist J. Richard Udry wrote an article entitled, “Sociology and Biology: What Biology do Sociologists need to Know?” Although Udry’s article represents an important early step in the development of the biosocial perspective, the full impact of his thesis is blunted by the fact that he fails to discuss in sufficient detail the mechanisms underlying the biosocial relationships he identifies. Nor, for that matter, does Udry provide a sufficient metatheoretical/metamethodological explanation for how biological data can and should be incorporated into existing social science theory and research. Finally, and of no fault of his own, Udry’s article was published a few years before several extremely important discoveries regarding the neurological foundations of many psycho-sociological processes fundamental to micro-sociological theory. This dissertation is intended to serve as a follow-up to Udry’s (1995) original essay in that it seeks to overcome the above limitations by both broadening and deepening the scope of the ‘biology that sociology needs to know,” as well as articulating a framework for how said insights can be incorporated into sociological research.

The integrated meta-framework developed here is designed to create two sets of analytical tools to guide the construction of biosocial theory and to carry out biosocial research. The first of these are the taken-for-granted substantive positions provided by the life sciences regarding the biological mechanisms underlying how the ‘body’ generates ‘mind’, as well as the substantive questions every biosocial theory must answer. The second set of analytical tools contains the substantive and methodological working strategies that provide the conceptual definitions, operational definitions, scope conditions, and empirical referents that serve as the building blocks for biosocial theories. Moreover, the biosocial meta-framework also specifies two sets of analytical processes for creating the above tools. The first of these sets specified how to transform one or more discursive social theories into a format that is conducive to the integration of biological data. The second set, in turn, specified how to gather biological data about a psycho-social process and then integrate it into a social theory.

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Figure 2 (Page 38): A schematic representation of Ritzer & Zhao's concept of a meta-study. Like the Berger et al model, this schema can be divided and subdivided into component parts. In subsequent sections of this chapter I will transform this formulation into a more dynamic representation. As described in the text, this dynamic version of a meta-study would be used to produce a modified version of Berger et al's concept of an orientating strategy.

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Chapter 1: Presenting the Problem. Suggesting a Solution. Mapping the Course Ahead.

Part I: Introducing the Problem to be addressed

With increasing frequency social scientists are investigating how an individual's biology, social networks, and culture reciprocally interact to cumulatively influence their personality, cognitive-behavioral patterns, and psycho-physical health (Fowler and Kam 2007; Cacioppo and Patrick 2008; Guo, Roettger et al. 2008). According to many, this line of research represents a watershed for the social sciences for at least four reasons (Udry 1995; Camerer 1999; Cacioppo, Berntson et al. 2000; Cacioppo and Berntson 2006). First, it is argued that the incorporation of biosocial dynamics increases the explanatory power of the social sciences' micro-level theories by replacing philosophical assumptions about human nature with more empirically informed insights. Second, it is argued that the inclusion of biosocial dynamics improves the accuracy and precision of micro-level theories by identifying hitherto unrecognized scope conditions and sharpening the epistemic relationship between abstract concepts and their physical referents. Third, it is claimed that the consideration of biosocial dynamics increases the internal validity of social science research by improving the operationalizability of concepts and proposed causal mechanisms. And finally, it is claimed that the incorporation of biosocial dynamics promotes the development of cumulative knowledge by standardizing the orientating assumptions and conceptual referents of competing micro-social scientific theories.

To be sure though, not all social scientists agree with this assessment (Hanson 2010; Lucal 2010); in fact, some argue that this “biosocial perspective” is fundamentally flawed and should be abandoned immediately (Duster 2003; Duster 2006). Generally speaking, these negative opinions are motivated by three criticisms (Gul and Pesendorfer 2005; Dovidio, Pearson et al. 2008; Harrison 2008). First, it is claimed that the biosocial perspective fails to properly explain how it is biological processes influence the psycho-social phenomena that they are shown to statistically correlate with. Or, in other words, researchers reporting a statistically significant correlation between “Biological Process X” and “Psycho-Social Phenomenon Y,” often fail to explain the step-by-step mechanism by which process “X” is believed to cause phenomenon “Y.” A related version of this criticism further argues that the biosocial perspective fails to explain how the various biological correlates of psycho-social processes correlate with each other. For example, although “Gene X” and “Neurological Process Y” can both be shown to correlate with “Mental Process Z”, it is never explained if, how, or why, “Gene X” is correlated with “Neurological Process Y.” As such, these critics argue, the biosocial perspective fails to present a cohesive argument for how biological processes act *in toto* to generate a mental process. A third criticism is that the biosocial perspective is overly inductive due to a lack of theoretical support explaining *a priori* why a biological process should be related to a psychological or social phenomenon. And fourth, critics argue that even if above critiques could be satisfactorily addressed, it still would not be clear how or why the results generated by the biosocial perspective are applicable to the larger body of social research.

In light of these dissenting opinions, it appears that the biosocial perspective's promise is being undercut by several analytical weaknesses. Clearly then, the criticisms noted above must be effectively dealt with in order for the biosocial perspective to meaningfully contribute to social science research.

Part II: Identifying the Underlying Causes of the Problem and Suggesting a Solution.

One way to go about addressing the above criticisms is to begin by posing the following question: Do each of the individual critiques reflect a unique analytical weakness in the biosocial approach; or, does each critique merely represent a single example of a single systemic problem? In my opinion, the benefit of answering this question is this: if the individual critiques can be shown to be specific manifestations of a single underlying problem, then one can save a considerable amount of energy by focusing their attention on addressing it rather than on the multitude of individual examples. Or, to put it in more metaphorical terms, it is more efficient to attack the problem at its roots than to endlessly hack away at its many branches.

I make the assertion here that the individual critiques being leveled against the biosocial perspective are indicative of a single, systemic problem; specifically, that the approach has yet to formally establish for itself a proper meta-theoretical framework. In a very general sense, such a framework consists of a set of inter-related presuppositions regarding how and why scientific research should be carried out. The reason that I believe this solution will address the above limitations is because the function of a meta-theoretical framework is to provide the kind of information that the critics of the biosocial perspective say the approach lacks– i.e. how exactly theory, method, and the empirical results of a study are related to each other; how the knowledge produced by a research program relates to the larger body of scientific knowledge; why certain research questions should be pursued over others; etc. As such, I argue that the best way to address these criticisms is to address this absence. In very broad strokes, the purpose of this dissertation is to do just that.

Suggesting such a solution though immediately begs a second question: why is it necessary to formulate a new meta-theory specifically for the biosocial perspective? Or, in other words, why is it not possible to simply apply an already existing meta-theory to meet the demands required by the biosocial perspective? The answer to this is two-fold. First, the biosocial perspective is working with concepts and processes that the social sciences have hitherto had little-to-no experience with (i.e. genes, neurons, neural networks, etc); hence, the social sciences do not possess a pre-established meta-theoretical tool kit for addressing the limitations noted above (e.g. explaining how genes, neurons, and neural networks interact to generate cognitive dispositions and behaviors). And second, much of sociological meta-theory has long been criticized for being a vacuous enterprise that distracts from the creation of *real* theory (Turner 1985; Collins 1986; Skocpol 1987; Turner 1990; Turner 1992); for this reason, special care needs to be taken in order to make sure that the meta-theory the biosocial perspective adopts does not possess the same weaknesses as those from the past. Of course, none of these concerns requires us to formulate a meta-theory *de novo*; indeed, it is perfectly reasonable to instead cherry-pick from existing meta-theories those aspects that are amicable to the incorporation of biological research and then integrate them to form the basic outline of a framework. Once this skeleton is formed, it can then be further modified to handle the unique type of data examined by the biosocial perspective.

In Part II, Sections 1-3 of the chapter, I will present and discuss the details of three meta-theoretical frameworks that have proven over the years to be highly effective for guiding the development effective scientific theories. My main goal here will be to: 1) demonstrate the general applicability of each meta-theory to accomplishing the task at hand; 2) to explain specifically what each meta-theory can offer the biosocial perspective; and 3) highlight why this offering needs to be supplemented by aspects of the other meta-theories being considered. Along with this, I will also demonstrate 4) how all three frameworks can be synthesized into an integrated perspective. In Part II, Section 4 of this chapter, I will then turn to refining this synthesized framework further to meet the unique requirements demanded by the biosocial approach. The final product of this endeavor will serve as the meta-theoretical framework for developing in Chapters 2-6 a handful of axioms and sensitizing concepts to be employed by future biosocial research.

Section 1: A Summary of Berger et al's Concept of an Orientating Strategy

The first meta-theoretical framework I will discuss is called an orientating strategy, which was originally developed by Joseph Berger, David Wagner and Morris Zelditch (Wagner 1984; Wagner and Berger 1985; Wagner and Berger 1986; Berger and Zelditch 1993; Berger and Zelditch Jr 1998; Berger, Willer et al. 2005). In the most general sense, Berger and Zelditch (1998:78)[1] define an orientating strategy as a system

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[1] The concept of an orientating strategy was formulated by Joseph Berger, Morris Zelditch, and David Wagner as a part of a larger analytical framework they developed for understanding how sociological theories grow over time. Like most analytical concepts, the meaning of an orientating strategy–both in-of-itself and in relation to other concepts

of interrelated concepts, goals, standards, presuppositions, and directives that guide the construction of scientific theory.

According to Berger & colleagues, the general concept of an orientating strategy can be divided into a series of sub-categories, each of which offers a unique set of analytical tools for developing a theory (see figure 1 for a schematic representation). The first set of analytical tools is called foundational aims. The foundational aims ($\mathrm{F_a}$) of an orientating strategy specify in very general terms the substantive and methodological positions and goals of a research program. Here, Substantive positions ($\mathrm{F_{a_{sp}}}$) are defined as presuppositions about very abstract concepts and relationships, such as monistic versus dualistic theories of consciousness, the relation between agency and structure, and the relation between biological and cultural determinism. Generally speaking, these presuppositions are aptly characterized as metaphysical arguments about the fundamental essence of these concepts and their inter-relations. Methodological positions ($\mathrm{F_{a_{mp}}}$), in turn, delineate the ontological and epistemological assumptions of a research program. Presuppositions of this sort are intended to specify for a researcher the aspects of reality that they are permitted to take-for-granted as being true, as well as the philosophical justification for how and why this reality is “knowable” by the researcher. Examples of these assumptions include the broadly defined philosophies of nominalism, realism, positivism, and constructivism. Finally, a foundational aim’s substantive and

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within their larger framework– has evolved considerably over the years. A full review of this intellectual history is both beyond the scope of this chapter and unnecessary for the task at hand. As such, I will only review here the basic definition of the concept for the purpose of providing an intellectual context for the orientating strategies that I will develop in the subsequent sections of this chapter.

methodological goals- which I will refer to here as $\mathrm{F}_{\mathrm{a}_{\mathrm{sg}}}$ and $\mathrm{F}_{\mathrm{a}_{\mathrm{mg}}}$, respectively– specify the types of phenomena, processes, and empirical questions a research program should examine; why such examinations are important; as well as the methodological objectives the research program should strive for. As the term is used here, a methodological objective refers to the type of knowledge claim being produced; i.e. a universal explanatory law, a context-dependent description, etc.

The second set of analytical tools offered by Berger & colleagues' meta-theoretical framework is called working strategies. According to Berger and Zelditch (1998:79), working strategies (Ws) as a whole differ from foundational aims to the degree that the presuppositions of the former utilize more concrete and specific concepts and directives for how to construct theory. Like foundational aims, working strategies can also be divided into substantive and methodological subtypes. Berger and Zelditch (1993:12) argue that methodological working strategies deal with 'how to' problems: how to construct a theory, how to formulate an explanation, and how to assess theories." A good example of the difference between a methodological position (discussed above) and methodological working strategy (discussed here) is the difference between Positivistic Philosophy and the Deducutive-Nomological Model for how to construct a positivistic explanation. Specifically, Positivistic Philosophy is a broadly defined argument for a particular kind of epistemology; the Deducutive-Nomological Model, in turn, is a specific prescription for how to develop positivist knowledge claims. The first-- due to its generality-- is an example of a methodological position; the second--due to its specificity and concrete applicability-- is an example of a methodological working strategy. In a similar fashion, Berger & colleagues define substantive working strategies as dealing with the 'about what' problem: what kinds of concepts to use when constructing theory, what kinds of principles to formulate, and what specific theoretical questions to ask and answer. In short, substantive working strategies are functionally responsible for directing an investigator to solvable problems, providing them with the basic concepts and principles for framing the nature of a problem, and for providing them with other concepts and principles they need to solve the problem.

Section 1.1: What the Concept of an Orientating Strategy can offer the Biosocial Perspective

I argue that juxtaposing the definitions of the component parts of an orientating strategy with the criticisms of the biosocial perspective noted above reveals the following correspondences; these relationships are what I believe the concept of an orientating strategy can offer the biosocial approach. First, the development of a set of foundational aims for the biosocial perspective can provide the approach with a strategy for specifying: 1) its substantive assumptions about how biological processes as a whole are generally related to the totality psycho-social processes; 2) its methodological positions regarding why sociological theory needs to consider the biological foundations of both psychological and social processes; and 3) its substantive and methodological goals regarding how a biosocial theory relates to the larger body of sociological knowledge. Of course, critics of the biosocial perspective are free to reject these explanations due to either personal or ideological preferences, but this is different than rejecting the approach because it has failed in its responsibility to specify the nature of these relationships. And second, the development of a series of working strategies for the biosocial perspective can be used to specify; 1) how specific biological processes enable, constrain, and/or modulate specific psycho-social processes; 2) how specific biological processes interact with each other to enable, constrain, and or modulate specific psycho-social processes; and 3) when and why a researcher can assume, a priori, that one or more biological processes are related to a specific psycho-social process. For example, one set of substantive working assumptions could specify the neurological processes underlying the psycho-social process of taking-the-role-of-the-other; another set could specify the genetic and cellular interactions underlying said neurological processes; while still another set could specify how environmental process can influence how the genetic and cellular dynamics unfold (which, in turn, would also modify how the neurological processes unfold and the psycho-social process operates). Moreover, if the totality of these processes is known to operate regardless of context, then a researcher would be warranted to assume a priori that they hold for the specific situation they are examining-i.e. taking-the-role-of-the-other during an economic exchange.

Although the concept of an orientating strategy is useful for framing how to deal with the criticisms of the biosocial perspective, Berger & colleagues are rather limited in regard to specifying how one actually constructs the orientating strategy itself. Given that the construction of a biosocial meta-theoretical framework is the primary goal of this dissertation, this is somewhat problematic. It is for this reason that I argue that it is necessary to incorporate the insights of Ritzer and Zhao (Ritzer 1990; Ritzer 1991; Zhao 1991) in order to specify the steps needed to articulate a meta-framework.

Section 2: Summarizing Ritzer and Zhao's Concept of a Meta-Study

As I perceive it, the process required to develop an orientating strategy is near identical to engaging in what Zhao & Ritzer (Ritzer 1990; Ritzer 1991; Zhao 1991) refer to as conducting a meta-study. According to Zhao (1991), the goal of a meta-study is to synthesize the results of previous analyses; examine the methodological problems they encountered; prescribe solutions for how to resolve these problems; and reflect upon where a field of study has been, where it is now, and where it appears to be going. Importantly, Zhao (1991) states that the need to conduct a meta-study arises when there occurs some fundamental shift in the conception of the subject matter of a discipline, which consequently, requires a revision of the methodological logic that had hitherto prevailed. While I am not focusing on an entire discipline per se, I believe that the biosocial perspective's shift to incorporating genetic and neurological data represents the type of "revision of the methodological logic" Zhao (1991) references; moreover, the goal of a second-order analysis that Zhao (1991) specifies–i.e. to overcome the conceptual and methodological problems encountered by past research– is also the stated goal of this dissertation as well. Because of these similarities, I argue that the tools utilized by the meta-study approach are relevant to the task at hand.

As conceptualized by Zhao (1991), a meta-study is carried out by conducting three types of analyses called and meta-data-analysis, meta-method, and meta-theory, Each of these analyses, in turn, can be further divided into a series of sub-types that focus on particular aspects of the larger analysis of which it is a part (see figure 2 for a schematic representation).

Section 2.1: The Meta-Data-Analysis Dimension

The meta-data-analysis dimension of a meta-study involves three types of examinations: the first is the study of the underlying assumptions of various data-analytic procedures; the second is the comparison of different forms of data in terms of their quality and utility; and the third is the synthesis of the findings of a range of research studies that are related to the same phenomenon (Zhao 1991:379). Although Zhao (1991:385) is careful to point out that meta-data-analysis has yet to fully develop within sociology (at least at the time of his writing), he does note two ways meta-data-analyses are being conducted. One of these involves the use of statistical techniques to synthesis large collections of empirical results taken from individual studies into a single interpretation; the other involves a similar task, but focused on synthesizing the empirical results of qualitative and mixed-types of data. In either case, the purpose of a meta-data analysis is to give researchers the opportunity to summarize what is currently known about a phenomenon and then reflexively step back to assess the larger meaning of the data. At the same time, a meta-data-analysis also serves as an opportunity to reflect upon where future research should be directed in light of this larger meaning, as well as assess what obstacles need to be overcome in order to move that direction.

Section 2.2: The Meta-Method Dimension

Like meta-data analysis, the meta-method dimension of a meta-study involves different subtypes of examination. Specifically, these include: an examination of the methodological presuppositions necessary for carrying out sociological research; the evaluation of extant sociological research methods in terms of their weaknesses and strengths; and the codification of new procedural rules for sociological research.

Although Zhao (1991) does not specifically delineate it as such, he appears to suggest the relevance of a fourth examination that focuses on evaluating the operational definitions that have been applied by past research to their respective problem areas. Similar to meta-data analysis, the overall goal of the meta-method dimension is to summarize and evaluate a disciplines methodological assumptions and practices; and, in light of this, reflect upon how these assumptions and practices should evolve in the future.

Section 2.3: The Meta-Theory Dimension

Following Ritzer (1990), meta-theory is said to consist of three, multi-component branches of theorizing devoted to producing three end-products. The first branch-- which Ritzer labels as M_u-- involves examining existing social theory in order to produce a better, more profound understanding of it (Ritzer 1990:4); this deeper understanding, in turn, can then lead to uncovering interesting, important, and sometimes surprising insights that had hitherto gone unrealized. Importantly, this branch of meta-theory can be further subdivided into four categories, each of which focuses on developing its insights within a particular intellectual or social context; three of the more pertinent to the task at hand are called internal-intellectual internal-social, and external-intellectual studies.

As originally stated by Ritzer (Ritzer 1988), an internal-intellectual study involves re-examining the work of one or more theorists to find insights for building new concepts, theories, foundational assumptions, and working strategies, as well as in terms how to move social theory in a new direction (191). An internal-social study, in turn, focuses on the theorists themselves and the social and institutional networks within which they developed their ideas. Knowledge of these larger contexts can be important because they can help clarify or elaborate otherwise ambiguous or underdeveloped ideas. Or, in more concrete terms, if “Theorist A” both worked with and was heavily inspired by “Theorist B”, knowledge of Theorist B's work can aide in clarifying or elaborating related ideas found in the work of Theorist A. Finally, external-intellectual studies examine how fields of knowledge outside of a discipline can be used to either elaborate or extend existing theory in new directions. At the same time, an external-intellectual study can also examine how exogenous ideas, tools, concepts, and theories have influenced the development of theories in the past. Like internal-social studies, this subtype of meta-theory can help clarify or elaborate knowledge of existing theories by deepening our understanding of the larger set of ideas underlying their construction.

The second branch of meta-theory is referred to by Ritzer as M_p. According to Ritzer (1990), M_p meta-theorizing serves as a prelude to the development of new sociological theory; e.g. the development of theory on the basis of a careful study of, and reaction, the work of previous theorists. Examples of M_p meta-theorizing, Ritzer (1990:5-6) notes, include Marx’s development of his theory of capitalism after a systematic engagement with Hegelian philosophy, as well as the Parson’s development of his action theory after his careful study of Durkheim, Weber, Pareto, and Marshall. In short, M_p meta-theorizing is responsible for reflecting upon the current state of knowledge with an eye toward advancing it in a new direction.

Finally, Ritzer (1991) refers to the third branch of meta-theorizing as M_o. The goal of this dimension is to examine existing theory in order to create an overarching theoretical framework. Here Ritzer lists several examples of M_o metatheories, including Wallace's positivist prescription for transforming sociology into a natural science and Ritzer's 'integrated sociological paradigm. It is important to note that Ritzer (1991) argues that there are two conditions that can disqualify a meta-theory as a M_o subtype. The first disqualifier is if the meta-theory formulizes its presuppositions without a direct consideration of sociological theory; i.e. the presuppositions appear to 'materialize out of the imagination of the creators' instead of being derived organically from existing theoretical frameworks (Ritzer 1990: 4).' The reason this is problematic, Ritzer asserts (1991), is because it is impossible to assess how the presuppositions came into existence. The second disqualifier is if the presuppositions are deduced exclusively from theories outside of the sociology. Although Ritzer (1991) is not clear why this should be a problem per se, a close reading of his argument reveals two potential reasons. First, it is not clear how ideas outside of sociology are relevant to social theory; and second, a lack of familiarity with the outside literature can also lead to an inability to assess how the presuppositions were developed.

Given that my ultimate goal is to use portions of Ritzer’s (1991; 1990; 1988) framework to incorporate biological insights into sociological theory, this proscription against the use of ideas stemming from outside of the discipline could undermine my ability to accomplish this task. This concern will be addressed below in Section 4.1.

Section 2.3.1: A Model of how the Three Branches of Meta-Theory are related

At the end of his summary, Zhao (1991:383) makes an interesting comment about a possible relationship between the three branches of meta-theorizing; specifically, he notes:

> "In sum, metatheorizing in sociology has completed the whole sequence of meta-study: starting with the descriptive examination of the underlying structures of extant theories (M_u), moving on to the prescriptive search for new directions of future theoretical developments (M_o), and ending with the actual construction of new sociological theories (M_p). While Mu is a necessary step to M_o, M_o is a prerequisite for M_p."

While Zhao (1991) does not elaborate upon this point further, I believe that the following represents a legitimate extension of his logic. In short, the three branches of meta-theory can be viewed as three steps of a single process of theory construction; indeed, as specified above, Zhao's interpretation of this process can be schematically represented as: $M_u \rightarrow M_o \rightarrow M_p$. Discursively, this schematic can be summarized as: [M_u Theorizing] leads to [M_o Theorizing] leads to [M_p Theorizing].[2]

Alternately though, one could also suggest a process involving: $M_u \rightarrow M_p \rightarrow M_o$. According to this scheme, M_u theorizing is functionally responsible for developing as clear and accurate of an interpretation of a theory as possible. Given the outcome of this process, M_p theorizing is then responsible for evaluating the M_u version of a theory in terms of its conceptual clarity and accuracy; moreover, M_p theorizing can also be used to simplify a single theory down to its bare-bones argument, or, for that matter, reducing multiple theories down to a single, synthesized model. In either case, the final goal of the

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[2] From here on out, the symbol → will be used in place of "leads to." Likewise, the symbol ←→ is intended to convey a reciprocal relationship.

$\mathrm{M_p}$ step in the meta-theory process is to transform the $\mathrm{M_u}$ version of a theory into a clearer, more accurate, more precise, and more concentrated knowledge claim that is more amicable to further testing or development. Finally, the final step of the process involves generalize this $\mathrm{M_u}$ version of a theory to produce an overarching $\mathrm{M_o}$ meta-theory to guide subsequent theory development. This last step is clearly suggested by Ritzer's (1990: 9) comment that:

> "…while [the production of an overarching theoretical perspective] is the distinctive role of M_o, it is possible for M_u and M_p to function in similar ways. For example, M_u work on the paradigmatic structure of sociology led to the generation of a transcendent orientation, the integrated sociological paradigm [i.e. the M_o meta-theory by Ritzer noted above]."

Section 2.4: How $\boldsymbol{M_u}$ and $\boldsymbol{M_p}$ analyses can be used to create an Orientating Strategy

Having specified how M_p, M_u, and M_o meta-theory may relate to each other, we can now ask how Ritzer (1991; 1990) & Zhao's (1991) concept of meta-study relates to Berger & colleagues 's concept of an orientating strategy . Here I argue that a juxtaposition of Ritzer's (1990) definition of M_o meta-theory with Berger & colleagues' definition of a foundational aim can reveal two important similarities that warrant the claim that they are roughly interchangeable. First, both Ritzer & Zhao and Berger & colleagues define their respective concepts as over-arching strategies for guiding theory construction and research. And second, both sets of theorists make reference to highly abstract ontological and epistemological positions as examples of their respective concepts. Of course, Berger & colleagues 's concept of an orientating strategy also consists of the less-abstract set of working strategies; in my opinion, these correlate with the more concrete versions of M_o that are derived from M_u or M_p meta-theories (see

Ritzer's (1990) comment above). In either case, the ability to substitute the concept of M_o for the concepts of foundational positions and working strategies allows us to specify the schematic relationship seen in figure 3 regarding how to *craft* an orientating strategy. Discursively, this relationship can be summarized as the following steps: first, one engages in M_u meta-theorizing to specify in the clearest terms possible the conceptual and theoretical arguments of one or more theories; second, one then engages in M_p meta-theorizing to transform the product of M_u meta-theorizing into a new meta-theory, or multiple M_u products into a smaller set of theories; finally, if the product of the M_p process is of sufficient abstractness and generality, it can be used as either a substantive or methodological position. If, instead, the M_p product is relatively more concrete and specific, then it can be used as a substantive working strategy. From here on out I will refer to this stage of the integrated model that I am trying to develop as the BRZ model.

To be sure, meta-theory was only one dimension of Ritzer & Zhao's larger concept of a meta-study. What about meta-method and meta-data analysis? What role can these aspects of a meta-study play in formulating an orientating strategy for the biosocial perspective? In the case of the meta-method dimension, I believe that it is possible to perform a similar synthesis using the schematic: Meta-Method (M_m) →Methodological Working Strategy (W_m). The logic underlying this schematic can be explained as follows. Recall from above that Berger & colleagues defined a methodological working strategy as specifying the answers to 'how to' problems: how to construct a theory, how to formulate an explanation, and how to assess theories. Here I am arguing that it is possible for the product of a meta-method study to serve as the answers given by the W_m. Or, to put it another way, I am arguing that once can engage in a meta-method study of relevant existing literature *in order to answer the questions*: how does a researcher construct at theory, formulate an explanation, or assess theories?

In the case of meta-data analysis though, neither Ritzer & Zhao nor Berger & colleagues appear to offer in their original formulations an answer for how this dimension relates to an orientating strategy. In the next section I will argue that Turner's (Turner 1990; Turner 1991) approach to meta-theorizing can fill this important gap in the BRZ model.

Section 3: A Summary of Turner's definition of a Meta-Theory.

Of all the meta-theoretical frameworks reviewed in this chapter, Turner's (1990; 1991) is without doubt the most pragmatic and the most concise. The reason for this is due to Turner's belief that meta-theorizing is done best when done for the explicit purpose of generating new theories and for strengthening the relationship between empirical research and abstract theorizing. True to this position, Turner (1990; 1991) summarizes his meta-theoretical framework as a list of prescriptions and proscriptions regarding how and how not to construct a meta-theoretical framework.

In terms of his prescriptions, Turner (1990:40) argues that meta-theorizing should focus on:

1. Evaluating the clarity and adequacy of concepts, propositions, and models
2. Suggesting points of similarity, convergence, or divergence with other theories
3. Pulling together extant empirical studies to assess the plausibility of a theory

4. Extracting what is viewed as useful and plausible in a theory from what is considered less so
5. Synthesizing a theory, or portions thereof, with other theories
6. Rewriting a theory in light of empirical or conceptual considerations
7. Formalizing a theory by stating it more precisely
8. Restating a theory in better language
9. Making deduction from a theory so as to facilitate empirical assessment.

Regarding his proscriptions, Turner (1990:39) asserts that researchers engaging in meta-theorizing should:

1. Avoid talking about theorists per se; in other words, meta-theory should avoid becoming simply a biographical sketch that traces an individual's intellectual influences, or an attempt to reinterpret them as an "idealist," a "materialist," etc.
2. Avoid talking about the intellectual context or social milieu within which a concept or theory was developed; in short, meta-theory should focus on developing general theories about how the social world operates and not discourses on the history of ideas.
3. Avoid philosophical debates over ontologies, epistemologies, metaphysics, and ideological positions; instead, simply commit to the pragmatic assumption that there is a world out there; that the properties of this world exist regardless of whether or not humans understand them; and that science is capable of understanding this world through the use of the scientific method.

Section 3.1: Synthesizing Turner's meta-theoretical prescriptions with the BRZ Model

I will begin my synthesis by highlighting several important similarities between Turner's prescriptions and the BRZ model; my reason for starting here is to demonstrate that these two seemingly very different frameworks are, in fact, addressing related issues in a comparable way (see table 1 for a summary). First, prescriptions 4, 7, and 8 above, are all very similar to the M_u component of BRZ synthesis. Indeed, both direct the researcher to critically engage with existing theoretical frameworks in order to make them as accurate and precise as possible. Second, prescriptions 2, 4, and 5 are all very similar to the $M_p$component of the BRZ model. In this case, both can be seen as directing the researcher to evaluate the accuracy and clarity of a theoretical framework, as well as to reduce by synthesis multiple individual theories into a more abstract and general model. And third, both prescription 9 and the W_S of the BRZ model argue that meta-theoretical propositions can be used to guide research or interpret findings.

With prescriptions 3 and 6 though, we begin to see an important difference between Turner's model and the BRZ framework; it is here, I believe, that the bridge between meta-data analysis, meta-method, and meta-theory can be found. Unlike the Ritzer & Zhao model, Turner does not separate the meta-data analysis and meta-theorizing into separate dimensions; instead, he explicitly builds into the meta-theorizing process a place for the consideration of empirical data. Here I argue that prescription 3 can be schematically represented as:

[Summation of Empirical Results]→ Evaluation of Theory

Discursively, this can be stated as 'a set of empirical results are used to evaluate the validity of a theory. Likewise, prescription 6 can be schematically represented as

Theory→ [Evaluation of Empirical Results]

Or discursively as: a theory is used to explain or interpret a set of empirical results. If we recognize the similarities between the Turner and BRZ models just discussed above, then we can substitute either M_U or M_p in place of THEORY; this substitution results in the following schematics:

$$(M_U) \leftarrow\rightarrow \text{[Set of Empirical Results]}$$

$$(M_p) \leftarrow\rightarrow \text{[Set of Empirical Results]}$$

Here, the first schematic can be discursively summarized as either 1) the product of an M_U analysis is used to interpret a set of empirical results; or 2) a set of empirical results are used to validate the product of an M_U analysis. *Mutatis mutandis*, the second schematic can be summarized discursively in the same way.

Now, recall from above that Ritzer & Zhao defined one dimension of meta-data analysis as the synthesis of a range of research results; for the sake of quick reference, let us label this dimension as M_{DA}. If we recognize the conceptual similarity between Ritzer & Zhao's definition of their M_{DA} dimension and Turner's discussion of synthesizing sets of empirical results, we can substitute [Set of Empirical Results] with M_{DA} to form:

$$[M_U] \leftarrow\rightarrow M_{DA}$$

$$[M_p] \leftarrow\rightarrow M_{DA}.$$

Again, this schematic can be discursively summarized as: the product of meta-theorizing can be used to interpret the product of a meta-data analysis; or, as the product of a meta-data analysis can be used to evaluate or validate a meta-theory. I argue that this integration solves the problem of how to begin to incorporate the meta-theory and meta-data analysis dimensions of the Ritzer & Zhao and BRZ models.

Section 3.2: Synthesizing Turner's meta-theoretical proscriptions with the BRZ Model

Having integrated Turner's prescriptions into the BRZ model, I will now turn to addressing how to integrate his proscriptions as well. The first proscription I will focus on is number 3, i.e. Turner's suggestion that researchers avoid philosophical debates and simply adopt the pragmatic assumption that the world exists and that the scientific method can be used to understand it. Because the substantive and methodological foundational positions of the Berger & colleagues' model directly reference the type of debates Turner discusses here, this proscription appears to create an obstacle to integrating the two models. I argue though that his obstacle is easily remedied by simply reducing these parts of the Berger & colleagues' model to the positions suggested by Turner. In other words, instead of framing the foundational positions of the BRZ model in abstract metaphysical, ontological, or epistemological terms, these positions should be stated in terms of the empirical insights derived from the biological sciences. For example, instead of adopting a philosophical argument to serve as a substantive position for how 'mind' is related to 'body' (Hume 1978; Descartes 1989; Kant 1999), one could simply state this relationship in terms of the biological research specifying how mental states are generated by complex neural dynamics (Koch 2004; Buzsáki 2006; Llinás 2007). Due to how confusing and esoteric debates about philosophy can be– especially for social scientists not versed in this literature– I argue that this deletion not only removes the obstacle to integrating Turner into the BRZ model, but improves the over-all utility of the BRZ framework as well.

Beyond this substitution, though, I do believe that the foundational substantive goals component of that model still has relevance. Recall from above that this component of the Berger & colleagues' model was responsible for specifying the types of phenomena, processes, and empirical questions a research program should examine, as well why such examinations are important. As was already discussed in section 1.2, the relevance of these substantive goals is twofold. First, they provide a clear response to critics for why biosocial researchers should study the biological foundations of psycho-social processes; in short, research focus on these things because the substantive goals of the perspective that they adopt direct them to do so. And second, they provide a clear outline for what the various components of the BRZ should be focusing on when performing their particular task. In other words, they provide a running list of the types of information that the M_{U}, M_{P}, M_{DA}, and M_{M} meta-analyses should be developing.

In my opinion, it is possible to maintain the substantive goals component of the BRZ model– while still avoiding the type of philosophizing Turner warns against– by simply specifying said goals as a series of standardized, concrete questions; the purpose of these would be to serve as a set of standing questions that each biosocial research program needs to eventually answer. Moreover, these questions could also serve as a bench-mark for evaluating competing theories; specifically, the better theory is the one that is able to provide answers to the most questions. Examples of these types of such questions include:

- What is the step-by-step mechanism underlying how a specific biological processes is able to influence a specific psycho-social process?

- How do multiple biological processes reciprocally interact to generate a psycho-social phenomenon?

- How do either environmental or psycho-social process feedback to affect the biological process(es)?

- To what degree can future researchers assume– a priori– that the identified biological process may be involved in or related to a psycho-social process in contexts other than those first identified; in other words, how generalizable is the process?

- What do the social sciences gain by knowing that a biological process is related to a psycho-social process; i.e. what is the larger relevance of the finding?

Like proscription 3, proscriptions 1 and 2 also create the potential for integrating Turner's framework into the BRZ model. In this case Turner's proscriptions appear to argue against the need to engage in M_U meta-theorizing; i.e. examining the social and intellectual influences that shaped the development of a concept or theory. As I read Turner though, this proscription only applies to M_U meta-theorizing that treats this type of examination as an end in-of-itself. As such, there does not appear to be any conflict between the two frameworks if M_U meta-theorizing is strictly done for the purpose of clarifying concepts and theories so that they may then serve as the basis of either M_P meta-theorizing or as a W_S.

In short, then, the integration of Turner's proscriptions into the BRZ model reinforces the framework's commitment to the development of pragmatic orienting assumptions devoted to the development and improvement of social theoretical knowledge. From here on out, I will refer to this fully integrated version of the model as the BRZT framework. The schematic representation of this model can be seen in figure 4.

Section 4: How to develop a Meta-theory for the Biosocial Perspective

Having outlined the basic skeletal structure of a meta-theoretical framework, I will now turn to refining the model so that it can incorporate the unique type of data handled by the biosocial perspective. Here I want to advance the argument that there are two ways to incorporate information about biological processes into social theory. The first way, I claim, is qualitative in nature and involves incorporating into social theory the *idea* that a psycho-social process is produced by a series of biological interactions; or, in other words, this type of integration is labeled qualitative because it does not involve the incorporation of an explicit, quantitatively measurable process. The second way, in turn, is quantitative in nature and involves the incorporation of concrete empirical data about how biological processes generate psycho-social dynamics.

Section 4.1: A Method for Performing a Qualitative Integration (with an example).

As I see it, the best way to qualitatively integrate biological processes into the W_S of the biosocial perspective is through the M_U component of the BRZT model. Recall from above that the M_U component can be divided into at least three types of analyses: 1) internal-intellectual studies that focus on developing a deeper understanding of a theorist's work by carefully re-examining their arguments; 2) internal-social studies that examine the social-intellectual contexts stemming from within sociology that influenced the development of a theory; and, 3) external-intellectual studies that analyze the influence of ideas and research from outside of sociology on the development of a theorist's ideas. In the case of the internal-intellectual subtype, a qualitative integration would involve carefully analyzing a theorist's argument for explicit references to a biological substrate. Once located, their argument would then be clearly specified within the context of this biological reference.

George H. Mead's definition for the value of an object provides a good example of how to carry out a qualitative integration using the internal-intellectual dimension of M_U. According to Mead (1934) the value of an object– i.e. the meaning an individual ascribes to an object– is determined by how the individual is prepared to behaviorally act toward it. In regard to the meaning of a telescope, Mead says:

> "If we want to trace the responses of the astronomer, we have to go back into his *central nervous system*, back to a whole series of *neurons*; and we find something there that answers to the exact way in which the astronomer approaches the instrument under certain conditions….the values which we say the instrument has are values through the relationship of the object to the person who has that sort of attitude. If a person did not have that particular *nervous system*, the instrument would be of no value. *It would not be a telescope* (Mead 1934):29; emphasis added)."

Notice here the degree to which Mead binds this concept of meaning to the existence of some neurological substrate; indeed, in the last line of the quote he explicitly notes that the neurological processes underlying the behavioral attitude toward the telescope is exactly what makes the telescope a telescope. Without this biological substrate, the telescope-as-such would not exist. Clearly then, the biological substrate referenced is an important dimension of the concepts definition.

A the same time, though, Mead does not reference a specific biological process per se; in other words, he does not identify for us which series of neurons account for the meaning of the telescope, nor does he describe explicitly how their interactions are able to account for or represent the intentions of the astronomer acting toward it. Instead, he offers only a vague and general indication that some sort of biological process is intrinsically involved in the psycho-social dynamics he is considering. As such, an internal-intellectual analysis would involve formally defining Mead's concept of the meaning as the neurological processes involved in carrying-out the behaviors directed toward an object. Specifically, this analysis would involve describing in detail which parts of the nervous system are involved and the nature of the biological mechanism underlying the process.

This same logic can be applied to both the internal-social and external-intellectual subtypes of M_U as well. In both of these cases, this would involve performing the following three steps: first, one would begin by identifying the intellectual and social influences on a theorists; second, one would then conduct an internal-intellectual study on these influences to identify any references to biological processes; and third, one would then incorporate this identified biological dimension into the areas of the theorist's framework that were influenced by these sources (see figure 5). For example, the Symbolic Interactionist Perspective is heavily indebted intellectually to the ideas of George H. Mead. As such, one could carry-out an internal-analysis on each of the concepts comprising Mead's theoretical framework and then import the results of this analysis into the corresponding concepts found in Symbolic Interactionism.

Along with this, one could also perform what I call a temporal analysis of internal/external influences. This type of analysis involves tracing the intellectual development of an influencing concept over time, and then applying this evolutionary process to the sociological theory that was influenced by the original version of these ideas. For example, it is widely known that Mead's sociological theory was heavily influenced by his associations with John Dewey, William James, and other Functional Psychologists (Turner, Beeghley et al. 1995). Interestingly, many of the ideas developed by this school of thought were transformed over the years– via the process of scientific discovery– into the foundational principles underlying contemporary neuroscience (Kandel, Schwartz et al. 2000). As such, I argue that it is possible to examine how the early insights of the functionalist perspective were transformed into their contemporary neurological counterparts, and then extrapolate from this process what the similar ideas found in Mead would look like if they were to have undergone the same course of development (see figure 6). An important benefit stemming from this type of analysis is that it provides a direct link between sociological concepts and contemporary biological research.

Before turning to discuss what I mean when I use the term *quantitative integration*, I want to pause for a moment and address the concern that drawing insights from biology violates Ritzer's proscription discussed in Section 2.3. As I interpret it, this proscription is solely arguing against focuses non-sociological insights being *imposed* on sociological theory without any clear understanding of where they came from, or, how they relate to the theory to which they are being applied. The reason that I do not believe that Ritzer's proscription applies to the task at hand is this: by utilizing M_U analysis in the manner just discussed, I am not *imposing* biology onto a theorist's ideas; instead, I am *excavating* the already existing biological kernel from their framework and then simply up-dating it in light of recent scientific discoveries. In other words, I am asking: "Given the underlying logic for why the theorist referenced a certain biological process, what would this concept or theory have looked like if they had access to the current understanding of how that process operated?" Although this is a subtle distinction, it is an important one none-the-less.

Section 4.2: How to Quantitatively Integrate Biological Research and Social Theory.

I argue that empirical biological data can be incorporated into the BRZT model through a modified version of the $\mathrm{M_P} \leftarrow\rightarrow \mathrm{M_{DA}}$ component. First, though, let me address why we cannot use this component in its current form. In short, the reason is exactly the same as was stated by the critics of the biosocial perspective: there is not clear relationship between psycho-social concepts and biological data. In other words, we can engage in all of the M_P meta-theorizing of existing theory and Md meta-data analysis of existing biological data all that we want, and still be left with no clear bridge for how to combine the two. As such, this bridge is exactly what we need to focus on developing here.

My solution to this problem is to use the fourth dimension of the $\mathrm{M_M}$ component of the Ritzer & Zhao model to connect the $\mathrm{M_P}$ and $\mathrm{M_{DA}}$ components of the BRZT framework. Recall from above that the fourth dimension of a meta-method analysis consisted of evaluating the validity and adequacy of operational definitions used in past empirical work. Also recall that an operational definition consists of the set of procedures that describe the activities a researcher needs to perform to establish the empirical existence of the concrete phenomenon described by the abstract conceptual definition (Frankfort-Nachmias and Nachmias 2000). Finally, recall too that the function of an operational definition is to bridge the conceptual-theoretical and empirical-observational levels of analysis by defining what to do and what to observe in order to make the phenomenon being studied perceivable and understandable (Frankfort-Nachmias and Nachmias 2000).

By claiming that an $\mathrm{M_M}$ analysis can bridge the gap between M_P theorizing and M_{DA} analysis, I am arguing that a quantitative integration can be successfully accomplished by treating an empirical biological process as the operational definition of the more abstract conceptual definition provided by a social theory. For example, the abstract concept of a *reflected appraisal* is defined as the mental process through which an individual imagines how others perceive and evaluate them (Burke and Stets 2009). At the same time, neuroscience research indicates that the neural correlates of reflected appraisals involve a dynamic interplay between the orbitofrontal, insular, and temporal regions of the medial prefrontal cortex (Ochsner 2005). In other words, the coordinated dynamic neural activity occurring in and between each of these regions generates the cognitive processes involved in reflected appraisals. As such, the dynamic interplay between the above brain regions represents the *operational definition* for the abstract concept that is defined by the discursive description of the associated mental process.

Of course, it could be claimed that this bridge plays a little too fast and loose with what it means to say that an operational definition defines what a researcher should observe when matching an abstract concept to a concrete phenomenon. The reason for this is because one does not actually observe neural activity per se; instead, one observes either changes in blood flow or changes in the electrical activity of groups of neurons (Buzsáki 2006; Bear, Connors et al. 2007). In response to this potential criticism, I would say then that a biological process equals the concrete referent of the abstract concept, i.e. the physical objects believed to be responsible for producing the phenomenon referenced by the abstract concept; the operational definition, at least in terms of the biological dimension of the concept, would then be defined as what is actually observed when measuring the activity that is believed to indicate the presences of the biological process. To distinguish between these two understandings of the term, I will refer to M_M analyses that focus on blending conceptual definitions with empirical referents as $M_{M_{cr}}$, and M_M studies that focus on creating operational definitions as $M_{M_{od}}$.

Like the other components of the BRZT model, the relationship between M_P, $M_{M_{cr}}$, and M_{DA} can be schematically represented as:

$$M_P \leftrightarrow M_{M_{cr}} \leftrightarrow M_{DA},$$

$$M_{M_{od}} \leftrightarrow M_{DA}.$$

Discursively, these models can be summarized as follows. In the case of $M_P \leftarrow\rightarrow M_{M_{cr}} \leftarrow\rightarrow M_{DA}$, one would first engage in M_P theorizing to reduce multiple theories into a single synthesized model. Next, one would then carry-out an M_{DA} analysis of existing natural science research that examines the biological foundations of the type of psycho-social processes referenced in the M_P theory in order to produce a basic empirical model of said psycho-social processes. After completing this, the next step would be to reformulate the M_P theory to explicitly reference the biological processes identified by the M_{DA} analysis as the concrete referents of its abstract concepts. Finally, one would then specify the operational definition of the biological referents in order to indicate the types of empirical values need to be observed in order to conclude that the biological process–as well as, by default, the psycho-social process– is present.

With these final integrations in place, my development of the BRZT model is complete. From now on, this completed version of the model will be referred to as the "biosocial meta-framework." Its schematic representation can be seen in figure 7.

Part III: Summary and Preview of Things to Come

A new approach to understanding how biology, culture, and social interactions dynamically interact is emerging within the social sciences. Although this line of research exhibits a tremendous potential to revolutionize our understanding of human dynamics, it currently suffers from a number of important analytical weaknesses. The purpose of this chapter was to formally create a meta-theoretical framework for how to address these concerns.

The integrated meta-framework developed here is designed to create two sets of analytical tools to guide the construction of biosocial theory and to carry out biosocial research. The first of these are the taken-for-granted substantive positions provided by the life sciences regarding the biological mechanisms underlying how the ‘body’ generates ‘mind’, as well as the substantive questions every biosocial theory must answer. The second set of analytical tools contains the substantive and methodological working strategies that provide the conceptual definitions, operational definitions, scope conditions, and empirical referents that serve as the building blocks for biosocial theories. Moreover, the biosocial meta-framework also specifies two sets of analytical processes for creating the above tools. The first of these sets specified how to transform one or more discursive social theories into a format that is conducive to the integration of biological data. The second set, in turn, specified how to gather biological data about a psycho-social process and then integrate it into a social theory.

The remaining chapters of this dissertation will be devoted to using portions of this meta-framework to create a handful of substantive assumptions and working strategies to be employed in future biosocial research. Generally speaking, the first set of substantive assumptions will focus on explaining how hierarchically-nested biological processes generate mental processes through dynamic and reciprocal interactions within and between levels of organization. My reason for focusing on this topic specifically is two-fold: first, this discussion will explicitly address the criticism noted in the introduction that the biosocial perspective has yet to formally explain these relationships; and second, once these relationships are formally identified, future generations of biosocial researchers can take them for granted and focus their attention instead on developing new theoretical insights.

The development of this first set of substantive assumptions will not be easy; the reason for this is because the biological processes involved are made up by a plethora of hierarchically-nested and non-linearly interacting parts (Sporns 2011). In order to deal with this complexity, it is common in the biological sciences to categorically divide an organism into several levels of analysis, including: molecular, intra-cellular, cellular, tissue, organ, and organ-system levels (Bear, Connors et al. 2007). Once divided in this manner, the goal of biological research is to describe how the component parts of each layer interact to produce their defining characteristics, as well as identify how said interactions are influenced by the processes occurring at the other levels of the hierarchy.

In humans, the brain is an organ embedded in a larger organ system called the nervous system- both of these, in turn, are comprised of tissue made up by a densely connected network of specialized cells called neurons. These individual neurons are both comprised of and communicate with a host of molecular structures and processes- most of which are in some way dependent upon the proper expression of specific genes. Working together via a tightly orchestrated division of labor, the component parts of the nervous system are able to collect information about the external world and the internal state of the body, interpret that information, determine how that information conforms to the needs and goals of the organism, and to formulate an appropriate behavioral response to accomplish those goals (Byrne and Roberts 2009). In order to fully understand how this is possible it is necessary to carefully trace the structural and functional mechanisms involved from the molecular to the system level.

In very general terms, then, Chapter 2 will focus on performing an M_{DA} analysis on the intra-cellular dynamics responsible for creating the structural and functional properties of the individual neuron. In Chapter 3, I will then perform an M_{DA} analysis on how individual neurons interact to create neural circuits that are capable of representing and processing information about an organism's external and internal environment. Further, I will also perform here an M_M analysis on how the mathematics represented by dynamical systems theory can be used to operationally define and model the processes taking place at the neural circuit level. Chapter 4, in turn, will focus on performing an M_{DA} analysis on how the brain is structurally organized into functionally distinct regions. Moreover, I will also discuss here how these structural and functional divisions are initially determined by person's genetic code during embryonic development, but are then subsequently shaped over time by their life experiences. In chapter 5, I will then perform an M_{DA} analysis to describe how sets of the brain regions coordinate their dynamics to generate what are called intrinsic connectivity networks. Further, I will also perform in this chapter an M_M analysis of how the mathematics represented in graph theory can used to operationally define and model these dynamic co-ordinations. In Chapter 6 I will explore how three of these intrinsic connectivity networks enable several sociologically relevant cognitive capacities. Chapter 7 will focus on performing an Mu analysis of Alfred Shutz's theoretical framework in order to identify the neurological correlates of his basic concepts and arguments; the goal of his analysis will be to produce a second set of working assumptions that can be used as an orientating strategy for micro-sociological theory. Chapter 8 will conclude with a brief discussion of the analyses carried out in Chapters 2-6 can serves as the bases for future research.

Chapter 1 Figures and Tables

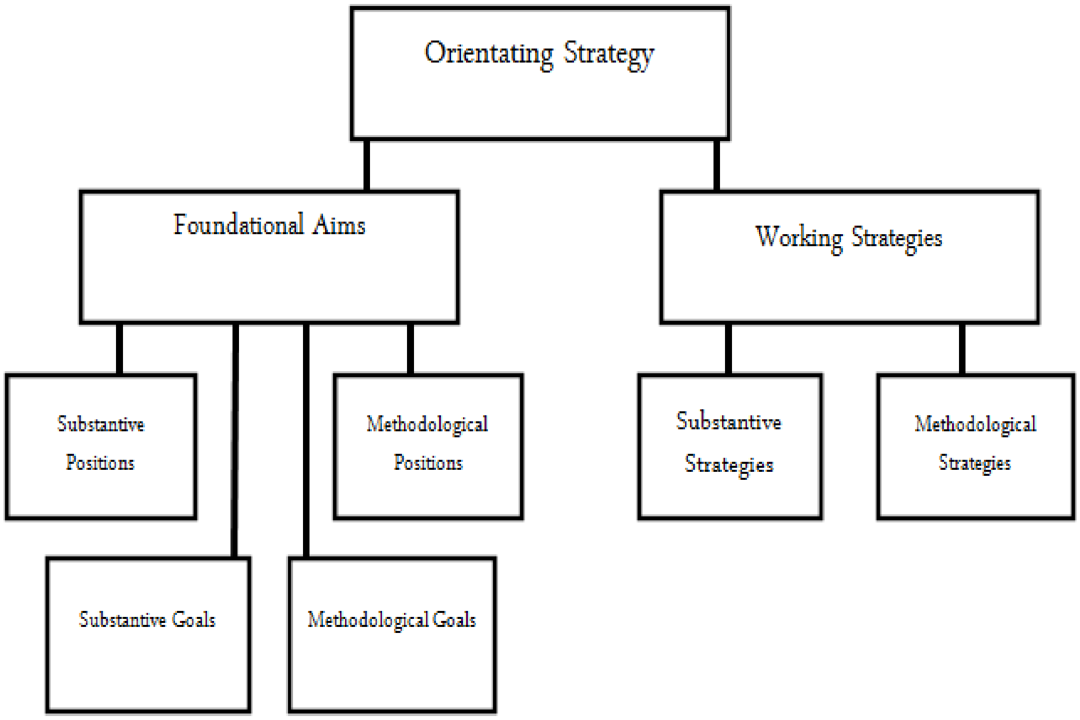


Figure 1: A schematic representation of Berger et al's concept of an orientating strategy. As noted in the text, an orientating strategy can be divided into two main components; each of these, in turn, can be subdivided further. In section 1.1 I will discuss how each of these component parts has the potential to offer a different type of response to the critics of the biosocial perspective. Although how I define an orientating strategy will evolve over the course of the chapter, its ultimate goal is to produce an orientating strategy such as this in order to address the limitations of the biosocial approach noted in Part I.

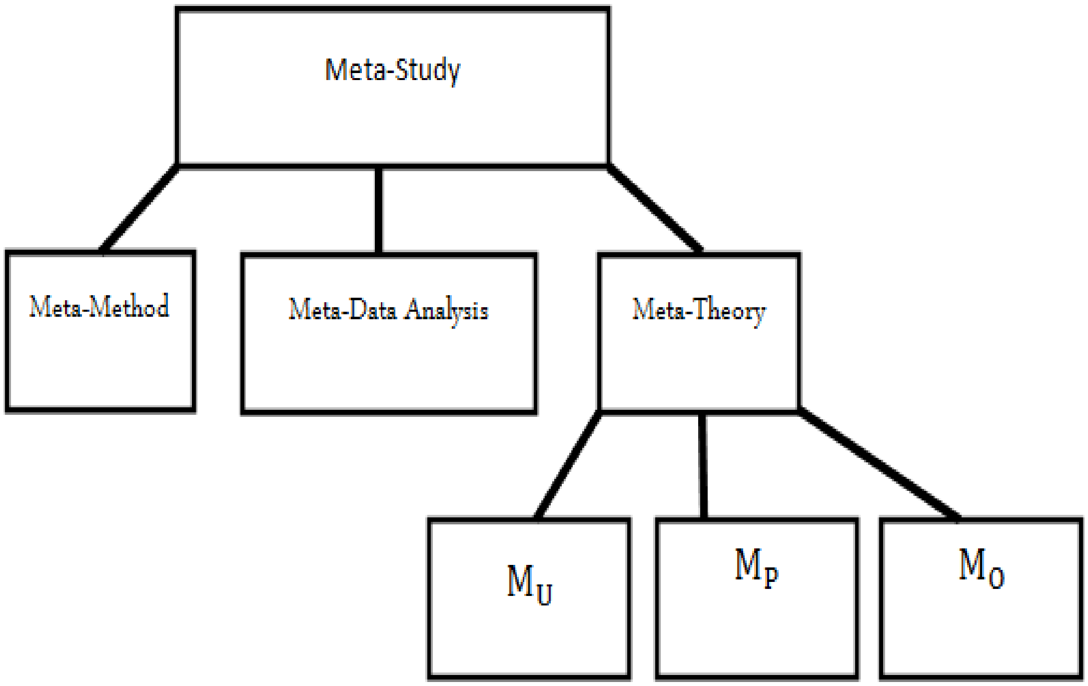


Figure 2: A schematic representation of Ritzer & Zhao's concept of a meta-study. Like the Berger et al model, this schema can be divided and subdivided into component parts. In subsequent sections of this chapter I will transform this formulation into a more dynamic representation. As described in the text, this dynamic version of a meta-study would be used to produce a modified version of Berger et al's concept of an orientating strategy.

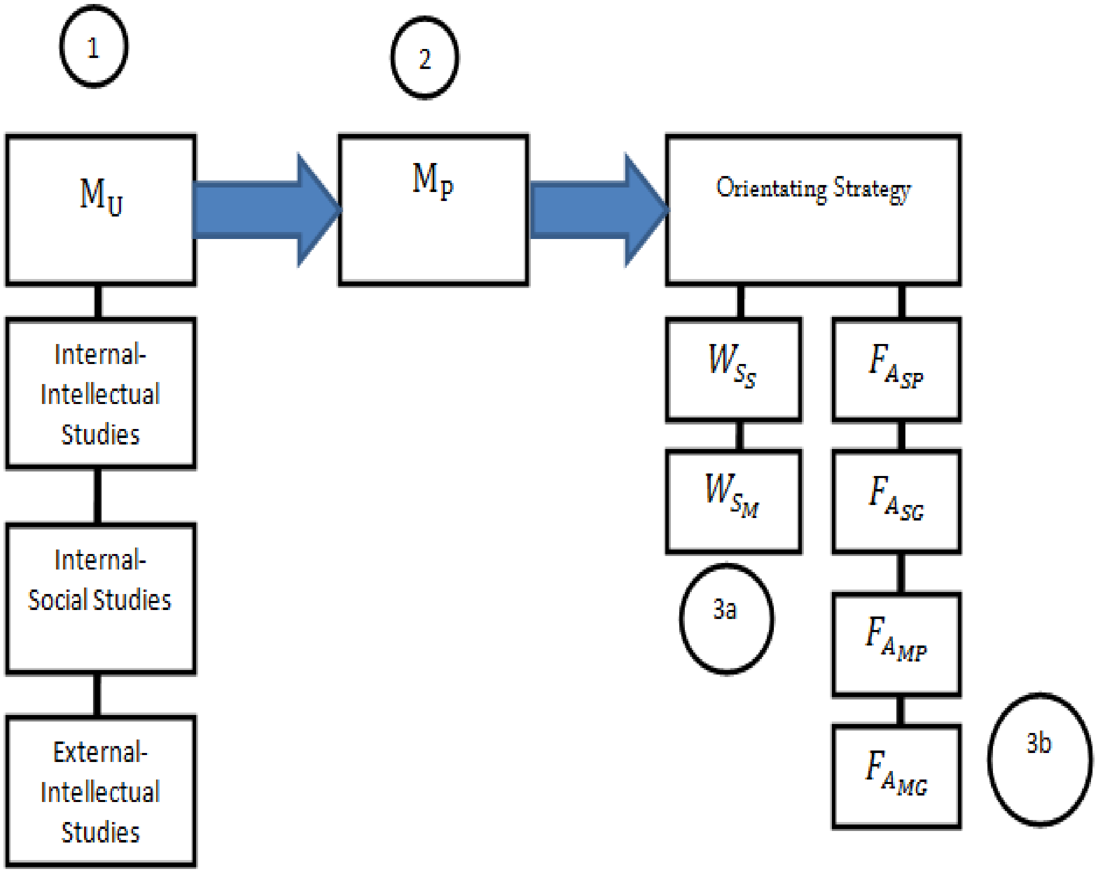


Figure 3: This is a schematic representation of the integrated Ritzer & Zhao and Berger et al model. Step 1 of the integrated model involves engaging in Mu analyses to establish a clear and accurate understanding of a theorist's framework. The product of these analyses then becomes the input for the Mp meta-analyses that takes place at step 2. Here the goal is to integrate and synthesize the various Mu components into a single concept or statement. If the product of step 2 is relatively concrete, then it becomes a working strategy for subsequent biosocial research (3a). If the product of step 2 is more concrete, then it becomes a foundational aim for subsequent research (3b).

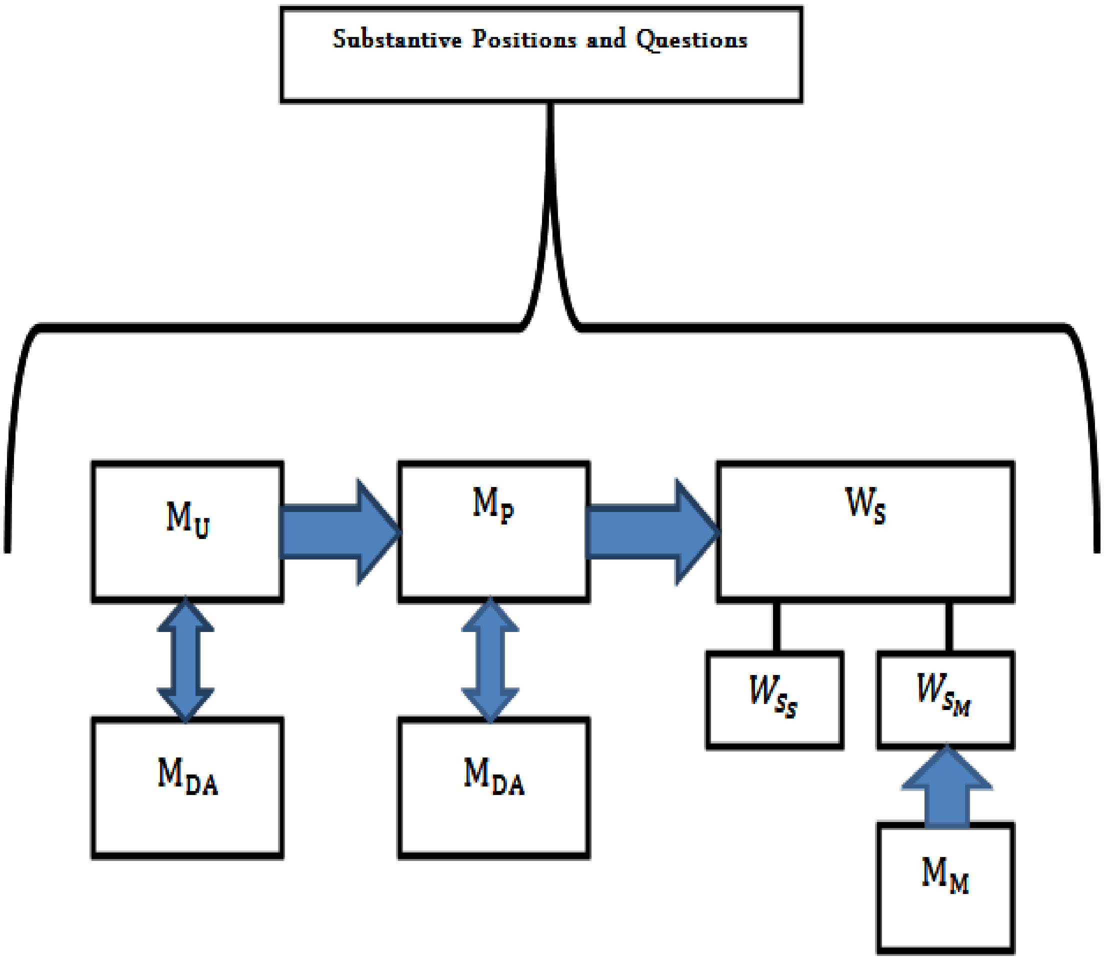


Figure 4: This is the schematic representation of the BRZT model. Like the Ritzter & Zhao/Berger et al model, this framework consists of a three step process that begins with Mu analyses and ends by producing a Ws. Of course, there are several important differences. First, the more abstract substantive and methodological foundational aims have been removed from the model; now the sole products are the more concrete Ws. Second, Mda analyses have been added to the Mu and Mp portions of the model, as well as an Mm analysis to the Wsm portion of the working strategies component. Finally, a list of substantive questions has been added to serve as a guiding reminder of what each component of the model should focus on when conducting its analyses.

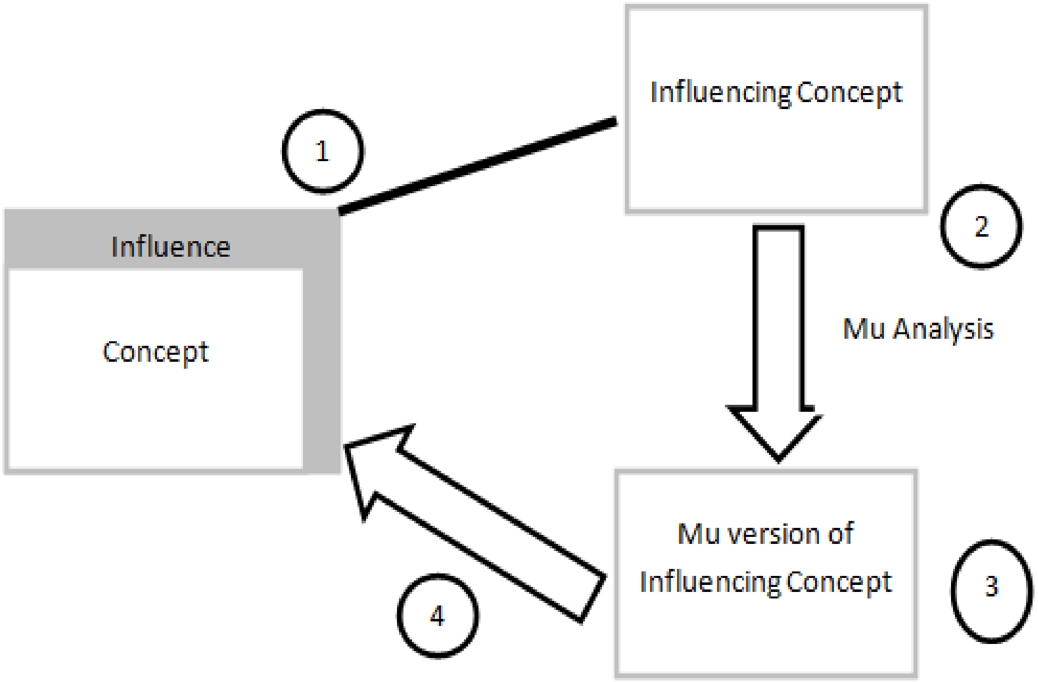


Figure 5: This is a schematic representation of how to carry out a qualitative integration through either an internal-social or an external-intellectual Mu analysis. Step 1 begins by first identifying within a concept or theory the "influenced" component. In Step 2, one then carries out an Mu analysis on the "influencing concept" in order to identify and highlight the biological undertones. The product of this analysis is the Mu version of the influencing concept (Step 3). In Step 4, one then revisits the "influenced portion" of the original concept in order to modify it in light of the Mu analysis carried out

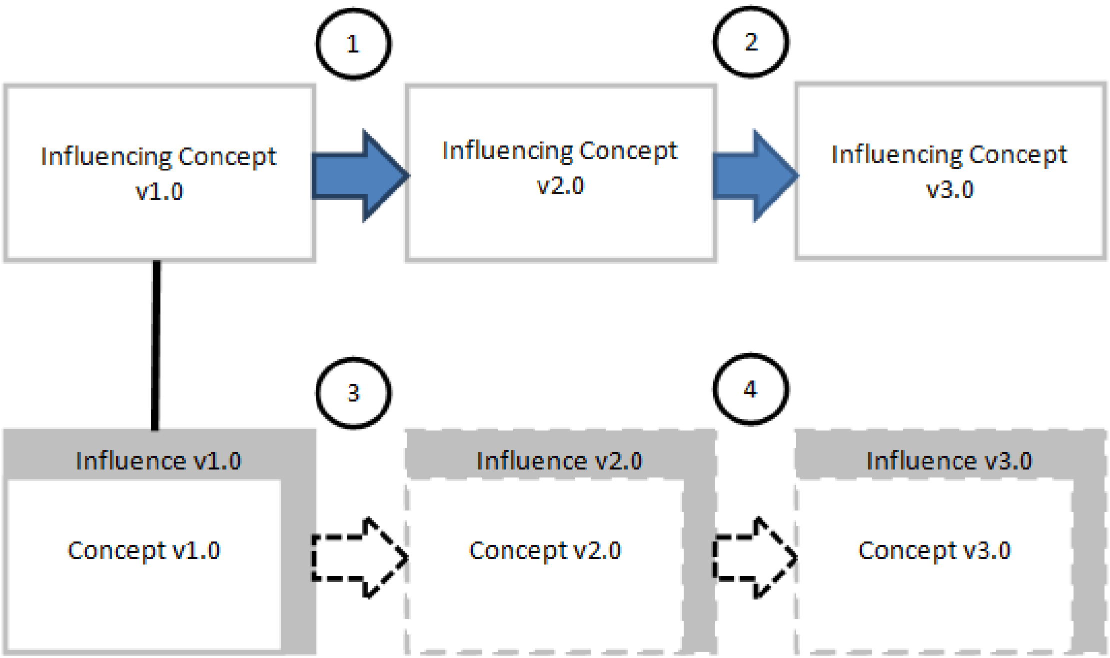


Figure 6: This is a schematic representation of how to carry out a qualitative integration using a temporal analysis. Like the qualitative integration seen in figure 5, this method involves examining an "influencing concept." The main difference here, though, is one examines how this concept evolved over time in light of ongoing scientific research (Steps 1 and 2). Given this development, one then recreates a similar developmental path for the influenced component of the concept being examined (Steps 3 and 4).

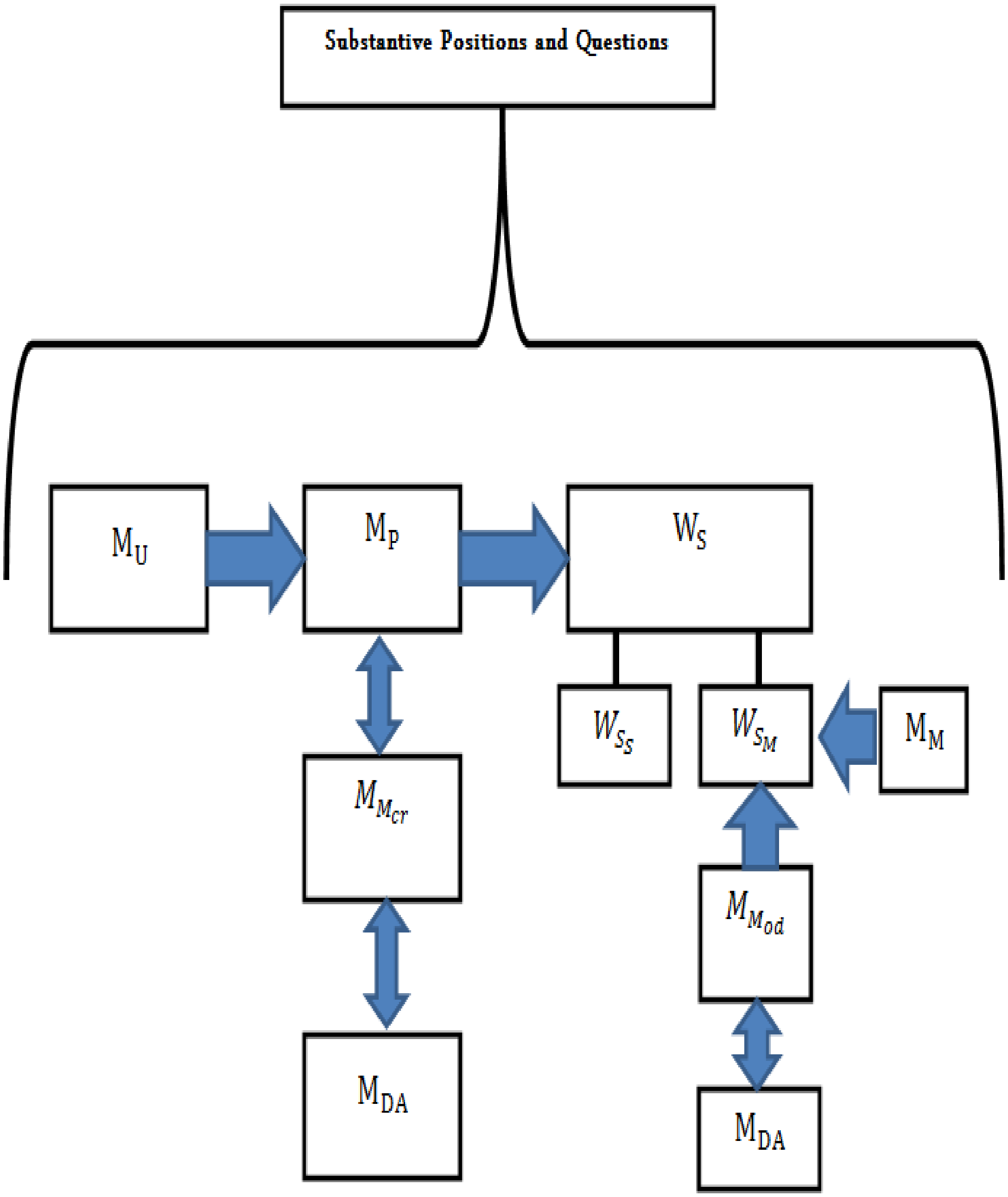
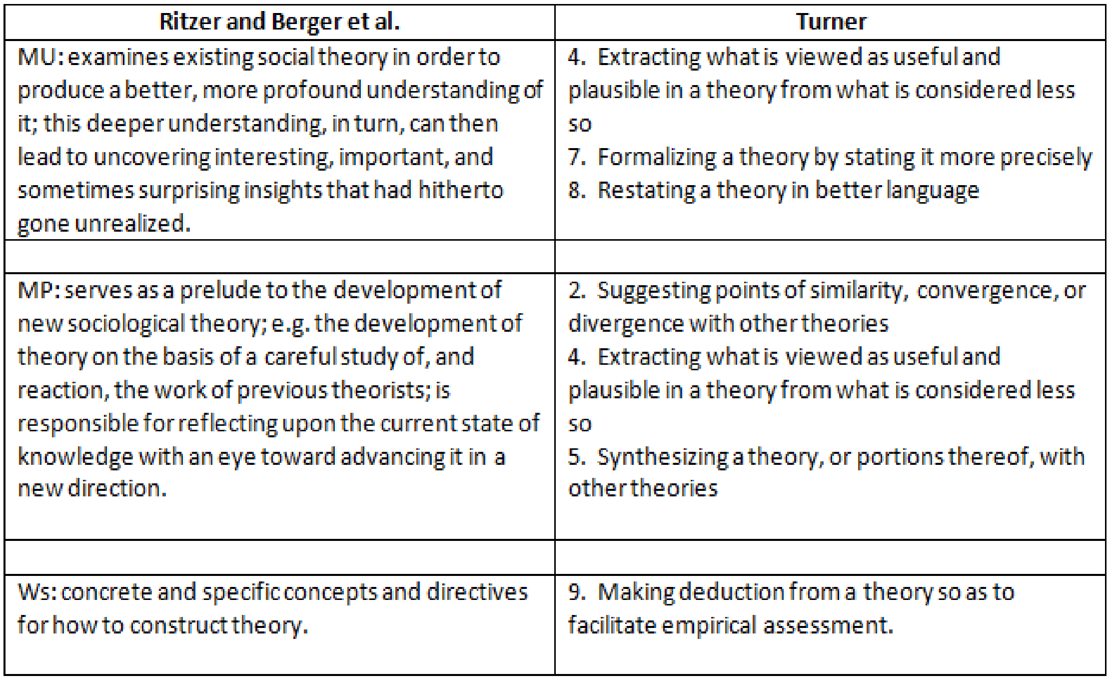


Figure 7: This is the schematic representation of the biosocial meta-framework. The main differences between this model and the BRZT framework is the addition of the Mm components serving as a bridge between Mda analyses and the Mp and Wsm analyses.



Ritzer and Berger et al.	Turner
MU: examines existing social theory in order to produce a better, more profound understanding of it; this deeper understanding, in turn, can then lead to uncovering interesting, important, and sometimes surprising insights that had hitherto gone unrealized.	4. Extracting what is viewed as useful and plausible in a theory from what is considered less so 7. Formalizing a theory by stating it more precisely 8. Restating a theory in better language
MP: serves as a prelude to the development of new sociological theory; e.g. the development of theory on the basis of a careful study of, and reaction, the work of previous theorists; is responsible for reflecting upon the current state of knowledge with an eye toward advancing it in a new direction.	2. Suggesting points of similarity, convergence, or divergence with other theories 4. Extracting what is viewed as useful and plausible in a theory from what is considered less so 5. Synthesizing a theory, or portions thereof, with other theories
Ws: concrete and specific concepts and directives for how to construct theory.	9. Making deduction from a theory so as to facilitate empirical assessment.

Table 1: A comparison of how Turner and Ritzer & Berger et al. define the purpose of metatheory.

Chapter 2: An $\boldsymbol{M_{DA}}$ Analysis of the Molecular, Organelle, and Cellular Levels of Consciousness

Chapter Introduction

The fundamental building block of the nervous system is the individual neuron (Kandel, Schwartz et al. 2000; Bear, Connors et al. 2007). As such, it is essentially to understand the structural and functional characteristics of neurons in order to fully understand how cognitive processes emerge out of the nervous system. For this reason, the goal of this chapter is to carefully detail how the structural and functional properties of neurons emerge from the orchestrated interactions taking place between genes, proteins, ions, lipids, and other molecules. Moreover, this chapter will also explain how the structural and functional properties characterizing the emergent neuron feedback to alter the biological processes that give rise to it. In terms of the criticisms discussed in Chapter 1, this chapter will serve as an initial step toward addressing the claim that the biosocial perspective fails to explain how genes and neurological processes dynamically interact.

Part I: The Anatomical and Physiological Properties of Neurons and Synapses.

Neurons are cells. As such, they possess several structural characteristics common to all cells found in the body (Kandel, Schwartz et al. 2000; Bear, Connors et al. 2007). Specifically, these characteristics include the possession of a cell body, a set of organelles contained within the cell body, and a plasma membrane separating the inside of the neuron from the extracellular environment. At the same time, neurons can be differentiated from most other types of cells by several unique structural features and functional capacities. Structurally, neurons are unique to the degree that their cell body possesses two protrusions called an axon and dendrites; a myelin sheath that surrounds portions of the axon; and a series of ion channels embedded in the plasma membrane. Regarding their physiological capacities, neurons are relatively unique in their ability to generate and propagate an action potential. As will be carefully demonstrated below, each of these characteristics and capacities plays a very specific role in bringing about the overall information processing/communication dynamic performed by the nervous system.

Section 1: The Cell Body (or Soma)

The cell body, also called the soma, is the internal environment of the neuron and consists of the cytoplasm of the cell (Kandel, Schwartz et al. 2000; Lodish 2008). Cytoplasm, in turn, is made up of two components: the cytosol, which is an aqueous fluid composed of water, ions, and macromolecules; and the organelles, which are structurally discrete units suspended within the cytosol that are responsible for the initial development and ongoing maintenance of the neuron. Although all of a neuron's organelles play an important role in the normal functioning of the cell, I will only discuss here the nucleus and the cytoskeleton.

Section 1.1: The Nucleus is the Organelle that Stores the Neuron's Genetic Information.

Arguably the most important organelle found within the cytoplasm is the nucleus. Derived from the Latin word for nut, the nucleus is a very small, spherically-shaped body that is enveloped within a double membrane and centrally located within the cytoplasm (Bear, Connors et al. 2007). The nucleus' functional importance stems from its role as the storehouse of a cell's DNA and the production site for copying bits of said DNA into transcripts. DNA is the complete set of biological instructions needed to correctly form an entire organism; structurally, DNA consists of a long chain of four repeating nucleotides –adenine, thymine, guanine, and cytosine, specifically– that alternate in a very precise pattern. A transcript, in turn, is simply a subset of those instructions for how to produce the individual component parts of the overall organism. These bits of DNA used to produce a transcript are called genes. Although the DNA housed in the nucleus is the same for every cell in the body, which sections are actively used by a cell to produce a transcript are unique to each type of cell. In other words, what distinguishes a neuron from a liver cell or a heart cell is the genes "expressed"–i.e. translated from DNA into a transcript– within the nucleus over the life-course of the cell. Once a transcript is fully formed, it leaves the nucleus via the small pores located in the double membrane envelope and travels to a place within the cytoplasm called the translational cytoplasm. Here, it is decoded by one of four other organelles to create a particular type of macromolecule called proteins.

Section 1.2: Proteins provide a neuron's structural support and a means for communicating

A protein is a linear sequence of individual amino acids–called a polypeptide chain– that have been bonded together and then precisely twisted, folded, and coiled into a unique three-dimensional shape (Campbell and Reece 2009). Although the totality of proteins found in the human body are all formed using a common set of only 20 amino acids, proteins are extremely elaborate and diverse in terms of their structure and function. This remarkable level of diversity stems from the ability of individual proteins to distinguish themselves along four possible structural dimensions. The first dimension is called the proteins primary structure, which refers to the specific sequence of amino acids used to create the polypeptide chain; as just discussed in the paragraph above, this primary structure is determined by the recipe provided by the protein's corresponding transcript. The second dimension is called the secondary structure of the protein and refers to the particular twists and folds found along the polypeptide chain; a proteins secondary structure is produced and held in place by hydrogen bonds formed between pairs of amino acids as they are brought into close proximity to each other during the shaping process. The third dimension is called the tertiary structure, which consists of the protein's overall three-dimensional shape; the tertiary structure is the culmination of the twists, turns, and interactions between amino acids representing the protein's secondary structure. Finally, a large number of proteins also possess a quaternary structure formed by the combination of two or more polypeptide subunits; in other words, a quaternary structure is a macro-protein formed by an interaction between the tertiary structures of multiple subunit proteins.

One important set of proteins found in the cytosol are those used to form the neurons cytoskeleton. Structurally, the cytoskeleton is made up of three types of protein filaments: microtubules, microfilaments, and neurofilaments (Kandel, Schwartz et al. 2000; Bear, Connors et al. 2007; Lodish 2008; Campbell and Reece 2009). Microtubules are hollow helix-shaped tubes that run longitudinally down the entire length of the neuron's axon an dendrites. The functional purpose specific to microtubules is to provide a scaffold for supporting the shape of the neuron and for transporting material back-and-forth between the soma and the ends of the axon and dentrites. The walls of microtubules are comprised of two sphere-shaped proteins called alpha tubulin and beta tubulin that are linearly arranged end to end in an alternating pattern, and then braided like a rope with a hollow core to form the larger microtubule. The process by which a protofilament is constructed is called polymerization; the process by which it is deconstructed is called depolymerization. Importantly, the polymerization/ depolymerization of protofilaments is ongoing and dynamic; this means that the overall structure of the microtubules comprised by the protofilaments changes overtime as well. Equally important, gene expression responsible for carrying out the polymerization/depolymerization process can vary from neuron to neuron and within the same neuron overtime. As will be discussed in greater detail later on, this difference in gene expression is how neurons are able to modify their size and shape to meet different functional demands (Byrne and Roberts 2009). Microfilaments are much smaller than microtubules, but play an equally important role in the dynamics associated with the growth and modification of the neurons cytoskeleton. Similar to microtubules, microfilaments are composed of two intertwined strands of a polymerized protein. Generally speaking, microfilaments appear to be functionally responsible for positioning receptors and ion channels at specific locations within the plasma membrane, as well as for rapidly modifying the wiring of neural networks throughout the life course (see Chapter 4). Finally, neurofilaments are long, solid, ropelike fibrils that run in parallel along the length of the axon. Functionally, neurofilaments play an important role in determining the overall diameter of the axon, which, in turn, influences the speed at which an action potential is propagated.

Section 1.3: Ions provide neurons with a chemical and electrical gradient

An ion is an atom or molecule with an unequal number of electrons and protons (Campbell and Reece 2009). Because of this difference, it possesses either a net positive or negative electrical charge; specifically, the charge is positive if there are more protons than electrons and negative if there are more electrons than protons. The primary positively charged ions found with the neuronal cytosol include potassium (K+) and calcium (Ca+), while the primary negatively charged ions include the amino acids glutamate and aspartate, as well as several types of phosphates and proteins (Lodish 2008; Campbell and Reece 2009). Despite the fact that the individual ions found within the cytosol possess an electrical charge, the *net electrical charge* of a neurons internal environment is neutral; this is because the concentration of positively charged ions equals the concentration of negatively charged ions.

Positively and negatively charged ions can be found in the extracellular environment surrounding the neuron as well. Here, sodium (Na+) and chloride (Cl-) are the primary cations and anions, respectively. Like the cytosol, the overall net electrical charge is neutral due to an equal concentration of charged ions. Importantly though, the concentration of the individual ions *in the cytosol* is different than *in the external environment*. For example, the ratio of potassium ions located in the cytosol compared to the extracellular environment is 20 to 1; in the case of sodium, calcium, and chloride, the ratio of ions located inside versus outside is 1 to 10; 1 to 10,000; 1 to 11.5, respectively (Kandel, Schwartz et al. 2000; Lodish 2008; Campbell and Reece 2009). This difference in *ion concentration* is called a chemical gradient.

Along with the chemical gradient, there also exists what is called either an electrical gradient or a voltage; this is defined as a difference in the value of the net electrical charge of the extracellular environment compared to the value found in the intracellular environment (Kandel, Schwartz et al. 2000). Interestingly, the electrical gradient is a byproduct of the chemical gradient. The reason for this is rather straight-forward; if each ion possesses an electrical charge, an unequal distribution of ions will equate to an unequal distribution in the overall net charge. As will be discussed in the next section, both the existence of and the ability to manipulate this voltage is what gives the neuron the capacity to produce and transmit electrical signals.

Section 2: The Plasma Membrane

Having just discussed the internal properties of neurons, I will now turn to focus on how neural cells are able to maintain a separation from the external environment. Further, I will also discuss how the properties of this boundary allow the neuron to alter the content of its internal environment.

Section 2.1: The plasma membrane separates the neuron's intracellular environment from the extra-cellular environment.

The plasma membrane is functionally responsible for separating the entire cytoplasm of the soma from the external environment (Lodish 2008; Campbell and Reece 2009). Structurally, it consists of a double layer of phospholipids with various types of macromolecules attached to or embedded in it. A phospholipid is a molecular chain made up of a hydrophilic "head," a phosphate derivative "body", and a hydrophobic "tail". Due to their hydrophilic and hydrophobic nature, the "head" of a phospholipid naturally gravitates toward water and the "tail" naturally gravitates toward areas absent of water. Because of these tendencies, the phospholipids comprising the plasma membrane self-organize with the heads of each phospholipid of one layer facing the extracellular environment, the heads of the other layer facing the cytoplasm, and the tails of both layers “sandwiched” in the middle away from the water molecules found in either the extracellular or intracellular environment. The individual phospholipids are then held in place by a combination of the hydrophilic/hydrophobic attractions and van der Waals forces.

Regarding the various types of molecules embedded in the plasma membrane, the ion channels are perhaps the most important for carrying out the unique functions performed by the neuron (Kandel, Schwartz et al. 2000).

Section 2.2: Ions channels allow the neuron to manipulate its membrane potential

Ion channels are another type of protein formed by the transcripts created in the neuron’s nucleus (Kandel, Schwartz et al. 2000; Lodish 2008). Unlike the protein filaments discussed above, though, ion channels do not remain solely within the soma; instead, they transverses the plasma membrane to create a tunnel between the cytoplasm and the extracellular environment. As its nomenclature suggests, ion channels are functionally responsible for *enabling* ions to move in and out of the cytoplasm. Regardless of context– e.g. whether one is talking about a biological system or a mechanical system– the movement of a quantity of charged particles is how an electrical current is produced. Hence, neurons produce the electrical currents they use to communicate with each other by moving the ions located on either side of the plasma membrane in and out of the cytoplasm. How and why ions are *driven* through an ion channel will be discussed in the next section.

Importantly, ion channels are selectively permeable; this means that each channel is specifically shaped to only let certain ions pass through. In other words, only potassium can pass through a potassium channel, sodium through a sodium channel, etc. This selectability is due to the presence of a polypeptide chain– called a pore loop– that acts as the filter for selecting which ion is able to pass through. Another important structural feature of the ion channel is the ability to open and close in order to allow either more or less ions to pass in and out of the neurons cytoplasm. An ion channel either opens or closes in response to the introduction of a particular type of stimulus, which can include the stretching of the neuron, the binding of a ligand to the ion channel, or the voltage of the neuron passing a critical threshold. In either case, the application of the stimulus opens/closes the ion channel by deforming the quaternary structure of the protein to either expand or collapse the central pore. These two structural features impact the currents produced by neurons in two ways; first, the ability to selectively introduce or remove ions into the cytoplasm by selectively opening their corresponding channel means that neurons can create different kinds of current; i.e. one type of current associated with the movement of potassium ions, another type associated with the movement of sodium etc; and second, a neuron can increase or decrease the magnitude of the current it creates by opening or closing a larger number of ion channels; i.e. more ions moving equals a larger current and less means a smaller current.

Ions are driven through their respective ion channels by two types of forces; the first of these is called the diffusion force, and the second is called the electrostatic force (Lodish 2008). The diffusion force is defined as the propensity for ions to spontaneously move from regions of high concentration to low concentration regions until the ions in question are equally distributed between the two. The magnitude of the diffusion force at any given moment is determined by the size of the concentration gradient at that time; in other words, the greater the concentration gradient– i.e. the greater the level of disequilibrium between the amount of ions concentrated on one side of the plasma membrane compared to the other– the greater the magnitude of the diffusion force acting to drive the ions from the high concentration region into the low concentration region. The electrostatic force, in turn, is related to the electrical gradient already discussed above. By definition, an electrical charge is simply a physical property that causes ions to experience an attractive force when sufficiently close to ions possessing an opposite charge; specifically, ions with positive charges will be drawn closer to negatively charged ions, and vice-versa. Along with individual ions, this principle of “opposites attract” also applies to individual ions and groups of ions; i.e. individual positively charged ions are attracted to a group of ions possessing a net negative charge (and vice-versa). Following this, the electrostatic force is the tendency for individual ions to be pulled into or out of the cytoplasm by the attraction of the net opposite electrical charge associated with either the internal or external cellular environment. Like the relationship between the diffusion force and the chemical gradient, the magnitude of the electrostatic force is positively related to the magnitude of the electrical gradient. The summation of these two forces is called the driving force, which is defined as the total force acting to influence an ion to enter or exit the cytoplasm at any given moment (Lodish 2008; Byrne and Roberts 2009).

Diffusion and electrostatic forces interact in a very interesting way to produce what is called an ion's equilibrium potential. An equilibrium potential is defined as the "sweet spot" where the number of ions being drawn out of the cytoplasm by their associated diffusion force equals the number of ions being drawn in by their associated electrostatic force (Lodish 2008). This "sweet spot" is achieved in the following manner. To begin, let us establish a theoretical baseline: imagine for a moment a hypothetical neuron that is enclosed by a plasma membrane without any ion channels. Because of the lack of ion channels, the ions located inside of the cytoplasm are unable to leave and the ions located in the extra-cellular environment are unable to enter. In such a state the chemical gradient for, say, the potassium ion, would be present due to the concentration ratio noted above; but, importantly, the electrostatic gradient would be absent due to the fact that the neuron's internal and external environments are electrically neutral. Now, if we were to then insert into the plasma membrane a series of potassium ion channels, the potassium ions would then be free to diffuse down their chemical gradient by exiting the cytoplasm. Because the negatively charged anions located in the cytoplasm cannot pass through the plasma membrane, the exodus of positively charged potassium ions results in the intracellular environment becoming negatively charged. The emergence of this negatively charged environment establishes the electrostatic gradient, which, in turn, begins to pull the positively charged potassium ions back into the cytoplasm. As more and more potassium ions are pulled out of the cytoplasm by the chemical gradient, the electrostatic gradient gradually increases until the equilibrium potential for potassium is achieved. In the case of potassium, -80 mV is the voltage at which the equilibrium potential is established. For sodium, calcium, and chloride–i.e. the other major cations and anions present in the neuron's intra and extracellular environments– the equilibrium potentials are 62 mV, 123 mV, and -65 mV, respectively (Byrne and Roberts 2009).

Another type of potential possessed by a neuron is called the resting membrane potential (RMP) (Bear, Connors et al. 2007; Byrne and Roberts 2009). A neuron's RMP is defined as the value of the neuron's voltage when the neuron is at rest– i.e. when the neuron is not receiving or transmitting a signal. Qualitatively speaking, the RMP represents the dynamic equilibrium from which a neuron is disturbed to produce a communicative signal. Quantitatively, the resting membrane potential is calculated using the Goldman Equation (Kandel, Schwartz et al. 2000). Using only potassium and sodium as an example, the Goldman equation is measured as:

$$\text{RMP } (measured\ in\ milivolts) = 61.54\text{mV } \log \frac{P_k[K^+]_o + P_{Na}[Na^+]_o}{P_k[K^+]_i + P_{Na}[Na^+]_i}$$

Where:

61.54 is a constant measured in milivolts
P_k is the relative permeability of the plasma membrane to potassium.
P_{Na} is the relative permeability of the plasma membrane to sodium.
$\frac{[K^+]_o}{[K^+]_i}$ is the chemical gradient for potassium.
$\frac{[Na^+]_o}{[Na^+]_i}$ is the chemical gradient for sodium.

I describe the Goldman Equation in detail in order to highlight two key points. First, the value of the RMP is based upon the product of the permeability of the plasma membrane to its individual ions and the value of those ions' chemical gradients. As will discussed in greater detail below, the permeability of a neuron’s plasma membrane varies across the different types of neurons found in the nervous system; hence, the value of the RMP also various across neuron types. And second, a neuron is driven away from its RMP by altering its permeability to its ions; as was noted above, such an alteration occurs by opening and closing the ion channels via electrical, chemical, or mechanical stimulation. Importantly, an increase in the negativity of a neuron’s voltage past its RMP is called a hyperpolarization; a decrease in the negativity of the neurons voltage away from its RMP is called a depolarization; and finally, an increase in the negativity of a neuron’s voltage toward its RMP is called a polarization (Bear, Connors et al. 2007).

Section 3: The Action Potential

The action potential is a transient and ‘explosive’ depolarization that results after a neuron’s voltage is driven by a stimulus past a critical threshold (Bear, Connors et al. 2007). Functionally, the action potential is responsible for propagating the signal that allows individual neurons to communicate with each other. Interestingly, the structurally properties responsible for the production of the action potential are identical to those underlying the generation of both an ion’s equilibrium potential and the neurons RMP. In other words, an action potential is generated and propagated by a dynamic interaction between the plasma membrane, the ion channels, and the chemical and electrostatic gradients. What differentiates the action potential from the equilibrium and resting membrane potentials, though, is that the production and generation of the action potential also includes the dynamic interaction between a stimulus, the ion channels, and the relative permeability of the plasma membrane.

Section 3.1: Stages of the Action Potential

The action potential's underlying mechanism can be broken down into five stages (Bear, Connors et al. 2007). The first stage is characterized by a neuron being depolarized from its RMP to a specific voltage that is less negative in value. This value is called the threshold potential and generally equals 10 mv less than the RMP voltage. Said depolarization occurs in response to a stimulus opening up the hitherto closed ion channels that are selectively permeable to the cations located in the extracellular environment. Because the number of ion channels opened by a stimulus is proportional to the magnitude and duration of the stimulus, the threshold value is only achieved if the single stimulus is of sufficient size and duration, or if a series of stimuli add up to a sufficiently large magnitude and duration. In either case, once the critical threshold is reached, a large number of ion channels spontaneously open up and the positively charged ions come rushing down their chemical gradient and into the cytoplasm. This sudden rush marks the second stage of the action potential and is called the rising phase.

After a period of time the ion channels become inactivated due to a protein loop entering into the channel pore and blocking the continued inflow of ions. As a consequence of this, the neuron ceases to depolarize; the voltage at which this occurs is called either the peak voltage. It is important to note here the following distinction: although an inactive state and a closed state both prevent extracellular ions from entering the cytoplasm, the two states are distinguishable by one important point; a closed state means that ions cannot enter the channel, but it is possible for a stimulus to open the channel; an inactive state means that ions cannot enter AND the channel cannot be opened by a stimulus. In other words, it is impossible for another action potential to occur as long as the associated ion channels are inactivated. The period during which a set of ion channels are inactivated is called the absolute refractory period.

As the action potential approaches its peak voltage, the probability of a second set of ion channels opening becomes increasingly likely. Unlike the first set of channels, this set is selectively permeable to the intracellular cations. Because of the sudden influx of extracellular cations during the rising phase, the cytoplasm of the neuron has gained a net positive charge; as a consequence of this, the intracellular cations are driven through their now opened ion channels by both their chemical and electrostatic gradients. This efflux of cations repolarizes the neurons membrane potential back toward its RMP. This stage is called the falling phase of the action potential. In a similar fashion to the rising phase, the repolarization overshoots the RMP resulting in a brief period of hyperpolarization until eventually the membrane potential resettles at its resting voltage. This period of hyperpolarization is called the *relative* refractory period because of the decreased– but not impossible– probability that the neuron will fire another action potential. The reason the probability is decreased is because the hyperpolarization means that a larger magnitude stimulus is need to depolarize the neuron to the threshold value.

To say that an action potential "propagates" is to say that the five stage model sequentially proceeds from ion channel to ion channel in a forward moving direction. A good analogy of how this process occurs is the mechanism underlying the burning of a fuse (Bear, Connors et al. 2007). When a lit match is brought near a fuse, the heat emanating from the match flame increases the fuse’s temperature until a threshold is crossed and the fuse ignites. Once lit, the burning portion of the fuse increases the temperature of the unlit portion of the fuse directly in front of it until it too begins to burn; which, in turn, then heats the unlit portion of fuse directly in front of it until it too begins to burn, etc. Similarly, the action potential is ‘ignited’ by the stimulus initially depolarizing the neuron past a critical threshold voltage. The resulting influx of sodium ions associated with the rising phase consequently depolarizes the cytoplasm in the area immediately surrounding the open ion channel. As a result, the ion channels located directly in front of the “lit” ion channel are then “ignited”, which, in turn, drives the action potential down the plasma membrane “fuse.” Importantly, the forward movement of the action potential is also assisted by the absolute refractory period ion channels enter into after being “ignited.” Because the inactive ion channel is immune to the effects of depolarization (i.e. the channel cannot open again), its entire affect is completely focused in the forward direction. In a sense, this effect is analogous to the inability of a flame to turn back on itself due to the combustible portion of the fuse located behind the flame having already been spent. Without the availability of said fuel, the flame has no choice but to continue to move forward toward the remaining combustible material.

Section 4: The Axon

The axon is the portion of the neuron that is functionally responsible for propagating the action potential; to put it more specifically, it is the physical substrate housing the ion channels responsible for generating and propagating the five stage sequence associated with the action potential. Structurally speaking, the axon is a single, tubular projection that emanates from the neuron's cell body. The point at which the soma transitions into the axon protrusion is called the axon hillock; it is at the axon hillock that the waves of incoming impulses generated by stimuli are summed and the firing threshold is crossed. Directly in front of the axon hillock is the initial segment of the axon proper; this portion of the axon is where the rising potential of the initial action potential occurs. The subsequent length of the axon proper is the "fuse" along which the communicative signal carried by the action potential is transmitted. Neurons that possess very long axons that extend to other regions of the brain are called either Golgi type I neurons or projection neurons (Kandel, Schwartz et al. 2000; Byrne and Roberts 2009). Neurons with very short axons that connect to other neurons within the very near vicinity of the cell body are called local neurons or Golgi Type II neurons (Kandel, Schwartz et al. 2000; Byrne and Roberts 2009).

Finally, the end of the axon, i.e. the destination to which an action potential is propagating, is called the axon terminal. In some cases, the axon terminal splits into multiple branches, each of which is capable of forming a synaptic link. This collection of axon branches is called a terminal arbor. As will be discussed in greater detail below, the function of the axon terminal is to translate the electrical impulse that is the action potential into a chemical signal that can transferred onto the next neuron in the neural network.

Section 4.1: The speed at which an action potential propagates is affected by the myelin sheath

The speed at which an action potential propagates is called the conduction velocity; it is determined by how far the depolarization spreads ahead of the action potential and how fast the inflowing positive ions are able to travel down the axon (Bear, Connors et al. 2007; Byrne and Roberts 2009). Both of these conditions, in turn, are affected by the internal resistance (Ri) of the axon to the flow of ions and the membrane resistance (Rm) of the axon to ions crossing the plasma membrane. Because the speed of the action potential is correlated with the amount of ions traveling down the axon, water flowing down a leaky hose is a typical analogy used to explain how the structural features of the axon affect both of these resistances. If the hose is very thin and has a large number of holes, the amount of water being projected forward will be reduced due to a significant amount of fluid leaking out. If, on the other hand, the hose is wide and the holes are few, then the majority of the water will be projected forward due to less water being drawn out of the hose.

Given this relationship, one would expect that very fast action potentials would require large diameter axons with few pores. Due to the space constraints of the skull and the need for a large number of ion channels to generate action potentials, evolution was forced to come up with another solution for speeding up action potentials (Bear, Connors et al. 2007). This solution is called the myelin sheath, which is a protein and lipid encasing that wraps around the outside of the axon. Intermixed along the myelin sheath are several gaps called nodes of ranvier. The function of the myelin sheath is to act as an electrical insulator to increase membrane resistance of the axon without have to increase its diameter. In a sense, the myelin sheath acts like duct tape wrapped around the holes of the leaky hose to block the exiting water. The gaps offered by the nodes of ranvier are where the ion channels responsible for generating the action potential are located and, hence, where the action potential actually fires.

Section 5: The Dendrites

Generally speaking, the vast majority of dendrites are functionally responsible for receiving incoming signals from the axons of other neurons and then relaying these signals toward the neuron's axon hillock (Bear, Connors et al. 2007; Byrne and Roberts 2009). A neuron's dendrites can be physically described as a set of tapered, trunk-like projections– called primary dendrites– that successively divide into an intricate collection of individual branches– called dendritic branches. On average, neurons possess between one and nine primary branches; the number and volume of dendritic branches possessed by a neuron, though, varies systematically by neuronal type (Kandel, Schwartz et al. 2000; Byrne and Roberts 2009; Nolte 2009). For example, some neurons–called bipolar cells– possess only a single primary dendrite and a single axon; other neurons–called multipolar cells– possess several primary dendrites and single axon; while still other types of neurons–called pseudo unipolar cells– possess a primary dendrite and an axon that have been fused into a single protrusion that emanates from the cell body in a way that resembles the letter T. Another way the structure of dendrites can differ is in regard to whether or not they possess spines. A spine is a bulb-tipped, protein-filament protrusion that emanates from the dendritic shaft that is capable of forming synapses. Although the exact function of spines has yet to be fully determined, they are believed to enable certain neurons to dramatically increase the number of synapses they can form by expanding the total surface area available for receiving incoming signals.

The signal transmitted by dendrites toward the axon hillock is called a postsynaptic potential. Similar to the action potentials delivered by the axon, postsynapitic potentials are generated by manipulating the chemical and electrostatic gradients of the ions. Instead of relying on voltage-gated ion channels, though, dendrites utilize ligand-gated ion channels to alter the neurons RMP; this type of ion channel is called a receptor and will be discussed in greater detail below. For now, though, I will note that the amplitude of the postsynaptic potential is determined by the amount of ligands bounding to the ligand channel.

One important consequence of this difference in ion channel types is that ligand-gated channels do not become inactivated after opening (Kandel, Schwartz et al. 2000; Bear, Connors et al. 2007). As such, postsynaptic potentials do not possess a refractory period and, thus, can be repeatedly generated in quick succession. Another physical difference between dendrites and axons is that dendrites do not possess myelin sheaths; as a consequence of this, there is a tendency for postsynaptic potentials to dissipate over time as they move toward the axon hillock due to ions “leaking” from the dendritic “hose.” A further consequence resulting from this dissipating tendency is that postsynaptic potentials that are generated farther from the axon hillock reach their target with less magnitude than those generated much closer. As such, incoming signals possessing similar magnitude– i.e. involving similar amounts of ligands– may differentially affect the axon hillock depending upon the distance of their synapse from their target. Still another important difference between a postsynaptic potential and an action potential is that postsynaptic potentials are not all-or-nothing; in other words, a dendrites ion channels to not possess a voltage threshold that, once crossed, leads to a rising phase with a stereotyped peak. Instead, the duration and amplitude of postsynaptic potentials can vary depending upon the magnitude with which the incoming signal was able to alter the RMP.

Because postsynaptic potentials dissipate over the course of their journey to the axon hillock, it is often necessary for the influence of multiple postsynaptic potentials to be combined before the hillock's RMP is depolarized past the trigger threshold. The basic idea here is that a trigger threshold of -55mv can be crossed if the summation of say three postsynaptic potentials can sufficiently depolarize the RMP of the hillock from -80mV. There are two ways this summation process can occur. The first process is called spatial summation and involves the integration of multiple postsynaptic potentials that were simultaneously generated at multiple locations along the dendrites (see fig 13). The second process, referred to as temporal summation, involves the integration of multiple postsynaptic potentials generated by the same axon within a relatively short period of time. As will be discussed below, the dendrites' ability to aggregate multiple postsynaptic potentials plays an important role in a neuron's ability to perform simple calculations and "gate" which information is transferred on to other neurons in a neural network.

Section 6: The Chemical Synapse

A chemical synapse is the junction-point where the communicating neuron transmits a signal to the receiving neuron (Bear, Connors et al. 2007; Byrne and Roberts 2009). The communicating portion of the synapse is called the presynaptic membrane and the receiving portion is called the postsynaptic membrane. The space between the pre and postsynaptic membranes is called the synaptic cleft.[3] Although important variations exist, the axon terminal of one neuron typically serves as the presynaptic membrane and the dendrites of another neuron serve as the postsynaptic membrane. As its nomenclature suggests, this type of synapse utilizes a chemical transmitter to carry-out a synaptic transmission.[4]

Generally speaking, chemical synapses employ two types of chemical transmitters (Kandel, Schwartz et al. 2000). The first type is called small-molecule transmitters, which includes the amine acetylcholine; the biogenic amines dopamine, norepinephrine, epinephrine, serotonin, and histamine; and three amino acids called GABA, glycine, and glutamate. A unique feature of this neurotransmitter class is that they are synthesized in the axon terminal. Like many other intra-neuron molecules, small-molecule transmitters are formed by proteins made using the transcripts found in the nucleus. Once these proteins are formed, they are shipped down the microtubule tracks running along the axon proper and deposited in the axon terminal. Here, the proteins combine with the necessary precursors kept in the axon terminal to form the individual transmitters. Once

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[3] The two most common types of synapses are called chemical synapses and electrical synapses. As their nomenclature suggests, electrical synapses utilize electrical currents as the physical substrate for transmitting signals between neurons. Chemical synapses, on the other hand, are characterized by their utilization of neurotransmitters as their primary delivery mechanism. Because chemical synapses play the more significant role in the generation of cognitive processes, I will only examine here the structure and functional characteristics associated with this type of synapses.

[4] Although a fully comprehensive definition has yet to be achieved regarding what exactly constitutes a neurotransmitter, substances are generally classified as such if they fulfill the following four criteria: 1) the substance must be synthesized within the neuron; 2) it must be present in the presynaptic terminal and be released in amounts sufficient to exert a defined action on the postsynaptic neuron; 3) when administered exogenously as a drug in reasonable concentrations, the substance mimics the action of the endogenously released transmitter; and 4) a specific mechanisms exists for removing the substance from its action site (Kandel, Schwartz et al. 2000: 281).

the transmitters are completed, they are packaged into sacs–called vesicles– that are made from a phospholid bilayer that is similar to the plasma membrane. The second type of chemical transmitter is called neuroactive peptides; common examples of these include oxytocin, vasopressin, and prolactin. Unlike their small-molecule counterparts, this type of neurotransmitter is synthesized in the cell body. Specifically, a unique transcript for each neurotransmitter is delivered to the ribosomes embedded in the rough ER and translated into the corresponding peptide; once formed, the peptide is then transferred to the Golgi apparatus and packaged into a second type of sac called a secretory granule. After packaging, the peptide transmitter is transported down the microtubule track and delivered to the axon terminal. In either case, once the chemical transmitter reaches the axon terminal it is bound to the plasma membrane to await 'transmission.'

Like the sodium channels found along the axon proper, calcium ion channels open once the RMP of the presynaptic membrane becomes depolarized past a threshold. In the case of the chemical synapse, this threshold is crossed once the action potential completes its journey down the axon proper and arrives at the axon terminal. This sudden influx of calcium ions triggers a change in the proteins that bind the vesicle to the plasma membrane, which, in turn, results in the tearing open of the vesicle and the release of its contents into the synaptic cleft. Once released, the neurotransmitters diffuse across the cleft and bind to a corresponding ligand-gated receptor embedded in the postsynaptic membrane.

The ability of a neurotransmitter to recognize its corresponding receptor is tied to two structural arrangements. The first of these involves the dense clustering of the receptors directly across from the release site of their corresponding neurotransmitter. By maximizing the spatial-density of the clusters and their physical proximity to the chemical signal, the probability of the ligand finding its receptor is maximized as well. The second structural arrangement is tied to the three-dimensional structures of both the ligand and the receptor. Like a lock and key, the tertiary structure of the postsynaptic receptor protein is specifically structured to receive and temporarily bind to the structure of the ligand. As a result, receptors are able to ignore non-compatible signals and only respond to those delivered by their corresponding ligands.

Soon after the ligands complete their delivery, they are released by their receptors and, along with any other ligands left diffusing through the synaptic cleft, are eliminated by enzymes embedded in the postsynaptic membrane or reabsorbed back into the presynaptic membrane. This reabsorption process is carried out by a special type of presynaptic membrane protein called a neurotransmitter transporter. Although important differences exist, neurotransmitter transporters carry out their function using mechanisms similar to those used by ion pumps to establish and maintain the electrochemical gradients discussed in section 2.2. The reabsorption of ligands is important for two reasons: first, it quickly puts an end to a synaptic transmission by removing the chemical responsible for carrying the signal; and second, it helps to quickly ready the presynaptic membrane to deliver another transmission by recycling the neurotransmitter (Kandel, Schwartz et al. 2000; Byrne and Roberts 2009). Like their ligand receptors, each neurotransmitter possesses a corresponding transporter. As will be discussed in below, the ability to modify how long a neurotransmitter remains in the synaptic cleft also facilitates information processing carried out by a neural network.

Importantly, postsynaptic membranes possess two types of receptors (Kandel, Schwartz et al. 2000). The first type is called a ligand gated-ion channel, which is functionally similar to the voltage-gated ion channels found on the axon. One significant difference, though, is that ligand-gated channels are opened by the binding of the ligand signal and not by a change in voltage. Another significant difference is that ligand-gated ion channels are permeable to both cations and anions; as a consequence of this, the opening of a ligand-gated ion channel will depolarize the postsynaptic membrane if it is permeable to cations and polarize it if it is permeable to anions. A synaptic transmission is classified as excitatory if it results in the depolarization of the postsynaptic membrane, and is classified as inhibitory if it results in its hyperpolarization. The nomenclature for each of these results stems from their effect on the probability of the postsynaptic neuron generating an action potential. Because the depolarization of the postsynaptic membrane brings the RMP closer to its firing threshold, EPSPs are said to "excite" the neuron. Likewise, IPSPs are said to "inhibit" neurons due to the fact that they decrease the probability of a neuron firing an action potential by moving the RMP away from its firing threshold.

The second type of postsynaptic receptor is called a metatropic receptor or a G-protein coupled receptor. Unlike the ligand receptors just discussed, metatropic receptors influence the structure of their respective ion channels in an indirect manner. Specifically, incoming neurotransmitters bind to the metabotropic receptor on the outside of the plasma membrane. Once this occurs, a subunit detaches from the portion of the metabotropic receptor located on the inside of the cytoplasm. In some cases, these subunits migrate toward and attach to an ion-gated channel in order to change the permeability of the plasma membrane. Despite the intermediary step, the resulting effect is similar to that of ligand-gated ion channels. In other cases though, the subunit activates a series of enzymes called secondary messengers. These secondary messengers, in turn, modify the internal dynamics of the postsynaptic neuron to increase or decrease its overall sensitivity to future synaptic transmissions. Interestingly, this effect can last for up to several minutes. As will be discussed in future chapters, metabotropic receptors play an important role in learning and memory related processes.

Part II: Chapter Summary and Conclusion

In this chapter I examined the structural and functional properties of the neuron. As was described in Part I, the neuron is a special class of cell that is capable of generating an action potential. This unique capacity emerges as the *sui generis* product of a carefully orchestrated set of intra-cellular interactions taking place between the genes, proteins, lipids, and ions contained within the neuron. Moreover, this chapter also examined how the unique structural features of neurons combined with their capacity to generate an action potential to enable multiple neurons to communicate with one another. Once again, this communicative capacity emerges as the sui generis product of a carefully orchestrated set of interactions taking place between at least two neurons. By engaging in this analysis, then, we see our example of how hierarchically-nested biological processes reciprocally interact (e.g. intra-cellular processes generate the cell-level capacity to create an action potential; inter-cellular processes of synaptic communication that utilize the action potential feedback to alter said intra-cellular processes). As we will see in future chapters, this basic dynamic is what connects intra-cellular processes to cognitive processes.

As a conclusion, I want to point out that it is possible to classify neurons into unique categories based upon specific combinations of the various structural characteristics discussed above (Byrne and Roberts 2009). The first categorical type is called Inhibitory Local Circuit Neurons; neurons of this type possess short, Golgi type II axons and utilize the inhibitory neurotransmitter GABA during synaptic transmission. Common examples of ILC neurons include the basket cells, chandelier cells, and double bouquet cells most often found in the neocortex, the cerebellum, and hippocampus regions of the brain. The second categorical type is called Inhibitory Projection Neurons. Like ILC neurons, IP neurons contain the GABA neurotransmitter; unlike ILC neurons, though, IP neurons possess Golgi Type I axons and, thus, are able to form inhibitory synaptic links at much greater distances. Common examples of IP neurons include the medium-sized spiny cells found in the caudate nucleus and putamen regions of the brain, as well as the purkinje cells found in the cerebellum. The third and fourth types of neuronal categories mimic this pattern, such that there are Excitatory Local Circuit Neurons and Excitatory Projection Neurons. A common example of an ELC neuron is the glutamate containing spiny stellate cells found in the cerebrum and the glutamate containing pyramidal cells of the cerebrum are a good example of an EP type neuron. As will be discussed in Chapter 3, the creation of circuits comprised of different combinations of these neural types is how the nervous system is able to both represent and process information about an organism's external and internal environment.

Chapter 3: An $\boldsymbol{M_{DA}}$ Analysis of how Neural Circuits Generate Information about an Organisms External Environment

Chapter Introduction

In Chapter 2 I explained how the dynamic interplay between genes, proteins, ions, lipids, and other molecules generate the structural and functional properties of individual neurons, as well as how these emergent properties feedback to influence the biological processes that initially give rise to them. In this chapter I will continue the logic of this focus by examining how individual neurons dynamically interact to generate neural assemblies, as well as how the emergent structural and functional characteristics associated with an assembly feedback to influence the structural and functional properties of the individual neurons that give rise to it. In so doing, the combination of the analyses made in Chapters 2 and 3 will explain how dynamic interactions taking place between genes and molecules feed-up to influence neurons and neural ensembles, as well as how the dynamic interactions within and between neural ensembles feed-down to influence the molecular processes giving rise to neurons.

With that said, what is a neural assembly? Moreover, what are its characteristic structural and functional properties? The concept of a neural assembly was first introduced by the psychologist Donald Hebb in 1949 (Kandel, Schwartz et al. 2000). Interestingly, Hebb was a former student of Karl Lashley, who, in turn, was a former doctoral student of James Watson; as such, Hebbs work was primarily concerned with grounding psychological concepts that describe 'mental activity' in the material substrate of the central nervous system (Hebb 2002). Despite being an intellectual progeny of Watson, though, Hebb did not feel the need to dismiss the existence of mental processes a priori in favor of purely biological S-R arcs; instead, Hebb attacked the thorny problem head on by posing the question: how *could* mental processes such as thinking, perception, memory, ego, etc. be produced by the action potentials of individual neurons .

According to Hebb's reasoning, an initial step toward answering this fundamental question would be to specify how events unfolding in the external environment are represented as neural activity in the brain. In his famous book entitled *The Organization of Behavior*, Hebb postulated four hypothetical scenarios for how such a representation could occur (Hebb 2002; Bear, Connors et al. 2007). The first postulated that individual external stimuli activate a correspondingly unique set of neurons; because of this, an internal representation of an external thing can be considered to be merely the corresponding neural activity induced by its presentation to the organism. Or, in other words, the cognitive perception of a dog is the neural assemblies that respond when the dog is visually detected. Second, Hebb argued that the internal representation of a thing could be maintained in the absence of its physical presence if the corresponding cells were able to continue to produce the same activity generated by the actual presentation of the stimulus. Related to this, Hebbs third hypothesis argued that the internal representation of an external thing could be invoked in its absence by simply activating the corresponding set of neurons that respond to its actual presence. Again, to put it another way, the neural activity referenced in postulates 2 and 3 are the memory of the previously perceived object. In his fourth hypothesis, Hebb postulated that the internal representation of a thing was not present in the brain from birth, but was instead wired into it over time through reoccurring experience. The process by which this wiring occurs represents the biologically substrate of learning.

Following the above assumptions, Hebb structurally defined a cell assembly as a discrete network of strongly mutual excitatory neurons that is capable of acting briefly as a closed system (Hebb 2002). Here, the phrase 'strongly mutual excitatory neurons' refers to the high probability that an action potential generated by an intra-assembly-presynaptic-neuron will trigger an action potential in an intra-assembly-postsynaptic-neuron (Wennekers, Sommer et al. 2003). Building upon Ramon y Cajal's speculations regarding the neuroplasticity of synaptic connections, Hebb (2002) hypothesized that this increased firing probability resulted from some 'growth process or metabolic change' taking place in the presynaptic and/or postsynaptic neurons whenever they repeatedly or persistently fired concomitantly (ibid: 62). Further, the term "closed system," refers to a cell assembly’s capacity to generate a chain reaction of neural activity amongst its constituting parts that occurs independent from the influence of firing patterns occurring outside of their network (Wennekers, Sommer et al. 2003). Or, to put it another it another way, the commencement, dynamic properties- e.g. how the chain reaction unfolds overtime- and termination of the chain reaction is determined solely by the structural characteristics inherent to the cell assembly network, and, not by the structural features or neural dynamics occurring outside of it.

Functionally, Hebb (2002:xix) hypothesized that cell assemblies are responsible for generating an individual's perceptions and thoughts about reality, as well as the behaviors that arise in response to each of them. Regarding the mechanism underlying this functional capacity, Hebb postulated that each of the individual neurons comprising an assembly is responsible for coding for a different aspect of a thing; while the dynamic chain reaction generated by the entire cell assembly is responsible for combining the individual codes to create a holistic representation of the thing-as-a-whole. To clarify what this means, let us briefly consider a toy model of how a neural assembly could hypothetically generate the perception of a circle (Bear, Connors et al. 2007). For the sake of illustration, let a black circle represent the external stimulus and a grey network represent the corresponding cell assembly that responds whenever the circle is visually present. Further, let each node of the network represent a single neuron and each edge represent a synaptic link. In order to distinguish when a neuron fires an action potential, red nodes and edges will represent "neural activity" and grey nodes and edges will represent "neurons at rest." Finally, let us assume that each of the eight individual nodes codes for a 45* portion of the total 360* constituting the complete circle. The presentation of the external stimulus activates the entire cell assembly. In Step 2 we see the continued activation of the cell assembly after the stimulus is removed due to the associated neurons continuing to fire their action potentials. Over time, the continual, synchronous firing of the cell assembly strengthens the excitatory connections between the individual neurons, as well as increases the probability that a chain reaction will occur that sets off the entire assembly whenever a subset of its neurons activates. This third step of the model has since been dubbed “Hebbian Learning;” it is often summarized by the phrase: “neurons that fire together, wire together,” to reflect that idea that the synchronous firing of the pre and postsynaptic ends of a link results in the strengthening of their connection. In Step 4 we see the consequence of this increased firing probability by the activation of the entire assembly from the firings of neurons 2, 4, 6, and 8. According to Hebb, the fact that the entire assembly representing the circle stimulus is triggered by only a subset of neurons is how individuals are able to recognize a complete circle from only a partial presentation (Hebb 2002).

Although highly speculative at the time he originally formulated them, Hebbs hypotheses have proven to be incredibly accurate. Indeed, research carried out in the decades since has demonstrated considerable empirical evidence in support of his basic arguments (Squire and Kandel 2009). As a consequence, the concepts and mechanisms postulated by Hebb have served as the bedrock for the development of a significant portion of contemporary neurocognitive understandings of learning, memory, and cognitive development (Squire and Kandel 2009). At the same time though, said research has also succeeded in elaborating the empirical details that Hebb was not able to specify in his day, expanding the scope of his theory to include other mechanisms related to learning and memory, as well as correcting for minor inaccuracies (Squire and Kandel 2009).

In light of the above, the purpose of this chapter is to examine the underlying mechanisms of four related processes that are responsible for giving rise to the structural and functional properties that characterize neural assemblies: the first of these will involve explaining how environmental information is transduced and represented in the nervous system; the second will examine the structural features of several neural circuit motifs that physically enable neurons to generate different patterns of activity; the third will examine how these motifs give rise to complex patterns of assembly related neural activity; and the fourth will examine the molecular and cellular processes underlying the alteration of the synaptic connectivity structure constituting a given neural assembly.

Part I: How Environmental Information is transduced into the Nervous System

According to modern neuroscience, “the essential functions of the brain and nervous system are to collect information about the external world and the internal state of the body, interpret that information, determine how that information conforms to the needs and goals of the organism, and to formulate an appropriate behavioral response to accomplish those goals (Byrne and Roberts 2009: 513).” In Part I of this chapter I will examine how information about the external world first enters into the nervous system. This examination will involve answering the following questions: 1) what kind of information about the environment does the nervous system process? 2) How is this information collected, translated into an electrochemical impulse, and then “inputted” into the nervous system? And 3) how are the various dimensions of the environment represented and maintained throughout the nervous system? Or, in other words, how are the length, width, color, and location of an object individually accounted for, and how is the relationship between these properties maintained as the information is processed?

Section 1: What Kind of Information about the Environment does the Nervous System Process? How is this Information Collected, Translated into an electrochemical impulse, and then imputed into the nervous system?

The aspects of the environment that can be processed by an organism's nervous system are called sensory stimuli (Kandel, Schwartz et al. 2000; Bear, Connors et al. 2007). Each sensory stimulus is made up by a unique form of energy called a stimulus modality. The detection and processing of this energy is called sensation. Each modality corresponds to a different type of sensation and is processed by its own unique neural circuit called a sensory pathway. In most cases, each sensory pathway begins at a sensory organ filled with neurons and cells–called receptors– that are uniquely structured to detect their associated modality and translate it into an action potential; the total surface area devoted to detecting sensory stimuli is called a receptor field. Further, each sensory pathway conveys the information it receives to a very specific location in the brain via its own dedicated neural pathway. As such, what distinguishes taste from vision, or vision from touch, is the type of energy that is conveyed to an organism; the type of receptor involved in transducing this energy into the nervous system; the part of the brain to which the resultant neural signal is delivered; and the specific pathway traveled by the neural signal as it heads to its target.

Generally speaking, there are five types of sensory receptors (Campbell and Reece 2009). The first type is called mechanoreceptors, which detect physical deformations of the body that are caused by mechanical energy such as pressure, touch, stretch, and sound. Most mechanoreceptors consist of a neuron whose ion channels are connected to either a hair-like structure that extends outside of the cell or to a portion of the internal cytoskeleton. In either case, the application of a mechanical force to the attached structure generates a tension in the ion channel; if this tension is of sufficient size, the structure of the ion channel will twist open and become permeable to its corresponding ion. Like the voltage-gated ion channels discussed in Chapter 2, the resulting influx of ions alters the neurons RMP and, if the effect is sufficiently large, generates an action potential.

The second type of sensory receptor is called electromagnetic receptors; these receptors are responsible for detecting visible light, electricity, and magnetism. The photoreceptors located in the eye are the best example of this type of receptor in humans. Human photoreceptors come in two types called rods and cones. Although important structural and functional differences exist between the two cell types, both rods and cones utilize a similar molecular mechanism for transducing light energy into an action potential. In the case of rods specifically, the mechanism involves a light absorbing molecule called retinal that is bound to the cell membrane by a protein called opsin. The resulting combination of these molecules is called rhodopsin. When not being struck by the photon-energy of light, the molecular structure of rhodopsin exists in a cis-type arrangement. One consequence of this arrangement is that the sodium ion channels embedded in the photoreceptors are kept open and the cell is continually depolarized. A second consequence is that this constant state of depolarization produces a consistent release of the neurotransmitter glutamate into the synaptic cleft. When rhodopsin is struck by a lights photon-energy, the molecular structure of the retinal shifts from a cis to a trans arrangement. This change activates a near-by G-protein called trasducin, which, in turn, sets in motion a cascade that ultimately closes the sodium ion channels. The closing of the sodium ion channel hyperpolarizes the photoreceptor neuron, which then slows or stops the release of the glutamate neurotransmitter. As a consequence of this, the postsynaptic potentials in the postsynaptic membrane change, which, in turn, alters the action potentials produced by the postsynaptic neurons and thus changes the nature of the signal received by the brain.

A third type of sensory receptor is called chemoreceptors, which are designed to detect and respond to various types of chemical stimuli in the environment. A general chemoreceptor is one that tranduces information about total solute concentrations, while a specific chemoreceptor tranduces information about specific kinds of molecules. One example of a general chemoreceptor are the osmorecepetors responsible for detecting changes in the total solute concentration of the blood and stimulating thirst when osmolarity increases. Other general chemoreceptors are responsible for detecting carbon dioxide levels in the blood and altering breathing and heart rates to increase oxygen levels in response. Two types of specific chemoreceptors include the epithelieal cells making up the taste-buds and the olafactory receptor neurons located in the nasal cavity. In the case of taste-buds, specific chemicals called tastants bind to a corresponding receptor to produce one of five taste perceptions; i.e., the perception of sweet is produced by a sweet molecule binding to a sweet receptor, the taste of sour produced by a sour molecule binding to a sour receptor, etc. In many ways, this correspondence matches the "lock and key" like correspondence between a neurotransmitter and its postsynaptic receptor. In the case of the sweet, umami, and bitter sensations, the associated taste-bud receptors transduce the chemical signal embodied in the tastant into an action potential via a G-coupled protein. Unlike these sensations, though, the binding of sour tastants to the sour receptors directly results in the depolarization of the cell. Currently, the mechanism underlying how the sensation of salty is transduced is unknown. Despite the fact that taste-sensations and olafactory-sensations occur through very different sense organs and, ultimately, produce very different sensory perceptions, the molecular mechanisms leading to both are very similar. Indeed, like tastants, odorants bind to olafactory receptor neurons to produce neural signals via a G-coupled protein intermediary. Also like tastebuds, the various perceived "scents" are generated by specific odarant-olafactory receptor combinations.

The fourth and fifth types of sensory receptors are called thermoreceptors-- which are responsible for detecting changes in temperature-- and nociceptors receptors-- which are responsible for detecting damage to tissues. Unlike many of the other sensory receptors, the exact mechanism regarding how thermorecptors transduce temperature into an action potential is not fully understood (Nolte 2009). What is known, though, is that humans possess a number of kinds of thermoreceptors that are each tailored for a specific temperature range. For example, one type of thermorecptor-- called a *transient receptor potential cation channel subfamily M member 8*-- changes it permeability to sodium and calcium at temperatures below 28 degrees Celsius; likewise, another thermoreceptor, called a capsaicin receptor, alters permeability at temperatures above 42 degrees Celsius (Nolte 2009). A nocireceptor responds to sensory information that exceeds a particular threshold. Like many of the other sensory receptors just discussed, nocireptors come in a variety of types. For example, thermal nociceptors are activated by extreme high or low temperatures; mechanical nocipeptors, in turn, are activated when intense amounts of pressure are applied to the skin (Kandel, Schwartz et al. 2000; Nolte 2009).

In short, all sensory information is transduced into the nervous system through a three step process: 1) detection of stimulus energy, 2) transformation of stimulus energy into electrical impulse, and 3) the transmission of this electrical impulse into the central nervous system for further processing (Kandel, Schwartz et al. 2000). The fact that the transduction process standardizes all sensory stimuli into the same electrical impulse output, though, raises a very important question: how is the brain able to distinguish visual stimuli from taste or touch? Moreover, how is critical information such as the intensity or location of stimulus represented? The answer to this question is contained in what are called coding schemes.

Section 2: How are the Various Dimensions of the Environment Represented and Maintained throughout the Nervous System?

After transducing stimuli into modality specific pathways, the nervous system further refines its representation of the environment through the use of several types of coding schemes (Byrne and Roberts 2009). These coding schemes are *the* mechanism by which the nervous system *initially begins* to reconstruct the richness of an organism's environment in physiological terms.

Section 2.1: Place Codes

The first coding scheme is called a place code. As its nomenclature suggests, place codes are functionally responsible for coding the physical location of where stimulus occurs. This information is determined through what is called a topographic map. A topographic map consists of a collection of individual neurons that are grouped in such a way as to preserve information about where in either the physical environment or on the corporal body the sensory stimuli originated. For example, an eye's field-of-view refers to the total angular area of the environment that is capable of directing light-energy toward the electromagnetic receptors located in the retina when the eye is directed forward-center. A topographic organization of this field means that light emanating from 25-degrees-right-of-center is processed by one set of neurons, while light emanating from 20-degrees-left-of-center is processed by another set. Importantly, the information processed by each group of receptor neurons is then projected into the brain in such a way that the organization of the receptor field is replicated in the sensory target area. In other words, this means that if the group of cells coding for light emanating from 25-degrees-right-of-center are physically located below the group of cells coding for light emanating from 20-degrees-right-of-center, then the targets of the former group of cells will also be located below the targets of the latter group of cells. As a consequence of this, the spatial distribution of information in the environment is reproduced within the physical structure of the brain regions responsible for transforming the sensory information into a sensory perception (Byrne and Roberts 2009).

Along with the above, a place code also refers to the fact that the target regions of the brain that receive sensory information are differentiated in terms of the type of information they process. For example, within the visual cortex–i.e. the part of the brain responsible for processing visual stimuli– information about the color of a stimulus is processed by one set of neurons, while information about the how the stimuli is orientated in space, its speed, and its direction of movement are all individually processed by other sets. This information is further differentiated by segregating those values of stimuli received by the right eye from those received by the left.

Section 2.2: Rate Codes

A second type of coding scheme employed by the nervous system is called a rate code, which is defined as the number of action potentials generated by a neuron over a discrete time interval (Byrne and Roberts 2009); e.g. six action potentials fired per second, vs. ten action potential fired per second. In this scheme, the rate of neural firing is used to represent the intensity—e.g. the amount of stimulus energy received by the receptor—and the orientation of the stimulus attribute being encoded. For example, 10 psi of pressure delivered to a mechanoreceptor may stimulate a neuron to fire 7 action potentials per second, while the application of 20 psi may stimulate 10 action potentials per second. A good example of what is meant by the orientation of a stimulus is the angle at which a bar of light that strikes the retina. Some neuron display their highest firing rates when the angle of the bar is 25 degrees to the right of center, while others do so when the angle is 20 degrees to the right of center. Importantly, individual neurons are tuned to maximally fire for a certain range of intensity values, minimally fire for others, and for others still, not fire at all. The distribution of values to which a neuron will fire is called a tuning curve. For example, auditory receptor neurons exhibit tuning curves that measure changes in firing rate according to variations in both the amplitude and frequency of a sound (Byrne and Roberts 2009). Likewise, motor cortex neurons exhibit tuning curves for specific the directions and force of movements to which they preferentially respond.

Section 2.3: Temporal Codes

A third coding scheme employed by the nervous system is called temporal coding. Unlike rate codes that record information in terms of the number of action potential occurring *over the entire course of a discrete time interval*, temporal coding records information in terms of *when in the time interval* individual action potentials fire (Byrne and Roberts 2009). Because of this difference, it is possible to use temporally coded information to distinguish between different dimensions of a stimulus that may possess identical rate codes. For example, Richmond et al (1987 c.f. Byrne and Roberts 2009: 519) found that certain neurons in a monkey's inferotemporal cortex fired with the same rate code –but different temporal codes– when the animal was shown two different checker-board patterns. In the case of the first checker-board, the temporal code consisted of an initial period of rapid firing, followed by a period of relatively little firing, and then a period of firing. In the case of the second stimulus, the temporal code consisted of an initial period of no firing, followed by a period of repeated firing. Hence, even though both periods displayed the same *rate of firing*, it was possible to distinguish the two stimuli based upon *when* the axon firing took place during the display period. Furthermore, it is also possible for a single neuron to utilize both a rate code and a temporal code to record information about multiple dimensions of a stimulus simultaneously. Because this coding scheme involves multiple types of coding at the same time, it is referred to as a multiplexed code (Byrne and Roberts 2009).

Section 2.4: Population Codes

Along with the above, there also exists a second class of coding schemes called population codes. As the name suggests, population codes utilize the information contained in the firing properties of multiple neurons to represent the various dimensions of a stimulus. Like their single neuron counterpart, population coding schemes can be subdivided into two types (Byrne and Roberts 2009).

Section 2.4.1: Population Codes Subtype #1

The first population code type is called coarse coding, and is best explained in terms of an example. Imagine a single motor neuron that maximally fires whenever the organism moves in a “preferred direction” and fires at a reduced rate whenever the organism deviates away from this direction. Now imagine that the tuning curve of this neuron is Gaussian distributed with the maximum firing rate being equal to the mean rate of the distribution. Because the tuning curve is normally distributed, it would be impossible to know if the organism’s path deviated to the left or the right of its preferred direction; the reason for this is because the half-of-maximum rate appears on both sides of the mean. Such an ambiguity is extremely problematic for ‘downstream’ neurons that may utilize this information to determine their own firing patterns (Byrne and Roberts 2009).

To overcome this ambiguity, coarse coding synthesizes input from multiple neurons in order to determine which of the two possible directions the organism is actually moving in. This ‘synthesis’ works in the following manner. Imagine a convergence circuit with three input neurons-- called A, B, and C-- all synapsing onto a single output neuron, and all of which possessing a Gaussian distributed tuning curve. Now, imagine that the upper-half of neuron A's tuning curve overlaps with the lower-half of neuron B's tuning curve, and that the upper-half of neuron B's tuning curve overlaps with the lower half of neuron C's tuning curve. Because of the overlap between the upper-half of tuning curve A and the lower-half of tuning curve B, the direction of the half-of-maximum firing rate for neuron can be determined by the receiving output neuron due to the fact that both neurons A and B would be firing simultaneously. Similarly, the output neuron could detect if the half-of-maximum firing rate was less than the mean because only neuron A would be firing; the reason for this is because the direction associated with this firing rate is outside of the tuning curve of neuron B.

Section 2.4.2: Population Codes Subtype #2

A second type of coding scheme is called a sparse code. Like coarse coding, sparse coding involves multiple neurons interacting to represent the various dimensions of a stimulus; unlike coarse coding though, the tuning curves of sparse coding neurons only respond to a very narrow range of stimulus values. As a consequence of this, individual sparse coding neurons only play a role in representing a very limited number of stimuli. Indeed, in a study carried out by Quiroga et al (2005) it was found that a single neuron would only respond to pictures of Bill Clinton; while another only responded to the face of Michael Jordon; and another, only to the face of Jennifer Aniston. How this is structurally possible will be discussed in greater detail below.

The fact that there are two different kinds of population codes raises important questions: what are the benefits of broadly tuned neurons over narrow tuned neurons; and vice-versa? How are the two types of codes related to each other? Because coarse coding neurons respond to a wide range of values, they are able to pick up the generalities of stimuli and thus allow for fast processing of sensory information at a relatively low-level of resolution. At the same time, though, coarse coding neurons can work together to generate a very precise description of a stimulus as well. As such, coarse coding neurons are able to efficiently respond to a vast number of stimuli with a relatively few number of neurons. Sparse coding neurons, in turn, allow for highly specific representations to be formed. The benefit of sparse coding is that it reduces the problem of interference during memory formation. As will be discussed in greater detail below, memories are formed through the repeated, reciprocal interaction between sets of neurons. If coarse coding were the only option, there is a chance that the neural representations of two memories would conflict if there were a considerable over-lap between the two sets of respective neural populations. Sparse coding reduces this problem by reducing the amount of overlap between the neural populations involved. As such, the combination of coarse and sparse coding neurons allows for an efficient mix of general and discrete representations (Byrne and Roberts 2009).

Section 3: Summary of Part I

At the most basic level, an organism experiences its environment through the detection of one of five energy-based sensory modalities. Once detected by the appropriate sensory receptor, each form of energy is transduced into the *franca lingua* of the nervous system– e.g. the electrical impulse constituting the action potential. After being transduced, the various dimensions of a stimulus– i.e. its location, intensity, direction of movement, etc.– are coded for by different rates, combinations, and patterns of neural activity. The take away message from this section, then, is this: an organism experiences its environment purely in terms of neural activity. In short, this means that every perceived sight, sound, taste, touch, and smell is, in the final instance, the product of a highly complex combination of an incredible number of cooperating individual neurons. Once again, this fact raises a very important question: how are individual neurons able to coordinate the firing of their action potential to generate the coding schemes just discussed?

Part II: From Cells to Circuits

I will now turn to discuss the structural properties and dynamics that are responsible for enabling neural ensembles to coordinate their synaptic firing. Specifically, section 1 of this portion of the chapter will examine how the four types of neurons discussed at the end of Chapter 2 can be combined into ten discrete circuit motifs capable of generating a unique pattern of neural activity. Further, section 2 will then examine the structural and functional organization of the retina to illustrate how these circuits and the coding schemes discussed in Part I combine to create early-stage visual representations of environmental stimuli. As will be discussed in greater detail below, the structural and functional properties examined here represent the building block of the higher-order social-psychological processes that will be discussed in later chapters.

Section 1: Ten Examples of How the Four Neuronal Types can be combined to create a Functionally Distinct Neural Circuit

Just as various intra-neuronal properties can be combined to create specific classes of neurons, the four neuronal categories can be combined to create various types of neural circuits. Generally speaking, there are ten iconic types of circuits that are widely recognized as the building blocks of more complex neural systems (Byrne and Roberts 2009).

The first and most basic type of circuit is called a feed-forward excitation connection; structurally, it is characterized by a single neuron inducing an EPSP in another via a direct synaptic link. The directionality referenced in this circuit motif–e.g. feed-*forward*–stems from the customary assumption that information is sequentially processed from lower-order levels that first register sensory stimuli to higher-order levels that combine the many dimensions of a stimulus into a complex representation (Sporns 2011). In this context, then, a feed-forward excitation connection is functionally responsible for transmitting sensory information from one processing level to the next.

The second type of circuit is called a feed-back excitation connection. Like the feed-forward circuit, this type of connection is structurally characterized by one neuron sequentially inducing in another an EPSP. Unlike the feed-forward connection, though, a feedback excitatory circuit consists of the second neuron reciprocating a synaptic link with the first. As a consequence of this structural arrangement, the output of second neuron is able to influence the content of subsequent inputs into the first neuron. As reviewed by Sporns (2011), current research suggests that feed-back circuits play an important role in enabling the brain to categorize, infer, and predict information about incoming stimuli by biasing or re-enforcing certain signals over others. Importantly, the fact that the feedback synaptic link is flowing from a higher-order, more complex level of information processing to a lower-order, less complex level, this circuit is in effect using processed information to interpret incoming information that is still in the raw. As will be discussed in later chapters, this top-down modulation of lower-level signals is an essential mechanism in attention-related processes.

A third type of neural circuit is called a lateral excitation connection and involves multiple neurons at a single stage of a multi-stage process interacting with each other via EPSPs. Keeping in mind that sensory information is processed across hierarchical levels, lateral connections allow for a series of neural computations and refinements before the sensory information is sent on to the next level for further processing.

A fourth circuit motif-- called a convergence/divergence circuit-- represents a more complex version of the feed forward excitation circuit. Generally speaking, convergence refers to the degree which a single neuron receives synaptic input from a large number of other neurons; likewise, divergence generally refers to the degree to which a single neuron projects to a large number of neural targets (Byrne and Roberts 2009). A simplistic structural example of a convergent circuit would be three excitatory input neurons synapsing onto a single excitatory interneuron; likewise, the signal output of a single neuron being split amongst three individual output neurons is a simple model of a divergent circuit. Functionally, convergent neural circuits enable the brain to perform calculations and discriminate between categories of stimuli. In short this is done by the single receiving neuron requiring a certain number of incoming neurons to fire before it will fire an action potential. Divergent circuits, in turn, allow for a single neuron to affect a very large number of targets, which, functionally speaking, helps coordinate the neural activity of a large population of neurons due to all the members of the target set receiving the same information at the same time.

Similar to the convergence/divergence circuit, a recurrent excitation circuit is a more complex version of the feedback excitation motif. One version of this circuit consists of an excitatory input neuron synapsing onto an excitatory interneuron that then synapses onto both itself and an excitatory output neuron. Another version consists of a chain of excitatory interneurons that eventually lead to an output neuron that synapses with the initial interneuron. In either case, the functional consequence of this arrangement is the self-amplification of the initial input signal during subsequent cycles. According to Byrne and Roberts (2009), this circuit architecture plays a powerful role in generating the nonlinear, complex dynamics that are the hallmark of the more sophisticated forms of neural information processing.

A sixth circuit motif is called parallel processing. Structurally speaking, this circuit resembles a combination of several feed forward excitatory connections running in parallel that are also linked together by an occasional lateral excitatory connection. This type of organization is functionally useful because it allows for multiple dimensions of a stimulus to be simultaneously represented along several independent lines of processing, while at the same time allowing for the occasional interaction to facilitate calibration (Byrne and Roberts 2009).

The next three types of circuits are called feed forward inhibition, feedback inhibition, and lateral inhibition connections. In many ways, the structure of these circuits is very similar to their excitatory counterparts, except for a few important differences. The first of these, of course, is that the lower-level neurons of the circuit induce IPSPs in the higher-order neurons instead of EPSPs. Another difference is that these circuits tend to consist of a combination of long-range projection neurons and local circuit inhibitory neuron. In the case of the feed forward connections, this combination involves an excitatory neuron synapsing onto an inhibitory neuron, which, in turn, then synapses onto another excitatory neuron. In a feedback connection, the excitatory neuron synapses onto a second excitatory neuron, which, then, synapses onto an inhibitory neuron, that then feeds back to the original excitatory neuron. Finally, a lateral inhibition connection involves an excitatory neuron that synapses to a set of inhibitory neurons that then synapse to other excitatory neurons located at the same processing phase of the circuit as the initial excitatory neuron.

The final motif is called disinhibition and once again represents a combination of excitatory and inhibitory synapses. Unlike other combinations, though, a dishinibition circuit involves the inhibitory connection acting as an excitatory link. This seemingly paradoxical effect emerges as a consequence of the unique combination of connections making up the circuit. A hypothetical example of this motif begins with five neurons; three of which are excitatory and two are inhibitory. The first part of the circuit consists of an excitatory input neuron synapsing onto an inhibitory interneuron, which then synapses onto an excitatory output neuron. Further, the input excitatory neuron also synapses onto the excitatory output neuron via an axon collateral that leapfrogs over the inhibitory interneuron. Following this arrangement, the firing of the output neuron would be either dampened or neutralized by the simultaneous input received by the inhibitory interneuron. The ‘dis’inhibition portion of the circuit is introduced by the second part of the circuit, which consists of a second excitatory input neuron synapsing onto a second inhibitory interneuron, that, then, synapses onto the first inhibitory interneuron. In this case, the firing of the second input excitatory neuron activates the second inhibitory interneuron, which, in turn, then inhibits the first inhibitory interneuron. By "inhibiting the inhibitor," the second portion of the circuit enables in the first excitatory input neuron to fully activate the excitatory output neuron.

Section 2: The Visual System as an example of the structural and functional relevance of the above circuit motifs.

Before concluding this portion of the chapter, I would like to briefly examine the neural circuits involved in processing visual information from the retina to the visual cortex. My reasoning for doing so is two-fold. First, many of the motifs and coding schemes discussed above play an essential role in structural organization and functional role of the eye. As such, a brief discussion of the eye can provide a concrete example of how circuits and coding schemes combine to transform stimuli into information. And second, the synaptic organization of retinal neural circuits is both structurally and functionally similar to the neural circuits found in the brain; e.g. both exhibit laminar organization, or layers of structurally and functionally discrete cell types (Kandel, Schwartz et al. 2000). As such, the eye provide an early insight into the more complicated dynamics that will be discussed in subsequent chapters.

Structurally, the retina is comprised of seven layers of cells that proceed sequentially from the back of the eye toward the front. The first two layers contain the pigmented epithelium and the outer segments of the photoreceptors, which are responsible for trapping light energy and converting it into an electrical impulse, respectively. The next five layers are comprised in an alternating fashion of cell bodies and synapses between cells. The first of these layers is called the outer nuclear layer and consists of the soma of the rod and cone photoreceptor cells. The second of these five layers is called the outer plexiform layer, and is defined by the synaptic links between the rods and cones connect to two types of called bipolar cells and horizontal cells. Important for the task at hand, the synaptic link between a photoreceptor cell and a bipolar cell represents a feed-forward circuit. Horizontal cells, in turn, form a feed-back and a lateral processing circuit with both the photoreceptor and bipolar cells. Functionally, this means that horizontal cells act to modulate the feedforward signal transmitted from the photoreceptors and the bipolar cells. The third retinal layer is called the inner nuclear layer and is comprised of the soma of the bipolar, horizontal, and amacrine cells. The fourth layer of the retina is comprised of the synaptic links between the bipolar cells, amacrine cells, and what are called ganglion cells. And finally, the last layer is defined by the axons of the ganglion cells, which, in turn, project through a hole in the back of the eye– called the optic disc– and into the brain via the optic chasm. Once again, the bipolar cells form a direct, feed-forward circuit with the ganglion cells, while the amacrine cells, like the horizontal cells in layer two, form feed-back and lateral circuits with the bipolar and ganglion cells. Also like the horizontal cells located in layer two, the amacrine cells are functionally responsible for modulating the signal being transmitted through the feed-forward circuit.

The lateral connections formed by the horizontal cells create a convergence circuit that channels transduced light energy from multiple photoreceptors into a single bipolar cell. Similarly, the lateral connections formed by the amacrine cells create a convergence circuit that channels the output from multiple bipolar cells to a single ganglion cell. The unique set of photoreceptor cells that feed into a bipolar cell is called the receptive field for that bipolar cell. Likewise, the unique set of bipolar cells that feed into a single ganglion cell called the ganglion receptive field. The receptor field for a bipolar cell is roughly organized as two concentric circles: the photoreceptors located in the center circle are called the center field and consist of the neurons directly connect to the bipolar cell; the photoreceptors in the outer circle are called the surround field and consist of the neurons that are indirectly connected through the horizontal cell. This organizational pattern generates what is called a center-surround formation. In the case of the ganglion cell, the center of the receptive field consists of the totality of the photoreceptors connected to the bipolar cell to which it directly synapses; and the surround receptive field consists of the totality of photoreceptors connected to the bipolar cells to which the ganglion neuron indirectly synapses via the amacrine cells.

Importantly, center and surround cells come in two types called ON and OFF. An ON subtype is defined as a neuron that increases a bipolar or ganglion cells firing rate when stimulated. An OFF subtype photoreceptor is one that decreases the firing rate of the connected bipolar and ganglion cell. Moreover, ON-center cells have a low firing rate under dimly lit conditions and OFF-center cell have a low firing rate under well-lit conditions. As such, a rapid change in the intensity of the light striking either type of center cell is coded by a rapid increase in their firing. Equally important, the center and surround cells comprising a receptive field are always different, In other words, this means that if the center of a receptive field is made up of ON cells, then the corresponding surround region will be comprised of OFF cells; likewise, a receptive field center comprised of OFF cells will possess an ON cell surround.

Because both the center and surround cells connect to the bipolar cell, the intensity of the influence exerted on the bipolar cell is ultimately determined by the amount of light striking the photoreceptors *and* the degree to which the incoming light simultaneously strikes the center and surround regions. For example, a small spot of light confined to a single region of a receptive field has a minimal effect on the bipolar cells firing rate when compared to the full illumination. The reason for this is due to the number of photoreceptors participating in the transduction process; i.e. more photorecptors transducing light energy produces a greater amount of cellular signal output. The full illumination of the entire receptive field produces a negligible change in the firing rate of the bipolar cell. The reason for this is because the influence stemming from the "reduce firing rate" region is negated by the influence stemming from the "increase firing rate" region.

Once inside the skull, the optic nerves from both eyes meet at the base of the brain to form the optic chiasm. The optic chiasm is an X-shaped structure that directs the optic nerves of each eye into a pair of tracts that lead up into the thalamus. Importantly, the optic nerve of the left eye does not simply project down into the left tract; and, nor does the right eyes optic nerve simply project into the right tract. Instead, the optic chiasm splits each eyes optic nerve into a temporal half and a nasal half, and then combines and directs a temporal half and a nasal half from each eye down a single tract. Specifically, this means that the temporal half of the right eye and the nasal half of the left eye are combined and projected as a bundle down the right tract; similarly, the left temporal half and the right nasal half are bundled together and directed down the left tract. From this point of intersection on, the bundled optic nerves running down each side of the chiasm are now called the right and left optic tracts, respectively.

Once the left and right optic tracts are formed, the ganglion axons of both establish synaptic links with three different sets of target neurons. For the task at hand, the most important of these are located in the right and left lateral geniculate nuclei. The right and left LGN are two small groups of cells located on each side of the dorsal thalamus. Structurally, each of the LGN resembles six pancakes stacked on top of each other that are then bent around their respective optic tract; by convention, the six distinct layers are labeled 1 through 6 from the bottom up. Upon entering the right and left LGN, the projections emanating from each eye are once again separated. Specifically, the axons originating from the right eye create a synaptic link with the target neurons located in LGN layers 2, 3, and 5; while left eye axons link-up with layers LGN layers 1, 4, and 6. In short, this means that the receptor fields located in the retina of each eye are recreated in their corresponding LGN. From here, visual information is then sent to the visual cortex for further processing. As was the case from the retina to the LGN, the place coding of the visual stimuli is maintained as the sensory information is transmitted from the LGN into the visual cortex, and through-out the visual system.

Section 3: Summary of Part II

Recall that the over-all goal of this chapter is to illustrate how structural combinations of individual neurons are able to generate sui generis functional properties, as well as explain how these emergent characteristics can feed-back and alter neural and intra-neural processes. In Part II, Section 1 of this chapter, I analyzed how ten neural circuit motifs enable the brain to enhance, dampen, and generally control the firing rates of individual neurons. A *local consequence* of this capacity, as was discussed in Part I of this chapter, is the ability to generate different coding schemes to represent different dimensions of an incoming stimulus. In Part II, section 2 of this chapter, I provided a brief illustration of how different neural circuits and coding schemes interact to generate a receptive field that can represent the different properties of the external environment within the nervous system.

At the same time, though, my discussion of the visual system highlighted the fact that environmental information is processed across a vast number of discrete receptive fields. As such, the obvious question is this: how is the brain able to combine the individual neural representations of information into a single unified experience? Although much research remains, it is increasingly becoming apparent that the synchronization of neural activity plays an essential role in this process. In Part III of this chapter, I will focus on explaining how neural synchrony occurs and why it is believed to play such an important role in the emergence of consciousness.

Part III: From simple circuits to complex patterns of neural dynamics.

In short, neural synchrony is defined as the simultaneous oscillation of membrane potentials in a network of neurons. The level of simultaneity existing between two neurons can be measured using the following equation (Varela, Lachaux et al. 2001):

$$\phi_{xy}(t) = \left| n\phi_x(t) - m\phi_y(t) \right|$$

Where: $\phi_{xy}(t)$ is the difference between the phases of oscillations x and y at time t
$\phi_x(t)$ is the phase of oscillation x at time t,
$\phi_y(t)$ is the phase of oscillation y at time t, and
n and m are integers that indicate the ratios of possible frequency locking.

In order to fully appreciate what neural synchrony is achieved, we will need to briefly discuss how neural oscillations can be modeled as dynamical systems and what the above terms mean in this context.

Section 1.1: Defining the characteristics of a general oscillator.

Generally speaking, to say that something oscillates is to say that it repeatedly travels back and forth between two points (Pikovsky and Maistrenko 2003). Regardless of what the oscillating object may be, it is possible to model this type of motion as a periodic wave that propagates through the x,y coordinate plane. Here, time is measured along the x-axis and the distance the oscillating body moves away from an arbitrary starting point is measured along the y-axis. In mathematics, the term periodic refers to a function that, when graphed, repeats itself identically.

A good example of how this modeling format works can be seen in the mapping the periodic movement of a clock hand as it travels around a clock-face. As one moves from the clock located in the top-left corner to the one located in the bottom-right, the clock-hand progresses one-hour in a clockwise direction. Each subsequent progression of time increases the distance between the tip of the hand and the original horizontal starting point. The amount of time it takes to complete a full oscillatory cycle such as this is called the period of the dynamic system. A phase of an oscillatory cycle, in turn, refers to any portion of the cycle that the system moves through as it completes a period. Each portion could be considered a phase, as could the point where the wave begins to take on negative values on the y-axis.

Another important term used to describe oscillators is called phase shift. When used in reference to a single oscillator, a phase shift is defined as the translation of the graph of an oscillatory dynamic through phase space by some amount. The addition of pi shifts the graph of the oscillatory dynamics to the right by half of a period. When used to compare the graphs of at least two different oscillators, the term is used to describe the amount of difference between one phase and the other. Lastly, the frequency of an oscillator is defined as the number of periods completed per some unit of time. Conventionally, frequency is defined as 1 cycle per second and reported in hertz (Hz). For example, the completion of 4 cycles per second equates to a frequency of 4 Hz; while the completion of 7 cycles per second equates to a frequency of 7 Hz.

Two oscillating systems are said to possess phase synchrony if their respective dynamics enter into the same phase at the same time (Pikovsky and Maistrenko 2003). Anti-phase synchronization, in turn, consists of two oscillators entering opposite phases at the same time. The process of de-synchronization refers to two or more oscillators moving out of phase-synchronization either abruptly or over a period of time. Likewise, phase reset refers to the resynchronization of formally synchronized oscillators that had become desynchronized.

Lastly, cross-frequency phase synchrony is defined as a situation where there is a constant relationship between two or more frequencies, despite the fact that oscillators involved rarely enter into the same phase at the same time. Importantly, this constant value is captured by the m:n frequency locking measured mentioned in the above equation. Oscillators shifted in phase from one another are considered to be synchronized if the difference between their two periodic functions remains constant; this type of synchrony is called *phase-locking* (Pikovsky and Maistrenko 2003).

Section 2.2: Modeling Neurons as Oscillators

Given a constant input of electrical current, all neurons will exhibit oscillatory dynamics in the form of a repeated firing of an action potential (Wang 2010). A neuron can be treated as an oscillating dynamic system by labeling the x-axis of the model as time and the y-axis as the level of depolarization experienced by the cell. Like oscillators in general, the period of a neural oscillator is defined as the time it takes to complete a single cycle. In the case of a neuron, said cycle represents the five stages of the action potential that was discussed in Chapter 2; e.g. resting state, depolarization, repolarization, hyperpolarization, and return resting state. Likewise, the frequency at which a neuron oscillates is defined as the number of periods– or action potentials fired– per second.

When modeled as an oscillator, two neurons are said to be phase synchronized if both enter into the same phase of their cycle at the same time; e.g. both depolarize, repolarize, hyperpolarize, or return to their resting state simultaneously. Likewise, two neurons are said to be phase-locked if the difference between their phases remains constant over a period of time; e.g. Neuron A always depolarizes at the same time Neuron B hyperpolarizes. Moreover, two neurons can be frequency locked in the manner defined above if the difference between their phase differences remains constant over a period of time.

Section 2.3: Inducing Synchrony in Neural Oscillators

Neurons can become synchronized in a variety of ways (Buzsáki 2006); in order to simplify the discussion, I will only focus here on the mechanism involving a phase shift. Following the definition noted above, this processes involves the shifting the phase portraits of one or more active neurons until the entire group begins to fire in synchrony.

The ability for one or more neurons to influence the phase of one or more other neurons is tightly related to the molecular processes underlying the generation of the action potential. Indeed, recall from chapter 2 that a neuron’s action potential can also be divided into resting-state, absolute refractory, and relative refractory periods. Also recall that a neuron is most likely to fire an action potential during the resting period, least likely to do so during the relative refractory period, and completely unable to do so during the absolute refractory period. The reason for this difference is due to a combination of how close the resting membrane potential is to the firing-threshold and whether the ions embedded in the membrane are closed or inactivated. If the membrane is close to the threshold, as it is during the resting state, then the axon will trigger an action potential with relative ease. If the membrane is strongly polarized and the ion channels are inactivated, as they are during the absolute refractory period, it is impossible for the neuron to fire an action potential. And lastly, if the neuron is hyperpolarized and the ions are simply closed, the neuron will fire an action potential if the incoming current is strong enough.

For the sake of understanding how neurons synchronize their firing patterns, these firing probabilities can be quantitatively described by what is called a phase response curve (Wang 2010). In short, a phase response curve maps how the phase of an action potential is affected by the timing of when an incoming impulse is received. For example, one possible scenario is that the incoming signal makes the receiving neuron fire sooner than it would have done otherwise. This response occurs if the signal reaches the neuron during the latter part of the relative refractory period. If left alone, the neuron would have slowly depolarized from the hyperpolarized state and eventually crossed over the threshold and fired again. The speed of this process, as discussed in chapter 2, is normally determined by the rate at which the ion channels can re-establish their respective equilibrium concentrations. But, the arrival of the signal speeds the process up by forcing open the closed sodium channels to generate the sooner-than-normal influx of sodium ions that initiates the action potential. Another possible scenario is that the incoming signal delays the time at which the receiving neuron fires its next action potential. This occurs if the impulse arrives during the early portions of the hyperpolarization period of the action potential. The reason for this is because the depolarizing effect of the incoming signal slows the molecular processes involved in returning the membrane potential to the triggering threshold. Finally, a third possibility is that the incoming signal has no effect on when the receiving neuron fires an action potential. This scenario occurs if the incoming signal arrives during the absolute refractory period of the receiving neuron. The reason the incoming signal has no effect is because receiving the neuron's ion channels are inactivated and, thus, the membrane potential cannot be influenced. Given the above, the firing activity of two or more neurons can be synchronized by shifting their respective phases in the manner just described until they all fire in unison. In other words, the action potentials of neurons firing sooner than others can be delayed and those firing later can be sped up. At the same time, the existence of the absolute refractory period provides a brief window of time during which a neuron can ignore the influence of other neurons, and thus, remain unsynchronized. As will be discussed in the next section, a neuron's capacity to selectively ignore incoming signals plays an important role in enabling neural assemblies to become synchronized across multiple spatio-temporal scales.

Section 3: Populations of Neurons Synchronize within specific Frequency Bands

Recall from above that the frequency of neural activity is defined as the number of action potentials fired per second; e.g. seven action potentials fired in a second equal a frequency of 7 hertz. When collections of neurons synchronize their activity, they do so at very specific frequency bands (Buzsáki 2006). These bands are commonly identified by labels comprised of either a Greek letter or a descriptive term. For example, in mammalian brains ultra slow waves are defined as oscillatory cycles occurring at .007-

.05 Hz. Four bands of slow waves are defined as oscillatory cycles occurring at .05-07 Hz; .07-0.2 Hz; 0.2-0.5 Hz; and 0.5-1.5 Hz. Delta waves, in turn, occur at the 1-4Hz band; theta waves between 4 and 7.5 Hz; alpha waves between 8-13 Hz; beta waves between 14-30 Hz; gamma waves between 30 and 80 Hz; fast waves between 80-200 Hz; and ultra-fast waves between 200 and 600 Hz (Penttonen and Buzsáki 2003).

It is interesting to note that if the center points of these frequency bands are plotted on a natural logarithmic scale, they progress in ascending order as a linearly increasing continuum with a constant ratio of 2.17 between each band (Penttonen and Buzsáki 2003). The fact that this scaling ratio is a non-integer number is important; it means that different frequencies can ‘nest’ within each other or operate simultaneously without the problem of ‘harmonic and subharmonic frequencies.” In short, a harmonic and a subharmonic frequency is simply a multiple of some other frequency. For example, the harmonic of 50 Hz is 100 Hz, 150 Hz, 200 Hz, etc; while the subharmonic of 50 Hz is 5 Hz, 10 Hz, 25 Hz, etc. Such a correspondence is problematic due to the fact that a population of neurons firing at 50 Hz would fire in uninison with, say, a population firing at 100 Hz, every two seconds. As a result of the repeated bouts of simultaneous activity that would occur every two seconds, the two populations could synchronize relatively quickly. As is clearly evident in the case of seizures–which develop from the over-synchronization of functionally distinct brain regions– the ability to prevent the unwanted spread of neural synchronization is a critical component of normal brain function (Buzsáki 2006).

Section 3.1: Functional Significance of Discrete Frequency Bands

Related to this, researchers have been studying the functional significance of brain waves for more than a century (Buzsáki 2006). One general principle discovered is that higher frequency bandwidths, e.g. more action potentials fired per second, involve smaller populations of synchronized neurons than lower frequency bandwidths, e.g. less action potentials fired per second. Another general principle is that faster frequency band widths are typically involved in synchronizing neural populations that are located within close physical proximity of each other, while slower frequencies are involved in synchronizing more distant neural populations. Interestingly, these two points are related to each other by the fact that the capacity to synchronize populations of neurons is limited by the phase response curve. Recall from above that the phase shift required for synchronization can only occur during the resting state and relative refraction phase of the action potential cycle. Because the duration of these periods is relatively short in high frequency brain waves, and because the speed at which the action potential can travel down an axon is finite and relatively constant, a neuron sending or receiving a signal must be within a small physical distance in order for the impulse to arrive within the required window of opportunity. Similarly, the phase response curve of slower frequencies possesses a much longer ‘window of opportunity’ due to the fact less action potentials are being fired per second. As a consequence of this, slower frequencies are able to send and receive signals to a much farther and, thus, much larger, population of neurons (Buzsáki 2006).

Although researchers have been examining the functional significance of specific frequency bands for more than a century, I want to focus my attention here on two specific models regarding how two sets of brain waves interact to generate two different psychological processes. The first of these models attempts to describe how alpha waves and gamma waves interact to focus attention and combine sensations into a unified perception (Buzsáki 2006). In humans, the level of alpha frequency neural activity occurring in the occipito-parietal areas of the brain is functionally related to the detection of visual stimuli (Ward 2003). This functional relationship has long been empirically demonstrated by showing that a decrease in the power of the alpha frequency in the occipito-parietal areas strongly correlates with the perception of a visual stimulus, while a decrease in alpha power is positively correlated with the detection of a visual stimulus. More recently, this correlative relationship was shown to be in fact causative. This was done by using transmagnetic stimulation (TMS) to artificially disrupt alpha wave activity in the visual cortex of the brain. Interestingly, the application of the stimulation increased the salience of objects that were physically located in the region of the visual field that retinoptically mapped to the stimulated portion of the cortex. Moreover, the application of TMS also simultaneously increased the alpha wave activity in other parts of the visual field and, thus reduced the saliency of objects located in those positions. The combination of these empirical results has resulted in the current theory that alpha waves are (at least) partially responsible for “gating” the access of bottom-up stimuli to higher-order processing regions by shifting the phase response curve so that the associated neurons are no longer receptive to incoming signals (Da Silva 1991; Wang 2010)

In contrast to alpha wave activity patterns, gamma wave activity has been empirically shown to be positively correlated with the detection of sensory stimuli (Buzsáki 2006). An interesting theoretical model for explaining these empirical results was generated by Large and Jones (1999). Accordingly, their model argues that the gamma frequency of neurons involved in attention related processes fluctuates between .05Hz and 2Hz during inattentive states. Once a stimulus requiring attention is introduced, the electrical impulse detailing its properties phase-shifts the gamma frequency until it and the stimulus are synchronized. Interestingly, the model further argues that the alpha and gamma waves become anti-phase-locked to prevent the disruption of attention on specific stimuli. Many predictions offered by this model have been empirically demonstrated. For example, Rodriguez et al (1999) presented individuals with ambiguous pictures that could be perceived as either a meaningless object or a face. Immediately preceding the point at which the individual recognized a face, a number of wide-spread brain regions immediately synchronized in the gamma frequency band. In a similar experiment, McIntosh et al (1999) demonstrated post-stimulus increases in activity and synchronization across brain regions in participants that recognized that a tone preceded the presentation of a target when compared to participants that did not recognize the association. Because the individuals that recognized the tone also demonstrated faster response times to the presentation of the target, the post-tone activity was interpreted as the associated attention networks anticipating the arrival of the target and thus preparing to detect it. Further, Shapiro et al. (1997) showed that ‘attentional blink’ occurs when a second stimulus is presented before the gamma-firing neurons have fully recovered from detecting a preceding stimulus. Here, attentional blink is defined as the psychological phenomenon whereby a stimulus is correctly detected by a sensory organ but, nonetheless, is not consciously perceived. And finally, Singer & Gray (1995) empirically demonstrated that alpha and gamma activity are negatively correlated in associated brain regions during the attentive detection or anticipation of stimuli; while Worden et al. (2000) showed that alpha activity increases in visual areas of the brain when listening for or to audio stimuli. The meaning of this pattern was interpreted as the increased alpha waves being functionally responsible for blocking attention to distracting visual stimuli.

Part IV: Molecular and Cellular Processes Underlying the Modification of Synaptic Links

In the introduction I noted that Donald Hebb postulated how the structural and functional properties of neural assemblies could act as the biological correlates of learning and memory. Extensive empirical research occurring since has elucidated the molecular and cellular mechanisms underlying the learning process, as well as revealing how these mechanisms relate to nondeclarative and declarative memory (Squire and Kandel 2009). Generally speaking, nondeclarative memory consists of reflexive knowledge; e.g. unconscious or automatic responses that occur outside of conscious reflection. Examples of nondeclarative memory include motor and perceptual skills; habits; emotional learning; habituation; sensitization; classical conditioning; and operant conditioning (Squire and Kandel 2009). Declarative memory, in turn, consists of reflective knowledge; e.g. memories that can be deliberately recalled and considered in consciousness. Examples of these include semantic memories and episodic memories. Semantic memories consist of knowledge that is not tied to a specific temporal event; for example, one can recall that Paris is the capital of France, or that one has seen the movie “Fight Club” without having to recall a specific time or place when one either learned said information or viewed said movie. Episodic memory, in turn, consists of knowledge that is tied to a specific temporal event; e.g. memories about one’s trip to Paris when they were sixteen, or the recollection of specific scenes one saw in the movie Fight Club.

To conclude this chapter, then, I will examine the molecular and cellular processes underlying nondeclarative and declarative memory.

Section 1: Molecular and Cellular Mechanisms underlying habituation.

Habituation is defined as the process by which an individual learns to recognize through repeated exposure, and, thus ignore as familiar, unimportant stimuli that are monotonously repetitive. Further, habituation also refers to the process by which inappropriate or exaggerated defensive responses to harmless stimuli are eliminated, as well as to the process by which the ability for a novel or pleasurable experience to garner one’s attention decreases until it is exhausted (Squire and Kandel 2009). For example, the sounds associated with living in the city can be quite unnerving at first; e.g. the sound of a car backfiring can induce a strong startle response, or the honking cars, music, and conversation of hundreds of thousands of people can make it difficult to relax. Over time though, those living in the city become accustomed to this cacophony of noise and are no longer bothered by it. A good example of the habituation of a novel stimulus is the sexual habits of male rats. If given unlimited access to a receptive female, the male rat will copulate six or seven times in a one or two hour period (Squire and Kandel 2009). After this period, though the male rat will no longer be able to become sexually aroused and will begin to ignore the female. Although it would appear that this response is due to physical exhaustion, this is not the case; indeed, if presented with a novel receptive female, the male rat will immediately begin to copulate. Hence, the initial withdraw did not stem from the fact that the rat had become physically tired, but from the fact that he had become habituated to the novelty of the first female rat.

In the 1970s, studies on the gill-and-siphon-withdrawal reflex of the Aplysia revealed the cellular and molecular mechanism responsible for habituative learning. The Aplysia is a type of sea slug that withdraws its gill and siphon into its internal shell whenever the siphon is gently touched. Researchers studying this reflex found that it quickly habituated after the repeated application of a stimulus to the siphon. At the cellular level, the habituation process was found to involve the continuous weakening of the presynaptic neuron's ability to induce an action potential in the post-synaptic neuron that triggered the reflex movement. Recall from Chapter 2, Part I, Section 6 that the chemical transmission of a neural signal involves the tearing open of transmitter filled ventricles that are housed in the tip of the axon button. Using an electron microscope to view the internal structure of the habituated axon, it was determined that the source of this reduced impact stemmed from the presynaptic neuron releasing the contents of fewer and fewer vesicles of neurotransmitters with each subsequent stimulation. Specifically, the repeated stimulation of the reflex resulted in the depletion of the available pool of vesicles to the point where none are immediately available to participate in the signaling process.

Before turning to discuss sensitization, I want to highlight a very important point that will be repeated throughout this part of the chapter. Notice here how the behavioral phenomenon of the gill-siphon-withdraw-reflex occurs as the consequence of the dynamic interaction between molecular, cellular, and circuit levels of analysis. Indeed, the reflex behavior occurs as a consequence of a set of processes occurring across an entire circuit of neurons; the coordinated activity of the circuit is produced by the process occurring at the individual synapses comprising the circuit; the chemical transmissions occurring at each synapse are the product of the molecular processes occurring within each presynaptic neuron. The habituation process as a whole involves repeated interactions between the organism and its environment. Theses feed-down to alter the intra-cellular processes occurring in the presynaptic neuron, which then feed-up to modulate the nature of the interaction between the organism and its environment. As such, each level of the over-all habituation process plays an essential role, but, at the same time, the entire process is irreducible to a single level of analysis. As will be discussed in later chapters, this basic idea continues at higher levels of aggregation and should be considered the fundamental assumption of an integrated neuro-sociological approach.

Section 2: Molecular and Cellular Mechanisms underlying sensitization.

Unlike the reduction in synaptic strength associated with habitualization, sensitization is a form of learning that results from an increase in the ability of a presynaptic neuron to induce an action potential in its postsynaptic counterpart. Contextually, sensitization is the process by which an organism learns to quickly become more vigilant to a variety of stimuli once they encounter a particular harmful stimulus. For example, a person startled by a gunshot is likely to jump at any noise immediately after the fact; similarly, will respond defensively and more intensely to a soft touch after receiving a painful shock (Squire and Kendal 2009).

Once again, research on the Aplysia's gill-and-siphon-withdraw-reflex has provided important insights into the cellular and molecular processes underlying sensitization learning. Specifically it was found that the application of a noxious stimulus to the Aplysia's tail strengthened the gill-withdraw reflex; e.g. the gill was pulled much farther inside of the animal post-tail shock than pre-tail shock. At the level of the cellular circuit, sensitization was found to involve a version of what was referred to above as parallel processing. Here, the circuit causing the gill-and-siphon-withdraw reflex involves a feed-forward excitatory circuit that consists of sensory neuron embedded in the siphon linking to a motor neuron embedded in the gill. Hence, the stimulation of the sensory neuron feeds forward to excite the motor neuron to retract the gill. The Aplysia's tail also possesses a sensory neuron that feeds-forward, but with a coaxial that leads to what is called a modulatory interneuron as well. This interneuron then synapses onto the presynaptic terminal of the sensory neuron embedded in the siphon. The synaptic link between the interneuron and the siphon sensory neuron involves the kind of secondary messengers described in Chapter 2, Part II, Section 4; the function of this secondary messenger is to increase the amount of gulatamate-containg vesicles in the presynaptic terminal of the siphon sensory neuron. As a result of this, future stimuli activating the sensory neuron will result in a stronger signal being sent to the motor neuron in the gill due to the involvement of a greater amount of neurotransmitter. Interestingly, the sensitization process can override habitualization. This is because sensitization replaces the vesicles lost during the habitualization process. Such an occurrence is called dishabitualization.

Now, notice here that habituation and sensitization are differentiated at multiple levels of analysis. Indeed, at the behavioral level, the former involves a reduction in response and the latter involves an increase. At the circuit level, habituation is homosynaptic; this means that the change in behavior results from a change in activity in the same circuit that is involved in generating the initial reflex. Sensitization, in turn, is heterosynaptic; this means that the learning process occurs in a different neural pathway than the one initially activated by the noxious stimulus. And finally, at the molecular level, habituation involves the depletion of a neurotransmitter, while sensitization results from a second-messenger induced increase in neurotransmitter. As will be discussed in subsequent chapters, the fact that a behavioral or psychological process can be differentiated across so many levels of analysis is exactly why neuroscience can be used to increase the accuracy and precision of sociological concepts.

Section 3: Cellular and Molecular Processes underlying classical conditioning

Classical conditioning is the neurological process by which an organism learns to associate the properties of one stimulus with the properties of another. As is well known, classical conditioning was initially described by Ivan Pavlov while studying the digestive reflexes of dogs. While carrying out his research, Pavlov happened to notice that a dog would begin salivating whenever it saw food and/or whenever it saw the attendant responsible for feeding it approach. In terms of the later observation, this was true regardless of whether the attendant was carrying food. Believing there to be a cause to this pattern, Pavlov engaged in a series of experiments to determine its underlying mechanism. According to his analyses, an initially neutral stimulus can take on an effective meaning if it is repeatedly paired with another stimulus that already possesses an effective meaning. So much so is this the case, that, once, the neutral stimulus gains meaning, it can elicit the response previously associated only with the effective stimulus by itself. Further, a conditioned stimulus can once again become neutral if it is repeatedly presented by itself without the unconditioned stimulus. Such a situation is called extinction.

Formally speaking, the key characteristic that defines classical conditioning is the requirement that conditioned and unconditioned stimuli co-occur within a very specific timeframe. Specifically, this temporal window has been empirically demonstrated to be between 200 milliseconds and 1 second. Further, classical conditioning is most effective if the conditioned stimulus precedes the unconditioned stimulus and the two stimuli cease at the same time. Both of these requirements are directly tied to the cellular and molecular processes underlying this type of memory formation.

Regarding the associated cellular processes, classical conditioning is very similar to sensitization (Squire and Kandel 2009). In other words, the cellular circuits for the conditioned and unconditioned stimuli are interconnected by modulatory interneurons. Now, both the temporal requirement and the requirement that the condition stimulus precede the unconditioned stimulus is a result of the molecular processes involved. The first molecular process takes place in the presynaptic component of the synaptic link. As was discussed in Chapter 2, the action potential is driven down the axon by the influx of calcium ions. In sensory neurons, the calcium combines in the axon button with a protein called calmodulin. This calcium-calmodulin complex then binds to an enzyme called adenylyl cyclase; this enzyme plays an essential role in the secondary messenger sequence mentioned in my discussion of the sensitization that resulted in the increase of glutamate vesicles. As a consequence of the calcium-calmodulin complex binding to the adenylyl cyclase, the enzyme is more efficiently utilized and, thus, a greater amount of neurotransmitter is released when the presynaptic neuron fires. The second portion of conditioned learning takes place in the postsynaptic portion of the synaptic link. Specifically, the combined input arriving from both the conditioned and unconditioned stimuli circuits depolarizes the postsynaptic link to such a degree that several ion channels that do not normally open do so in this case. It is believed that the opening of one such channel releases a chemical signal that feeds back across the synapse to strengthen the output of the presynaptic neuron. As a consequence of this, the signaling strength between the conditioned stimulus and the response increases to the degree that the former will trigger the later without the involvement of the unconditioned circuit. And, this is how the association between the conditioned stimulus and response is established.

Section 4: The cellular mechanisms underlying declarative memory formation and loss

Notice in the above discussion that there exist strong similarities in the cellular and molecular mechanisms underlying habituation, sensitization, and conditioned learning. This trend can also be found in the molecular and cellular mechanisms underlying declarative memory. The reason for this is because it is much more efficient for evolution to reconfigure and elaborate upon existing pathways to create new functional processes than it is to constantly construct them from scratch. As such, instead of revisiting much of the above discussion, I will focus here on a relatively unique cellular process underlying declarative memory.

Specifically, this process involves the addition of receptors in the postsynaptic membrane of synaptic links that are frequently co-activated (Squire and Kandel 2009). Recall from Chapter 2 that the neurotransmitter signals sent by the presynaptic neuron bind to the receptors located on the postsynaptic membrane; as a consequence of this binding, the receptors alter their shape to allow the influx/efflux of ions. The resulting change in ion concentration generates a change in the membrane potential of the postsynaptic neuron, which, if strong enough, results in the generation of an action potential. Because the postsynaptic receptors are the channels through which ions enter and exit the cell, the more receptors available means the greater the magnitude of the change in ion concentration, and, thus, the higher the probability that an incoming signal will generate a corresponding action potential. In many ways, this process is similar to the increase in the signaling strength of a synapse vis-à-vis the increase in the availability of the number of vesicles in the presynaptic neuron that was discussed above. The important difference though is that this process involves the physical restructuring of neuron. Likewise, the reduction of synaptic signaling strength involves the removal postsynaptic receptors. In this case, the reduction in the number of channels reduces that amount of the ions that can transverse the membrane at any one time and, thus, reduces the probability that the postsynaptic neuron will fire an action potential. Because the co-activation of the presynaptic and postsynaptic neurons is essential for memory formation, the long-term effects of this reduction in probability is the eventual loss of the memory.

Part V: Summary and Conclusion

In the introduction of this chapter I briefly summarized the major postulates of Donald Hebbs theory of how the external world is represented in the nervous system as ideas and memories. The subsequent Parts that followed this introduction summarized the extensive empirical work demonstrating the underlying cellular and molecular processes of these postulates. Indeed, in Part I I examined how information about the environment is transduced into the electrical impulses constituting the action potential. Moreover, this portion of the chapter also explained how variations in the rate, timing, and population involved in neural activity are able to represent with incredible subtlety the multitude of dimensions possessed by environmental stimuli. In Parts II and III, I then turned to discuss how neural circuits comprised of different combinations of neural types are able to generate highly complex patterns of neural activity that are functionally responsible for, among other things, binding the representations of individual neurons or collections of neurons into unified perceptions. Further, Part III also examined how these complex patterns of neural activity interact to generate higher-order psychological processes such as attention. And finally, Part IV examined the cellular and molecular processes responsible for transforming the transient neural activity of assemblies into memories.

Continuing the logic established in Chapter 2, we see here in Chapter 3 how the sensory information and memories emerges as the sui generis product of the carefully orchestrated dynamics occurring between different classes of neurons. Moreover, and especially in the case of memory formation, we see how the intra and inter-cellular dynamics discussed in Chapter 2 feed-up to create the emergent properties discussed here, as well as how these emergent properties feed-down to influence said intra-cellular dynamics. As we will see once again in Chapter 4, these reciprocal interactions between hierarchically-nested processes are what bridge the gap between genes and cognitive processes.

Chapter 4: An MDA Analysis of the Structural Properties and Functional Divisions of the Brain

Chapter Introduction

The focus of this chapter is to explain how the aggregation of the structural and functional characteristics of neural circuits and their associated patterns of activity give rise to structurally and functionally discrete *brain regions*. Expanding upon the trend that was already seen in Chapters 2 and 3, this chapter will devote a considerable amount of attention to examining the dynamic and reciprocal interaction across the molecular, cellular, neural circuit, and brain region levels-of-analysis. Specifically, this will be done by dividing my analysis into four parts. First, Part I will examine three basic principles regarding how the human nervous system organized. Second, Part II will focus on illustrating how these organizational principles are manifested in the brain to generate several structurally and functionally discrete brain regions. Third, Part III will examine how the physical boundaries of and interactions between these structural and functional regions are genetically determined during embryonic development. In short, the larger purpose of this portion of the chapter is twofold: 1) to illustrate that the structural and functional properties of the human brain are not randomly determined; and 2) to suggest that the hard constructivist argument that nature is completely determined by nurture is incorrect. Fourth, Part IV will examine how the molecular and cellular processes discussed in Chapter 3 enable a person's experiences to meaningfully shape the genetically determined structures and functions of the brain. The purpose of this portion of the chapter is to suggest that the hard biological-determinist argument that nature fully trumps nurture is equally incorrect. Finally, Part V will conclude with a brief discussion of why the structural and functional properties of the brain are determined by the ceaseless dynamic interplay between nature and nurture; and, as such, to focus solely on either is factually incorrect and a detriment to the development of accurate micro-sociological theory.

Part I: Organizational Principles Underlying the Structure and Function of the Brain

The basic structural and functional organizational properties of the nervous system can be described by a few basic principles (Kandel, Schwartz et al. 2000). For the sake simplifying the discussion, I will limit my examination here to the following three.

Section 1: The Human Nervous System can be structurally divided into a series of functional regions and sub-regions

The human nervous system can be divided into several distinct sub-regions based upon the number, type, location, functional contributions, and topographic properties of the neurons they contain (Kandel, Schwartz et al. 2000; Nolte 2009). A first-order categorization divides the human nervous system into a peripheral and central component. Structurally speaking, the peripheral nervous system is defined as those neural networks that are not encased in bone; functionally, it is responsible for delivering to the central nervous system a continuous stream of information about the body's internal and external environment. The major divisions of the peripheral nervous system include the somatic and autonomic systems. The somatic component consists of the sensory networks responsible for delivering to the brain information about visual and tactile stimuli, as well as information about the current location and state of the body's muscles and limbs. The autonomic division of the peripheral system consists of the neural networks responsible for transmitting to the brain sensory information emanating from the viscera, as well as completing the delivering to the viscera the motor commands emanating from the brain. Further still, the autonomic division can be subdivided into the sympathetic system (which is involved in the body's response to stress), the parasympathetic system (involved in establishing and maintaining homeostasis), and the enteric system (involved in controlling the smooth muscle of the gut). The sympathetic and parasympathetic systems are functionally responsible for interacting with central nervous system to produce the phenomenal experience of emotions and motivational drives.

As a whole, the central nervous system is structurally defined as those neural networks that are encased in bone (Kandel, Schwartz et al. 2000; Nolte 2009). Functionally speaking, the central division is responsible for processing and interpreting the information transmitted by the peripheral system, as well as formulating and directing a behavioral response. The components of the central nervous system include the spinal cord, the brain stem, the cerebellum, the diencephalon, and the cerebral hemispheres. Because the structural and functional characteristics of both these components and their respective subdivisions are rather extensive, I will save a more detailed description of the more sociologically relevant of these for below.

Section 2: The central nervous system is deliberately connected by Identifiable Pathways to form Functional Systems.

The densely connected aggregate of neural circuits constituting the human brain is non-randomly organized into functionally discrete regions and pathways (Kandel, Schwartz et al. 2000; Nolte 2009). In short, this means three things: first, that it is possible to identify specific portions of the brain that only engage in a limited type or range of neural processes; second, that collections of these specialized regions interact through specific neural pathways; and third, that neither the brain regions nor the pathways between them are arbitrarily assigned.

Arguably, the best illustrations of this principle are the topographic maps found in the somatosensory cortex. In the case of the somatosensory system, a topographic map is defined as the ordered mapping of the entire body's surface onto specific locations in the somatosensory cortex (Kandel, Schwartz et al. 2000). This map is created by the axons of tactile sensory receptors located throughout the surface of the body projecting to an exact location in the brain. The ordering of sensory afferents in this manner allows the sensory neurons located in the hand and arms to accurately represent in the brain the physical and spatial properties of objects located in the environment. Single cell recordings done in the sensory cortex responsible for mapping tactile stimuli in the left index finger of the monkey are able to recreate the physical properties of the embossed letters being pressed against the corresponding appendage with a tremendous degree of accuracy.

Like the somatosensory system, the neurological underpinnings of various cognitive and behavioral processes occur at specific regions in the brain (Kandel, Schwartz et al. 2000; Nolte 2009; Sporns 2011). Also like the somatosensory system, the axons connecting the component parts of a functional system travel to their destinations through very specific pathways. Sometimes these projections can be seen with the naked eye because they involve such a large number of axons; examples of this are the corpus callosum that connects the right and left side of the brain and the pyramidal tracts responsible for connecting the cerebral cortex to the spinal cord. More frequently though, the axon projections are much less in number and, as a result, require the use of imaging technologies in order to be seen. In either case, said projections are generally identical across normally developed individuals in terms of their physical location and their network topologies (Biswal, Mennes et al. 2010; Sporns 2011). As such, it is possible to generalize findings about the structure and function of neural networks to larger populations.

Section 3: The Functional Systems Located within the Central Nervous System Processes Information in a Hierarchical Manner

In Chapter 3 I discussed how neural circuits in the visual system integrate sensory information through a hierarchically organized process. Recall that this integration involved neurons located in earlier stages of the processing sequence converging onto fewer and fewer neurons at each subsequent stage. Also recall that this hierarchical form of processing is what enables the visual system to generate a ‘gestalt’ representation of complex objects found in the environment.

Interestingly, this hierarchical organization of information processing also occurs between functional regions in the brain (Kandel, Schwartz et al. 2000; Sporns 2011). For example, multimodal association areas are responsible for combining different types of sensory information into a single coherent representation of an object. One such association area is located in a part of the cerebral cortex called the inferior parietal lobule (see below for more regarding regional divisions of the cerebral cortex). Here, visual information about where in the environment an object is located is combined with somatosensory information about how/where the organisms body is currently located in order to create an emergent representation that relates the location of objects to the body; i.e. the perceptual knowledge of: “THAT ORANGE (visual information) is physically located near MY LEFT HAND (somatosensory information).” Interestingly, multimodal association areas can themselves interact as well. For example, there is a brain region called the limbic association area that is responsible for combining interceptive information to produce an organism’s subjective awareness of their current homeostatic condition. Through neural pathways to be discussed below, information generated by both the limbic and inferior parietal association areas can converge to create a more complex representation of an objects location vis-à-vis the organisms current homeostatic state; specifically, a cup of water located near the hand will induce greater neural activity in the inferior parietal lobe if the organism is thirsty than if they are satiated (Kandel, Schwartz et al. 2000).

Part II: Major Structural and Functional Divisions of the Human Brain.

In this portion of the chapter I will use the above principles as a framework for describing the structural and functional properties of several brain regions. Because a full consideration of all of the regions of the brain is beyond the scope of this chapter, I will limit my consideration here to a few examples that will be shown in Chapter 6 to play an important role in three sociologically relevant intrinsic connectivity networks. Also, because my goal is merely to highlight how it is specific brain regions can be described as structurally and functionally unique, I will further limit my consideration of each of the following regions to a very basic description of their most distinguishing properties.

Section 1: The Structural and Functional Properties of the Cerebral Cortex

The cerebral cortex is defined as the outer-shell of the cerebral hemispheres[5]; it's most characteristic feature is its highly convoluted shape, which is formed by a collection of elevated regions–called gyri–that are separated by a series of grooves called sulci (Kandel, Schwartz et al. 2000; Nolte 2009). Despite being only a few millimeters thick, the cerebral cortex possesses roughly 25 billion neurons, 100 trillion synapses, and more than 100,000 km of axons; equally impressive, the cerebral cortex has a surface area of about 2 square-feet and represents about half of the brains total weight (Nolte 2009).

Section 1.1: The Cerebral Cortex

Recall from the end of Chapter 2 that there exists a variety of neuron types based upon differences in axon, dendrite, and signaling properties. Within the neocortex, these different classes of neurons are non-randomly organized into structurally discrete horizontal layers and vertical columns (Nolte 2009).

The internal structure of cerebral cortex consists of six laminated layers of neurons; it is believed that the functional purpose of this laminated structure is to provide an efficient means for organizing the complex roadmap of efferents entering and afferents leaving the neocortex (Kandel, Schwartz et al. 2000). The top layer- labeled Layer I and referred to as the molecular layer- contain no cell bodies and is instead made up solely of

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[5] The cerebral hemispheres are the two upper-most bulbous bodies one typically envisions when one thinks of the brain.

the dendrites and axons of the cell bodies located at lower levels. Directly underneath this layer is Layer II; because this layer mainly made up of granule cells, it is referred to as the external granular layer. The term “external” is used to distinguish Layer II from the Layer IV, which is also made up of granule cells. Because Layer IV is located closer to the center of the brain it is referred to as the internal granule layer. Layer III, which is located in between Layers II and IV, is largely made up of pyrimadial cells and, hence, is called the external pyrimadial layer. Again, the term external is meant to distinguish Layer III from Layer V, which also contains pyrimadal cells. Finally, the bottom-most layer, Layer VI, is called the polymorphic layer because it contains a variety of different neuron types. Importantly, each of the above layers can also be distinguished by the connections it makes with the other layers of the cortex and the functional contributions it makes toward a given process. For example, the dendrites located in layers I-III stem from the cell bodies located in layers V and VI, while dendrites in layer V and VI emanate from layers III and IV. Likewise, feed-forward processes tend to originate in Layer III and terminate in Layer IV; feedback processes, in turn, originate in layers V and VI and terminate in Layers I, II, and VI.

In terms of their vertical organization, neocortical neurons are arranged into at least three types of columns. As a whole, these vertical columns consist of a narrow chain of interconnected neurons that extends vertically across neocortical layers II-VI (Mountcastle 1997). The first type of vertical column is called a minicolumn, the core of which consists of roughly 80-100 individual cell bodies, as well as several bundles of axons and dendrites (Mountcastle 1997; Peters 2010). Further, the boundaries between individual mini-columns are established by a thin, cell bodiless area (Buxhoeveden and Casanova 2002). The second type of vertical arrangement is called a macrocolumn, and is made up by 60-80 minicolumns that are bundled together by short-range horizontal connections (Buxhoeveden and Casanova 2002). Finally the third type of vertical arrangement is called a hypercolumn, which consists of a collection of macrocolumns that are again bundled together by short-range horizontal connections (Buxhoeveden and Casanova 2001).

Although the exact functional relevance of vertical organization is not yet fully known, studies examining their physiological properties offer several important insights. First, experiments devoted to mapping the location of receptor fields on the body to specific locations in the somatosensory cortex have continually found that all of the cells comprising a single minicolumn respond to the same receptive field (Buxhoeveden and Casanova 2002). Or, in other words, sensory information processed by a specific region of the body is processed by the brain within a single cortical column. From this, it appears that sensory information is delivered through the horizontal layers and then processed by vertical columns. Second, receptor fields map to minicolumns in a one-to-one fashion and exhibit very little over-lap. Or, in other words, a single receptive field does not map to more than one minicolumn. As such, it appears that minicolumns specialize in processing information from specific sources. Third, the minicolumn's structural organization represents the minimal architecture needed to process an incoming sensory signal. In other words, a reduction in the number or kind of neurons found in minicolumns disenables its ability to generate the types of neural dynamics discussed in

Chapter 3. As such, the minicolumn is hypothesized to represent the minimal functional unit of the neocortex. Fourth, the individual minicolumns comprising a macrocolumn combine their respective receptive fields to create correspondingly larger bodily surface maps. Like their individual minicolumns, the boundaries of a single marcocolumn map exhibits little overlap with the receptor field maps generated by other macrocolumns. And finally, the total output generated by a macrocolumn reflects a “winner-takes-all” interaction between the constituting microcolumns (Koch 2004). This means that the macro-column integrates the inputs received by the constituting minicolumns in order to transmit only the most dominate signal.

Section 1.1.1: Structural Subdivisions of the Cerebral Cortex into Discrete Lobes Gyri

The cerebral cortex can be subdivided into four sets of gyri called lobes (Nolte 2009). Generally speaking, the boundaries of each lobe are determined by a specific set of sulci, and the cranial bone under which it resides determines the nomenclature of each. The frontal lobe is located underneath the frontal bone—i.e. the forehead. The gyri included in the frontal lobe extend from the anterior tip to the central sulcus located roughly at the midpoint of the top of the brain. The boundary located on the outer-side of the brain is defined as the lateral sulcus up to the point where it intersects with the central sulcus. On the medial surface of the brain, the lower boundary of the frontal lobe is defined by the cingulate sulcus. The backend of the frontal lobe is separated from the parietal lobe by an imaginary line that runs from the top of the central sulcus to the cingulate sulcus. The parietal lobe is located underneath the parietal bone, and extends from the central sulcus to an imaginary line that runs from the parieto-occiptial sulcus to the preocciptial notch. The lower boundary on the outer-side of the brain is defined as the lateral sulcus, plus an imaginary continuation of the lateral sulcus to the imaginary boundary running from the parieto-occipitial-preocciptial notch. On the inner-side of the brain, the parietal lobe is bounded by the subparietal/calcarine sulcus in the rear, the back-end of the frontal lobe, and the parietooccipital sulcus. The temporal lobe is located underneath the temporal bone and consists of the majority of the lower middle half of the outer side of the brain. Specifically the temporal lobe sits beneath the lower boundaries of the frontal and parietal lobes, and in front of the lower-half of the parietooccipital sulcus. On the inner-side of the brain, the boundaries include most of the collateral sulcus and another imaginary line running from the preocciptial notch toward the splenium of the corpus callosum. Finally, the occipital lobe is named after the occipital bone and is located at the very lower back end of the brain. It is formally bounded in the front by the parietal and temporal lobes.

Each of the above regions can be further subdivided into specific gyri (Nolte 2009). For example, the frontal lobe can be divided into the superior, middle, and precentral gyri. The inferior frontal lobe, in turn, can be further divided into an orbital part, an opercular part, and a triangular part. Moreover, the underside of the frontal lobe can be divided into the gyrus rectus, the orbital gyri, and the olfactory bulb. The parietal lobe, in turn, can be divided into the postcentral gyrus, the superior parietal lobule, and the inferior parietal lobules. Like the inferior frontal lobe, the inferior parietal lobule can be subdivided into the supramarginal gyrus and the angular gyrus. Another subdivision of the parietal lobe, called the precuneus, is located on the inner-side of the brain. The outside surface of the temporal lobe can be divided into the superior, middle and interior temporal gyri. Unlike the superior and middle gyri which are fully contained on the outer-side of the temporal lobe, the inferior gyrus extends from the outer-side to the under-side of the brain. Along with the extension of the inferior gyrus, the occipitotemporal gyrus and part of the superior temporal gyrus are located on the underside of the temporal lobe as well. The totality of gyri located on the outer-side of the occipital lobe are called the lateral occipital gyri. On the inner-side of the brain, the occipital lobe is subdivided into the cuneus and the lingual gyrus.

Section 1.1.2: The Functional Subdivisions of the Cerebral Cortex

Specific regions of the cerebral cortex are specialized for processing sensory information and motor commands, as well as performing associational functions (Kandel, Schwartz et al. 2000; Nolte 2009). Generally speaking, the primary sensory cortex for somatosensory information is located on the postcentral gyrus in the parietal lobe; the primary sensory cortex for visual information occurs at a specific occipital sulcus called the Banks of calcarine fissure; and the primary sensory cortex for auditory information is called Heschl’s gyrus in the temporal lobe. The primary motor cortex, in turn, is located at the precentral gyrus of frontal cortex.

Regarding the association areas, the unimodal somatosensory associations occur at the posterior parietal gyrus, while unimodal visual associations occur at the inferlateral surface of the occpitial/temporal lobes, and unimodal auditory association occurs at the superior temporal gyrus (Kandel, Schwartz et al. 2000; Nolte 2009). The unimodal association cortex responsible for the preparation of motor programs is located in the frontal lobe, rostral to the precentral gyrus. The multimodal sensory association area responsible for visuospatial localization, language, and attention is located at the junction between the parietal and temporal lobes. Finally, the multimodal association area responsible for motor planning, language production, and judgment, is located in the prefrontal cortex, in front of the premotor areas on the dorsal and lateral surfaces.

Section 1.2: Sensory and Motor Processing and Integration

The expression of Principle 3 within the cerebral cortex is represented most clearly in terms of how sensory information is processed by the primary region and the unimodal, and multimodal association areas. Regardless of modality—i.e. sight, touch, taste, or hearing—sensory information is first delivered from the peripheral receptor cells to the thalamus and then on to the primary sensory region (Kandel, Schwartz et al. 2000). The functional responsibility of the primary sensory region is to register the initial characteristics of the sensory stimuli. From the primary region, sensory information is then sent to the unimodal association area; the function of this region is to organize the sensory information from a single modality into an initial perception. The organized information is then sent to multimodal association areas where the sensory information from multiple modalities is combined into a single polysensory perception—i.e. the sight of the dog and the sound of its bark is combined into a single perception of that dog there is barking (Nolte 2009).

Although the production of motor commands follows a similar relay, the process does not follow the same order as the processing of sensory information (Kandel, Schwartz et al. 2000; Nolte 2009). For example, the primary motor cortex is the final point at which information is processed before a motor command is delivered to the appropriate body part. Instead, motor commands are first planned and compiled in the premotor cortex. Interestingly, the premotor cortex receives information from the motor nuclei in the thalamus, the primary somatosensory cortex, the parietal association cortex, and the prefrontal association cortex. As will be discussed further below, the inputs of the thalamus are used to calibrate and refine a motor command. In puts from the primary somatosensory cortex and the parietal association cortex, in turn, provide information about the current location of the body parts to be moved by the motor act, the relationship of these body parts to the objects to be acted upon, and feedback information about how the motor act is unfolding.

Section 2: The Structural and Functional Properties of the Diencephalon

Although the diencephalon represents only about 2% of the central nervous system by weight, it plays an essential role in normal brain functioning; this level of importance stems in large part from the incredible number of connections the diencepholon’s component parts establishes with the central cortex explicitly, as well as from its role as a central hub for sensory, motor, and limbic pathways in and out of the cerebral cortex (Nolte 2009). In short, the critical importance of the diencephalon stems not from its sheer weight but from the weight of its connections.

Once again, the diencephalon can be subdivided into four parts called the epithalamus, the thalamus, the subthalamus, and the hypothalamus. Further, each of these subdivisions can be further subdivided based upon the subcomponents topology of connections with other regions of the central nervous system. In order to simplify the discussion, I will limit my description here to include only the thalamus and the hypothalamus. My decision to focus on these two portions specifically is due mainly to their significant involvement in social psychological processes.

Section 2.1: Structure and Function of the Thalamus

Structurally speaking, the thalamus is a highly significant brain region due to the fact that it is the 'gateway' through which information from the external world and the periphery nervous system is trafficked into the cerebral cortex (Nolte 2009). Furthermore, the thalamus is also structurally significant to the degree that it serves as a densely connected central hub that is capable of relaying and reciprocating connections within and across the cerebral cortex.

More specifically, the thalamus is located roughly in the lower cetern of the brain, right above the brain stem and in front of the cerebellum; physically, it resembles an egg with a curled appendage attached to the back end (Nolte 2009). Internally, the thalamus consists of a dense mass of nuclei that are divided into specific regions by both the topology of the connections they establish with other regions of the central nervous system, and by a thin sheet of mylinated fibers called the internal medullarly. The internal medullary structurally divides the thalamus into an anterior, lateral, and medial section. The specific inputs received by the anterior section emanate from the mammillothalamic tract and the hippocampus; regarding its ouputs, the anterior section projects to the cingulated gyrus. The medial section is defined by the projections it receives from the prefrontal cortex, the olfactory structures, and the limbic structures; as well as by its projections to the prefrontal cortex. The lateral section of the thalamus can be subdivided into a dorsal tier and a ventral tier. The dorsal tier consists of the lateral dorsal nucleus—defined by inputs from the hippocampus and outputs to the cingulated cortex-- the lateral posterior nucleus—defined by reciprocal inputs and outputs from/to the parietal lobe-- and the pulvinar—defined by the reciprocal links between it and the parietal, occipital, and temporal lobes. The ventral tier consists of the ventral anterior nucleus, the ventral lateral nucleus, and ventral posterior nucleus. The ventral posterior nucleus, in turn, can itself be subdivided into the ventral posterlateral nucleus and the ventral posteromedial nucleus. Finally, the tail-like structure protruding from the back of the thalamus can be divided into the lateral geniculate nucleus and the medial geniculate nucleus.

Regarding its external structure, the thalamus consists of a thin sheet of cells called the reticular formation. Like the internal nuclei, the reticular formation receives neural inputs from the cerebral cortex and other thalamic nuclei. Unlike the internal nuclei, though, the reticular formation does not project to other parts of the cerebral cortex; instead it only projects back to the internal nuclei of the thalamus. These reticular projections are interesting for two reasons; first, each projection forms a feedback loop by targeting the internal nuclei from which it receives input; and second, the projections sent by the reticular formation are inhibitory (GABA) in nature. As will be discussed in further detail below, the combination of these two characteristics play an important role in the functional role played by the thalamus.

Inputs into the thalamus are of two types (Nolte 2009). The first type are called specific inputs; these are defined as inputs the passively receive and transmit a neural signal without modifying the content of its information. The second type is called regulatory inputs; in this case, the input contributes to decisions about the form in which information will leave the thalamus. Although most regulatory inputs come from the cortex, other sources include the renticular formation and the cholinergic, noraderergic, serotnergic, and dopaminergic endings from the brainstem.

A combination of distinct patterns of output destinations and specific inputs makes it possible to group thalamic nuclei to be grouped into three categories. The first type is called relay nuclei; the function of these is to deliver information from particular functional systems to the appropriate cortical areas. Important relay nuclei for sensory include the VPL/VPM and geniculate nuclei, while the VL and VA are important for motor relays. The anterior nucleus, on the other hand, is an important relay between the mammillothalmic tract and the cingulated gyrus. The second type of neuceli, called association nuclei, is responsible for gating the transmission of information between areas of the cerebral cortex. Two important examples of associational neuclei are the dorsomedial nucleus, which connects to the prefrontal association region of the cerebral cortex, and the pulvinar-LP complex, which is interconnected with the parietal-occipital-temporal association cortex. Finally, the third set of neuclei are called the intralaminar and midline nuclei; the functional purpose of these is to receive and transmit information from the basal ganglia and the limbic system and then transmit it to other parts of the cerebral cortex, as well as back to the basal ganglia and the limbic system.

Beyond the specificity of their connections, the pathways entering and leaving the thalamus are themselves organized by the internal capsule. The internal capsule is a compact bundle of fibers that consists of five regions. The first region is called the anterior limb and consists of the portion between the lenticular nucleus and the head of the caudate nucleus; it contains the fibers interconnecting the anterior nucleus and the cingulated gyrus, as well as most of the fibers interconnecting the dorsomedial nucleus and the prefrontal cortex. The second region is called the posterior limb, which is located between the lenticular nucleas and the thalamus; this region contains the fibers interconnecting the VA and VL with the motor areas of the cortex, as well as the somatosensory fibers projecting from the VPL/VPM to the postcentral gyrus. The third region is called the genu and serves as a junction between anterior and posterior limbs; the fibers of this region interconnect the frontal lobe and the pontine in the basal ganglia, as well as the dorsomedial nucleus and the prefrontal cortex. The retrolenticular region is the fourth part of the internal capsule and contains most of the fibers interconnecting the thalamus and the parietal and occiptical association areas, the pulvinar-LP complex, and lateral geniculate nucleus to the calcarine sulcus. The fifth and final region of the internal capsule is called the sublenticular region; along with more interconnections between the thalamus and the calcarine sulcus, the temporal association areas, and the pulvinar, the sublenticular region also contains the auditory radiation.

An interesting characteristic of thalamic neurons is their ability to fire in two very different ways. The first way is called the tonic mode and consists of slightly depolarized neurons firing in the typical fashion described in part I; i.e. a slight increase in the level of depolarization results in an action potential and a slight hyperpolarization results in a cessation in firing. Because these projections utizlize glutamate, they are able to modify the rate at which they fire to match the amount or intensity of the input. As such, specific inputs tend to operate under tonic mode due to their ability to reliably transmit a signal. The second firing type is called burst mode, which, due to the nature of the associated ion channels, consists of an initial action potential followed by a 100ms delay. The burst mode is established by the projecting neuron becoming hyperpolarized above the level during tonic mode. Because neurons in the burst mode are extremely sensitive to depolarization, and, hence, fire relatively easily, it is believed that their function is to serve as a wake-call for the cortex to begin to pay attention to a stimulus. But, because, of the long recovery time, neurons in the burst mode are not able to transmit a signal with a high degree of accuracy.

Section 2.2: Structure and Function of the Hypothalamus

In terms of gross anatomical boundaries, the hypothalamus is located below the thalamus, behind the optic chiasm, in between the optic tracts, in front of the mesencephalon, and on top of the pituitary gland (Nolte 2009). The hypothalamus as a whole is divided along the midline by a cavity called the third ventricle. Like other regions in the brain, the hypothalamus can be divided and subdivided into a series of areas and zones. The large scale areas, identified from the front of the hypothalamus to the back, are the anterior, tuberal, and posterior areas. Moving from the midline ventricle outward, the three zones are the periventricular zone, the medial zone, and the lateral zone.

There are several nuclei embedded within the cross-hatch of the above areas and zones (Kandel, Schwartz et al. 2000). The nuclei housed within the anterior area-periventralicular zone and the tuberal area-periventricular zone are called the suprachiasmatic nucleus and the arcuate nucleus, respectively. Functionally, the suprachiasmatic neucleus is the master clock that regulates an individual's circadian rhythms. This is done through an amazing interaction between changes in the amount of day-light and two molecular processes contained therein. Regarding its influence on behavior, the arcuate nucleus is critically involved in feeding behavior. Specifically, neurons located in the arcuate nucleus that contain neuropeptide Y, agouti-related protein, and GABA induce the desire to eat when activated by ghrelin. Another set of neurons containing the *proteins pro-opiomelanocortin*, and *cocaine- and amphetamine-regulated transcript* inhibit feeding when activated. Further, the lateral nucleus, which is located, in part, in the posterior-lateral zone, and the tuberomammillary nucleus, which is located in the tuberal-lateral zone, are also involved in the promotion of sleep, wakefulness, and arousal (Kandel, Schwartz et al. 2000).

Two of the nuclei housed within the anterior-medial zone are called the medial preoptic nucleus and anterior nucleus; these are responsible for the regulation of thirst and body temperature, respectively (Kandel, Schwartz et al. 2000). Two other nuclei housed in this region are called the paraventricular nucleus and supraoptic nucleus. Neurons located in these neuclei secrete the hormones oxytocin and vassopressin into the neurohypophysis of the pituitary gland. From the pituitary gland, these two hormones are then released into the blood stream to target the organs responsible for controlling water balance in the body and milk release.

Finally, the nuclei of the tuberal-medial zone are the dorsomedial nucleus and ventromedial nucleus. These neuclei play an active role in regulating complex processes such as the control of growth, maturation, and reproduction. The nuclei located in the posterior-medial zone, in turn, are called the mamillary body and posterior nucleus. Although the exact function of the mammillary body has yet to be determined, the posterior nucleus plays a role in the regulation of body temperature (Kandel, Schwartz et al. 2000).

Along with the above structural features, the hypothalamus possesses two categories of interconnections with other brain regions. The first of these are between the hypothalamus and various structures in the limbic system, including the septal nuclei and the nearby ventral striatum located in the forebrain; the hippocampus; the amygdala; and the insula (Nolte 2009) The axonal connections between the hypothalamus and the septal nuclei occur vis-a-vis the medial forebrain bundle. This bundle physically resembles a piece of frayed rope, such that afferent and efferent connections enter and leave the bundle at various points. These connections are primarily responsible for conveying information to the hypothalamus that is relevant to its function in mediating the visceral aspects of emotional responses. The remaining parts of the limbic system connect to the hypothalamus in a number of ways: the hippocampus via a fiber bundle called the fornix; the amygdala to the ventral medial nucleus via the stria terminalis bundle; and the insula and cingulate cortex via the medial bundle (Kandel, Schwartz et al.

2000). The second set of connections intertwines the hypothalamus with the brainstem and spinal cord. These latter connections are responsible for directly conveying visceral and somatic sensory information to the hypothalamus, which then compares this input with genetically determined set-points (Kandel, Schwartz et al. 2000). Much like the noxious sensory receptors described in Chapter 3, input values beyond the set-point trigger a response signal by the hypothalamus to put into motion the necessary physiological or behavioral responses required to reduce the discrepancy between the sensory signal and the set-point. For example, if the electrolyte composition of the body is off, the hypothalamus will generate a single to motivate the organism to drink; if the organism is to cool or to warm, the hypothalamus will generate a single to induce metabolic thermogenesis or to motivate the organism to move to a cooler environment; etc.

Section 3: Structural and Functional Properties of the Limbic Cortex.

Extensive research carried out in psychology and neuroscience has clearly demonstrated that how sensory information is perceived and stored is greatly affected by either its emotional content or the homeostatic state of the individuals (Forgas and Bower 1987; Ashby and Isen 1999; Zald 2003). For example, some sights, sounds, scents, tastes, and physical sensations instinctually make people feel either happy, sad, angry, calm, or disgusted; food is more desirable when we are hungry than when we are full; a sensual touch is pleasurable when it comes from a lover and revolting when it comes from a close family member (Nolte 2009). Moreover, we are more likely to remember in greater detail emotionally charged events than we are emotionally neutral ones. The part of the brain responsible for generating the emotional content of experiences is called the limbic system. Generally speaking, the portions of the brain making up the limbic system are the cingulate cortex, the parahippocampal gyri, the amygdala, the hippocampus, and the insula. In this portion of the chapter I will limit my discussion to only the amygdale and the hippocampus. The structural and functional significance of the remaining components of the limbic system will be discussed in chapter 6.

Section 3.1: Structural and Functional Properties of the Amygdala

Unlike many of the other brain regions discussed in this chapter, not much is known about structure and connectivity of the human amygdala (at least not with a high-level of precision); this is due in large part to the technological difficulties associated with studying deeply embedded neural regions in healthy living humans. As such, detailed research on the human amygdala is often based on findings from studies conducted on experimental animals (Whalen and Phelps 2009). Although the extreme differences in cognitive capacities existing between humans and animals would appear to rule out the possibility for such substitutions, extensive cross-species comparative research has shown that this is not the case. Indeed, the amygdalae of the rat, nonhuman primate, and human all demonstrate extensive homologies (Whalen and Phelps 2009). For this reason, my discussion here will focus primarily on describing the nonhuman primate amygdala as reviewed by Whalen and Phelps (2009).

Like the hypothalamus, the amygdala is comprised of a heterogeneous group of nuclei and subnuclei. It is located in the medial temporal lobe, near the hippocampal formation. For simplicity sake, said nuclei are conventionally grouped into three sets.

The first set is labeled ‘deep nuclei’ and consist of the lateral nucleus, the basal nucleus, the accessory basal nucleus, and the paralaminar nucleus. The second set is labeled ‘superficial nuclei’ and consists of the medial nucleus, anterior cortical nucleus, posterior cortical nucleus, nucleus of the lateral olfactory tract, and the periamygdaloid cortex. The last set is called the “remaining nuclei” and consists of the anterior amygdaloid area, central nucleus, amygdalohippocampal area, and the intercalated nuclei.

The nuclei of the amygdala are heavily connected to the rest of the brain through a series of afferents and efferents. For example, the lateral nuclei is the major cite in the amygdala that receives sensory input from the visual, auditory, somatosensory, olfactory, and taste pathways. This information is then sent to the central and basal nuclei. The central nucleus then projects to the brain stem, which, in turn, projects on to several behavioral and physiological control systems. It is believed that this neural pathway is responsible for generating the physical experience associated with emotions. In the case of ‘fear’, these would involve an increased heart-rate, skin conductance, etc. The basal nuclei, in turn, project to the striatal cortex, which is involved in generating behavioral responses to emotion. Again in the case of ‘fear’, these would involve the physical acts associate with a ‘fight or flight’ response (i.e. bearing of the teeth, clenching of the fist, running away). Because of these connection patterns, it is argued that the sensory pathways leading into the amygdala allow it to screen sensory information for potentially dangerous or rewarding stimuli and then cue the initiation of the appropriate behavioral and physiological responses. Interestingly, the sensory inputs into the amygdala originate from the higher-level association areas, while the amygdala projects to the areas involved in the earlier stages of sensory processing. Further, neural activity taking place in these early sensory areas has been shown to positively co-vary with increased neural activity in the amygdala. This relationship has been interpreted to mean that the amygdala increases the salience of incoming neural signals that possess emotional relevance so that they may be further processed by the prefrontal cortex. For example, the initial processing by the amygdala may signal "Warning, pay attention to this!", while the subsequent processing in the prefrontal cortex could determine "False alarm, this stimulus is in fact beniegn," or, "The stimulus is actually more dangerous than previously determined" (Nolte 2009).

Along with sending signals to the prefrontal cortex, the amygdala also receives a number of important projections from this region as well. Indeed, careful tracing experiments have demonstrated projections from the orbitofrontal and medial prefrontal cortices to the magnocellular division of the basal nucleus, the lateral nucleus, the medial nucleus, and the central nucleus (among others) (Whalen and Phelps 2009). Extensive empirical research focusing on the functional relevance of these connections has shown that they play an important role in the top-down modulation of an emotional response. Indeed, Ochsner and colleagues have repeatedly shown in a wide variety of contexts that activity in the prefrontal cortex can increase/decrease activity in the amygdala in order to increase/decrease the intensity of positive and negative emotions (Ochsner, Hughes et al. 2009; Koenigsberg, Fan et al. 2010; Ochsner 2010; Zaki, Hennigan et al. 2010). Or, to put it another way, it is possible to people to increase the intensity of an emotion by deliberately thinking about and 'working themselves' into an emotional fervor. Further, these same researchers have also shown that interactions between prefrontal and amygdala activity is strongly correlated with what is called cognitive reappraisal of emotion; in short, this involves the modulation of an emotional experience by altering the contextual significance of the situation. For example, although a person may experience a negative emotion when they see a person being physically hurt, the ability to tell themselves that the person being hurt is 'only acting' and is not 'really in pain' can reduce or completely extinguish the negative emotion .

Section 3.2: Structural and Functional Properties of the Hippocampus

Quite confusingly, the term hippocampus is often used to refer to two different brain regions (Nolte 2009). The first of these describes a gross anatomical region; the second refers to one of several subregions contained therein. For the sake of clarity I will follow the convention of referring to the former of these usages as the hippocampus formation, and the latter as the hippocampus (Andersen 2007). Structurally speaking, the hippocampus formation is a 5cm, doubly-curved piece of cortex folded into the inside surface of the temporal lobe and located in between the amygdala and the splenium of the coprus callosum. The subregions of the hippocampus formation are called the dentate gyrus, the hippocampus proper, the subiculum, the presubiculum, the parasubiculum, and the entorhinal cortex. Like the brain areas already discussed above, the subregions of the hippocampus formation can be distinguished in terms of their cellular make up. For example, the dentate gyrus and the hippocampus proper both possess three cell layers: a superficial molecular layer, a deep polymorphic layer, and an intermediate striatum layer. But, the dentate gyrus can be distinguished from the hippocampus proper by the fact that the intermediate striatum of the former consists of granule cells, while the latters' is comprised of pyramidal cells. Moreover, the dentate gyrus is generally thought of as a single, U-shaped region, while the hippocampus proper can be divided into three subregions called CA1, CA2, and CA3 based upon differences in the type and density of neurons. Similar differences in the type, quantity, and location of cells distinguish the entorhinal cortex, subiculum, presubiculum, and parasubiculum as well (Andersen 2007).

Also like the brain areas discussed above, the hippocampus formation exhibits unique and complex patterns of afferent and efferent connections within and between several brain regions. Regarding its inter-regional connections, the hippocampus formation sends and receives inputs to and from the neocortex, thalamus, hypothalamus, amygdala, and brain stem (Andersen 2007). Arguably the four most important intra-regional connections are the perforant path, the Mossy fiber pathway, the Schaffer collateral, and the links between subiculum/entorhinal cortex. Specifically, the perforant path consists of a bundle of axon fibers that project from the entorhinal cortex to the dentate gyrus. The mossy fiber pathway, in turn, is an axon bundle that projects from dentate gyrus to the CA3 in the hippocampus proper. Finally, the Schaffer collateral connects the CA3 to the CA1; while the CA1 projects to the subiculum, and the subiculum connects to the entorhinal cortex. Interestingly, the intra and inter-regional connections often combine to form a large-scale macro-circuit. For example, the unimodal and polymodal association areas located in the frontal, temporal and parietal lobes (see above), project axons to the entorhinal cortex vis-à-vis the parahippocampal and perirhinal cortex. After transversing the perforant, mossy fiber, and Schaffer collateral pathways, the signal is then delivered back to the entorhinal cortex and on to the original association areas vis-à-vis the same parahippocampal and perirhinal cortices.

According to current understandings, the intra and interregional connections defining the hippocampus formation are directly related to its functional role in facilitating the storage and consolidation of declarative memory (Kandel, Schwartz et al. 2000). Recall from Chapter 3 that a memory consists of a set of neurons that fire as an ensemble whenever an object is seen or thought of. Further, also recall that such an ensemble, and, thus, the memory it represents, is formed through the strengthening of the synaptic links that connect the individual neurons to each other. Memory storage and consolidation refer to the process by which a memory is formed. Although the exact mechanism has yet to be fully identified, the hippocampal formation fascillitates this process by reinforcing the relationship between neurons long after the initial stimulus as passed. For example, when a person sees an object, the sensory information is first processed in the unimodal visual association areas located in the neocortex. While this processing is occurring, the sensory information is concurrently sent through the hippocampal formation and back into the visual processing areas in the manner just described above. Even though neurons in the visual association areas will cease to process the visual information once the object is out of sight, the same visual signal will emanate from the hippocampus formation for days or weeks. Over a long enough period of time, the memory will be fully formed in the neocortex and the hippocampal formation will cease to transmit its signal. At this point, the memory will be a part of one's long term memory (Andersen 2007).

It is also interesting to note how the amygdala interacts with the hippocampus formation/neocortex macro-circuits to create emotional memories. First, the activation of the amygdala during the encoding process of a memory results in a significant increase in the strength and temporal synchrony of the neural activity occurring in the entorihinal cortex, hippocampus proper, and related sensory structures found in the cortex (Whalen and Phelps 2009). As was discussed in Chapter 3, both of these variables play an important role in the formation of the neural assembly constituting a memory. Second, the activation of the amygdala during an emotional event also results in the release of several stress-related hormones; this outcome occurs vis-à-vis the projections from the amygdala to the hypothalamus noted in section xx above. Once released, these hormones continually act upon a neural assembly during the memory consolidation and storage processes. In so doing, the amygdala again augments the influence of the hippocampus on these regions to strengthen and solidify the memory. And finally, the amygdala further interacts with the hippocampus formation during the recall of emotional memories; this is done through the amygdala triggering the same visceral responses discussed in section xx above that were originally experienced during the initial encoding process. Indeed, it is because of the amygdala's involvement that people often report reliving a painful experience when mentally recalling it (Kross, Davidson et al. 2009).

Along with its functional role in the formation of long-term declarative memory, the hippocampus formation is also involved in spatial-navigation and spatial memory (Andersen 2007). The ability of the hippocampus formation to engage in these types of behavioral and memory processes is, in part, related to the neural activities of a special type of hippocampal neuron called a place cell. Unlike other hippocampal cells, which are continually active and fire at the theta frequency, place cells are largely silent and, when they do fire, do so in short bursts at a slightly-higher-than-theta frequency. The reason that these neurons are called place cells is because they are only active when an organism moves through a specific region in their environment. Just as the receptive cells in the retina are able to map the visual environment by only firing when a visual stimulus is present within their receptive field, place cells map the spatial area of an environment by only firing when in a specific physical location called the place field.

Place cells are able to determine when an organism is in a specific location through a combination of environmental cues and information derived from the movement/position of the organism's body (Andersen 2007). The use of environmental cues is called a 'frame of reference' and consists of either specific objects or the relationship between objects that can be used to determine one's position in relation to them. For example, if a desired destination in the center of a room is located at the intersection point between two wall-signs spaced 90 degrees apart from each other, an organism can use this information to navigate to said position. Likewise, the propioceptive information that an organism's head or body was orientated in a certain direction when they were located in or traveling to an environmental location can be combined with sensory information to map the spatial layout of an environment. Regarding how these two types of information could interact, O'keefe suggests that "the input from the navigational system gates the environmental input, allowing only those stimuli occurring when the animal is in a particular place to excite a particular cell (cf. Andersen 2007: 499).”

Interestingly, surrounding theta-frequency neurons combines with the place cells to create a temporal code that indicates the distance the organism is from the center of the place field. For example, place cells begin to fire during the early phase of the theta cycle as the organism approaches the center of the field, then during the trough of the theta cycle as the organism reaches the center of the field, and finally during the later phases of the theta cycle as the organism leaves the center of the field (Buzsáki 2006). As was discussed in Chapter 3, the place fields of a collection of places cells can be used to determine the movement of an organism through space. This is because the firing of one place cell as it moves away from the center of its respective field will co-occur with the firing of another place cell as the organism moves towards the center of the next field. As was also discussed in that part of Chapter 3, changes in the firing rate can also be used to code information about a space. In the case of place cells, research has shown that changes in firing rate of subsets of cells coding for a place field correlate with if an expected object or reward was not found in that location; or, if a specific behavior was or was not carried out. As such, place cells not only code for where a location is in physical space, but also for what is or what happens there too (Andersen 2007).

Section 4: An example of how interactions within and between brain regions generate phenomenological experiences.

Recall from Parts I and II above the following points. First, the human nervous system is divided into several distinct regions, sub-regions, and sub-sub-regions based upon the number, type, location, functional contributions, and topographic properties of the neurons they contain. Second, individual sub-regions and sub-sub-regions are connected by discrete and non-randomly assigned neural pathways to form neural systems (i.e. peripheral nervous system, central nervous system, motor system, visual system, etc). Third, information is generally processed by the nervous system in a hierarchical manner, such that initially discrete pieces of information become increasingly integrated into a more holistic representation as said information travels from one region to another. Fourth, the somatosensory system located in the cerebral cortex is functionally responsible for processing tactile, proprioceptive, and nociceptive information that is delivered to the brain from the peripheral nervous system. Fifth, behavioral acts are first complied in the premotor cortex and then delivered to the primary motor cortex; the primary motor cortex refines these neural commands and then delivers them to the muscles of the body in order to initiate behaviors. Importantly, the content of the command that is compiled in the premotor cortex can be significantly influenced by neural activity taking place in the primary somatosensory cortex, the parietal association cortex, and the prefrontal association cortex. And finally, the affective dimension of sensory information is processed by the limbic system, which, along with the amygdala and hippocampus, includes the insula and the cingulate cortex.

In this section I will examine how these structural and functional properties of the human nervous system enable an individual to: 1) simulate the subjective tactile, proprioceptive, and nociceptive experiences of others, as well as any associated affective experiences; 2) automatically and subconsciously rehearse the potential motor acts that can be directed towards perceived objects; 3) automatically and subconsciously simulate the somatosensory experience that will result from the physical manipulation of a perceived object; and 4) simulate and subjectively experience the observed motor acts that others direct toward objects. Generally speaking, these capacities are made possible by three classes of neurons called somatosensory mirror neurons, motor mirror neurons, and canonical neurons.

Section 4.1: Somatosensory Mirror Neurons

Somatosensory mirror neurons are neurons that activate whenever an individual experiences or observes a somatosensory-related stimulation, or an emotion associated with said stimuli (Keysers, Kaas et al. 2010). For example, this means that seeing someone being pricked with a pin produces in the observers brain the same tactile, nociceptive, and affective neural response as if he or she had been pricked him or herself. Somatosensory mirror neurons enable an individual to vicariously experience the tactile, proprioceptive, and nociceptive sensations subjectively felt by others because of the unique structural and functional properties that define the areas comprising somatosensory system that was discussed above. As such, it is necessary to briefly review these properties in order to fully understand how somatosensory mirror neurons operate.

Like the rest of the cerebral cortex, the somatosensory system can be divided and subdivided into a series of distinct areas (Keysers, Kaas et al. 2010). The two main sub-areas include the insula/rostral cingulate cortex and the somatosensory cortices. The *insula and the rostral cingulate cortex* are functionally responsible for processing the affective dimension of somatosensory stimuli. As the term is used here, the affective value of a sensation refers to the desire to compulsion to act that occurs concurrently with the perception of a sensation. For example, the posetrior insula receives sensory information from the spinothalamic pathway about pain, temperature, itch, and crude touch; the affective values of these sensations include the compulsion to scratch the itch or withdraw the hand from the painful stimulus (Keysers, Kaas et al. 2010).

The *somatosensory cortices* include the anterior parietal cortex and the upper bank of the lateral sulcus (Keysers, Kaas et al. 2010). The anterior parietal cortex, in turn, can be subdivided based upon into four distinct areas called BA3a, BA3b, BA1, and BA2. Also like the rest of the cerebral cortex, these areas are defined by their specific cytoarchitecture and connectivity patterns to other regions of the brain. In terms of connectivity, area BA3a receives proprioceptive information through the ventroposterior superior nucleus of the thalamus, and shares connections with the motor cortex. Area BA3b processes tactile information received from the ventroposterior nucleus of the thalamus; moreover, this area also receives input from the venroposterior inferior nucleus, spinal cord, and brainstem regarding the intensity of a touch stimulus (ranging from light to painful touch). Area BA1 is believed to serve as a second stage of processing of propioceptive information because it receives strong activating inputs from BA3a. Area BA2, in turn, receives inputs form B3a, B3b, and B1, and, thus, is seen as a third level of processing of tactile and proprioceptive info. This input is further supplemented by direct inputs of proprioceptive information from the VPS. Because of these inputs, and the fact that BA2 is strongly activated when individuals explore or manipulate objects with their hands, it is believed to enable haptics. Further, because the

BA2 regions on each side of the brain can communicate vis a vis callosal connections, information received by both hands can be incorporated into a single representation of the object. And finally, area BA2 receives visual and auditory information from the ventral intraparietal area. Although each region is structurally and functionally unique, these four areas as a whole are commonly referred to as the SI region. The upper bank of the lateral sulcus, in turn, is called the SII region, and can be divided into the S2 and the parietal ventral areas. Along with these connections to the SI region, SII sends and receives information to and from several visual processing areas, auditory areas that also respond to somatosensory info, and the insula. Because the SII region receives inputs from all four SI regions and the insula, it is believed to represent a fourth level of hierarchical processing that generates a more complex and holistic representation of a somatosensory stimulus.

Taken as a whole, then, somatosensory information is processed by the somatosensory system in the following manner: initially segregated tactile and proprioceptive inputs emanating from the thalamus are combined in area BA2 and then sent to area SII for final processing (Keysers, Kaas et al. 2010). The resulting combination of this information creates haptic perception or the ability to determine the identity of an object based upon how the object feels against the skin and contorts the shape of the hand. The thalamus is also responsible for sending the sensory aspects of nociceptive information to area SI and the affective aspects to the insula and the rCC. Third, area BA2, area SII, the insula, and the rCC all receive direct inputs of auditory and visual information, while areas BA3b and BA1 only receive said information indirectly through connections with said areas. Intuitively, these structural connects should mean that visual and auditory information would most likely to influence tactile processing in SII, haptic processing in BA2 and SII, and nociceptive processing in BA2, SII, the insula, and the rCC. Further, BA3 and BA1 should only be weakly influenced by audio and visual information. As will now be discussed below, this is exactly what we find.

It is common in neuroscience research to use fMRI and EEG imaging technologies to observe changes in neural activity in response to the presentation of stimuli (see chapter 5)(Keysers, Kaas et al. 2010). In one fMRI experiment examining the response patterns of the somatosensory system to direct and vicarious stimulation of the leg by a rod, researchers found that both the SI and SII regions were activated in response to direct stimulation; only the SII region was though was activated while watching another being stimulated in the same region of the leg. In another fMRI experiment, researchers measured neural activity patterns in response to a human hand delivering a touch to various parts of the body. Unlike the above experiment, though, area SI and area SII responded in both the direct and vicarious conditions. Notice here the following two points about the second experiment: first, a human hand delivered the stimulus in the second condition (not a rod); and second, the SI region responded regardless of where on the body the human hand touched.

In other sets of studies, researchers focused explicitly on which subareas of region SI increased their acitivity during both the direct and vicarious conditions. Here it was found areas BA2 and BA1 only reacted during vicariously experienced touch if a human hand was involved. Further, area BA2 is more strongly activated when the participant is asked to focus his attention on the act of touching and not the act of being touched. Also in regard to area BA2, experiments have demonstrated that area BA2 strongly responds when an individual observes another individual's hand stretching in ways that are beyond the normal physiological range of motion. Given that areas BA1 and BA2 are consistently activated by visual stimuli involving either hands interacting with objects or hands engaged in extreme movements, neuroscientists have concluded that these SI subregions are responsible for the coding of somatosensory information related to the 'toucher' during observed interactions involving the hand. The SII region, in turn, is believed to be responsible for processing somatosensory information regarding the vicarious experience of being touched.

Finally, an experiment using EEG examined the temporal sequence through which areas in SI and SII activate during direct and vicariously experienced somatosensory stimuli. In the case of the direct experience situtation, area BA3 responded first and areas BA1, BA2, and SII responded second. During the vicariously experienced situation, though, only areas BA1, BA2, and SII were active. This and similar results have been interpreted to mean that area BA3 is responsible for coding if the somatosensory stimuli being perceived is being experienced from the first or third person perspective.

As was noted above, the insula and the rCC are responsible for representing the affective dimension of direct and vicariously experienced nociceptive stimuli. Like the studies discussed above, researchers have teased out the functional responsibilities of the insula and rCC by carefully comparing the activation patterns of brain regions during different contexts (Keysers, Kaas et al. 2010). For example, in one study changes in the neural activity of participants was measured using fMRI while they were shown three sets of images on a screen. The first consisted of a colored cue that indicated when another individual located in the scanner room with the participant received a painful shock. The next involved the participant viewing images of the second individual's face that visually indicated the amount of pain that he was experiencing in response to the shock. Finally, the participants viewed images of the second individual's hand being pricked by a pin or deeply penetrated by a hypodermic needle. In the case of the first two experimental conditions, e.g. during which the participant knew only that the second individual was in pain, but did not know where on his body he was experiencing the pain, only the insula and the rCC demonstrated an increase in neural activity. In the third case, e.g. when the participant knew that the second invidividual was in pain and where on his body he experienced this pain, the SI region, SII, region, insula, and rCC were activated. Importantly, the strength of neural activity observed in SI was positively correlated with the intensity of the painful stimuli.

Given this pattern of activation, researchers are increasingly concluding that regions SI and SII simulate the location and intensity of a sensory experience; or, in other words, regions SI and SII allow an observer to experience on the exact location of his or her own body the sensory stimuli experienced by the observed on her own. The insula and the rCC, in turn, allow the observer to experience both the sensory stimuli and the affective reaction. In the absence of information indicating location, observers only vicariously experience the latter. Importantly, because area BA3 of region SI does not show an increase in neural activity during the observation of another experiencing physical pain, it is argued that this area is functionally responsible for coding the difference between direct and vicariously experienced pain.

Although the exact mechanism for how individual's experience the subjective states of others still remains to be seen, interpreting the arguments outlined in this section in terms of the concepts of cell assemblies outlined in Chapter 3 can offer useful insights. Recall that a cell assembly is a dynamic chain reaction of neural activity that creates a holistic representation of the thing-as-a-whole. Recall too, that area SII represents a higher-level of processing within the somatosensory system that holistically represents somatosensory information and *that also receives visual input*. If we think of various somatosensory sensations as being holistically represented in area SII by a corresponding cell assembly, this means that the dynamic chain of neural activity constituting the sensation can be 'set off' by either an individual's personal experience of the sensation via the B3-B1-B2-SII pathway, or by the visual-information-of-the-experience-happening-to-another-SII pathway.

Section 4.2: Canonical and Motor Mirror Neurons

Canonical and motor mirror neurons are a special class of neurons located in the premotor cortex (Rizzolatti, Sinigaglia et al. 2008). Specifically, canonical neurons are neurons that activate whenever an individual directs a motor act toward an object, or whenever an individual sees and/or thinks about that same object. For example, the motor act of grasping the ring of a coffee mug with the forefinger and thumb activates the same neurons whenever an individual performs the act or simply sees the ring of the mug.

Interestingly, canonical neurons are highly selective for the kind of physical properties to which they respond. In the case of a coffee cup, this means that a different set of canonical neurons activate when an individual sees/acts towards the handle of the mug versus the top of the mug. Motor mirror neurons, in turn, are neurons that activate whenever an individual performs a specific motor act or observes another individual performing the same motor act. Further, motor mirror neurons also exhibit specialization, in that they are sensitive to the intended goal of the motor act. For example, this means that a different set of motor mirror neurons activates when an individual observes another individual engaging in the motor act 'grasping the mug in order to drink" than when he views her "grasping the mug to take it away."

To understand the underlying mechanism that endows canonical and motor mirror neurons with their unique properties it is necessary to review the structural and functional characteristics of what is sometimes called the visual-motor circuit (Rizzolatti, Sinigaglia et al. 2008). As the name suggests, the visual-grasping circuit begins in the inferotemporal cortex of the ventral visual stream and concludes in the motor cortex. According to current understandings, the purpose of this circuit is to translate visual information about the properties and location of objects in the environment into a motor act directed that is targeted toward said objects. Generally speaking, the ventral stream is functionally responsible for identifying what is being seen (e.g. object recognition based upon physical properties). Like in the somatosensory system discussed above, visual information is hierarchically-processed and compiled as it moves through the various stages of the ventral stream. The inferotemporal cortex is located near the end of stream and thus is responsible for processing highly detailed and holistic representations of seen objects.

The visual information processed by the ventral stream is then sent to the anterior intraperietal area– part of which includes the somatosensory cortex discussed above. Importantly, there are three kinds of neurons located within the anterior intraperietal area: motor dominant neurons that only respond to specific muscular movements in the hand; visual dominant neurons that respond to the visual perception of specific three-dimensional objects of different geometrical shapes, sizes and orientations; and visual/motor neurons that respond when specific three-dimensional objects are seen *and* during the commission of motor acts involved in shaping the hand to physically grasp these three-dimensional objects. In the parlance of psychology, the combination of visual information describing the environment and the motor acts required to interact with the environment is called an affordance (Rizzolatti, Sinigaglia et al. 2008).

Also important, all three types of neurons located in anterior intraparietal area are highly sensitive to the object properties to which they respond. In short, this means that some visual neurons only respond to the perception of cylinders, while others only respond to squares, and still others only to rings. This specificity of response also holds true for motor neurons; in this case though, differentiation is due to the different hand shapes required to grasp a cylinder versus a cube. In the case of the visual-motor neurons, the specificity of response patterns is generated from the permutations of different visually-specific and motor-specific responses (i.e. visual-cylinder/motor-cylinder; visual-cube/motor-cube; etc.). Because of these response patterns, it is believed that the anterior intraparietal area is responsible for deconstructing what is being holistically represented in the ventral visual stream into a series of individual parts based upon the various affordances possessed by the object. In the case of the coffee cup example, this means that the "circle" of the mugs rim is distinguished from the "cylinder" of the mug's body and the "ring" of the mug's handle due to the different visual and motor properties associated with each.

The next stage of the visual-grasping circuit is the premotor cortex. Like the anterior intraparietal area, the premotor cortex possesses motor dominant and visual-motor neurons; unlike the intraparietal area, the premotor cortex does not possess purely visual neurons. As such, this means that the anterior intraparietal area is the gateway by which visual information about the environment enters into the premotor cortex. Because the premotor cortex is functionally responsible for generating motor plans for behavioral responses, it is argued that this region transforms the input it receives from the intraparietal area about the affordances possessed by an object into a deliberately targeted motor response. Also like the anterior intraparietal cortex, some motor and visual-motor neurons located in the premotor cortex are highly sensitive to the kind of affordances to which they respond. For example, some neurons are only active during reach-and-grasp-with-precision-grip, while others are only active during reach-and-grasp-with-whole-hand movements. Interestingly, other premotor neurons are only active during grasp-with-precision-grip-in order-to-bring-to-mouth plans and others only during grasp-with-precision-grip-in order-to-place-somewhere-else motor plans.

Like the sensations processed by somatosensory system, it is useful think of the motor acts processed by the premotor cortex in terms of cell assemblies as well; here, the various types of motor acts (i.e. grasp-cylinder-with-precision-grip, grasp-cylinder-with-whole-hand-to-drink, etc.) are each represented by a specific cell assembly. In this context, canonical and mirror motor neurons are subsets of neurons embedded within such an assembly that can be activated by visual information related to the commission of a motor act. If we recall from chapter 3 that a cell assembly is comprised of 'strongly mutual excitatory neurons', the activation of canonical and mirror neurons by visual stimuli will trigger the activation of the entire assembly. Like somatosensory neurons, then, canonical and mirror neurons enable individuals to experience potential motor acts to be directed toward objects and the motor acts performed by others by enabling visual information to directly stimulate the associated motor cell assembly located in the premotor cortex.

The fact that objects often possess multiple affordances simultaneously raises an important question: how does the premotor cortex select one affordance over another when crafting a potential motor response? The answer to this question stems from the inputs that the premotor cortex receives from the prefrontal cortex. As will be discussed in further detail in Chapter 6, the prefrontal cortex plays a functional role in the generation of executive processes (e.g. deliberately created and willfully controlled mental and physical acts). In short, the goal-directed intention is first generated in the prefrontal cortex; the pattern of neurological activity representing this intention is then sent to the premotor cortex, where it is then used as a filter to select the relevant affordance (how this filtering process occurs in general is also discussed in Chapter 6).

In a similar fashion, how is it that mirror motor neurons are able to respond to the intention of an observed motor act before it takes place? The fact that the premotor cortex is influenced by the intention created in the prefrontal cortex means that final motor plan sent to the motor cortex by the premotor cortex represents the goal-directed intentions of the motor act; or to put it another way: the neural activity representing the affordance of the targeted object, the beginning of the behavioral response toward the object, and the behavioral response to be performed once the individual comes into contact with the object are all packaged together in the motor plan sent to the motor cortex by the premotor cortex. Importantly, this means that information conveyed during the beginning of the behavioral act is strongly correlated with information to be conveyed as the behavioral act is concluded. In neurological terms, this also means that mirror motor neurons triggered by the visual information conveyed at the beginning of the observed behavioral act is strongly correlated with neural activity that will occur at the end. Recognizing once again that the cell assemblies underlying various motor acts are comprised of 'strongly mutual excitatory neurons,' this initial neural activity triggered by the beginning of the observed behavioral act will immediately result in the triggering of the neural activity associated with the completion of the act that is processed by the rest of the assembly (Fogassi, Ferrari et al. 2005).

Section 4.3: Section Summary

By combining visual, somatosensory, and motor processing, mirror motor neurons enable individuals to phenomologicaly experience the subjective states and behavioral intentions of observed others. Importantly, this ‘experiential understanding’ is generated by the coordination of hierarchically processed activity occurring within and between structurally and functionally distinct brain regions. As will be discussed in Chapter 6, this same coordinated dynamics is what gives rise to more complex psychological processes such as one’s sense of self, reflective understanding of oneself and others, role-taking, etc.

Part III: Embryonic Development of the Brain

An important theme that has underlined most of the discussion presented here in this dissertation up until now has been the importance of timing and the proper articulation of neural connections. Indeed, as was noted particularly in Chapter 3, information processing and neural synchrony require specific interactions between certain types of neurons at precise moments; a failure to meet these requirements can have severe consequences. Now, in Parts I and II of Chapter 4 we see this same precision and specificity in terms of where specific types of neurons are located in the brain, as well as in terms of the afferent and efferent pathways between brain regions. In short, the brain is not randomly organized, nor randomly connected (see also Chapter 5 for more evidence of this). The thing that I will attempt to explain here in Part III is this: How do neurons ‘know’ where to locate in the brain, as well as with which neurons to connect? As we will see in the sections below, the answer to both questions is related, once again, to the careful orchestration of interactions between genes, proteins, and other signaling molecules.

Section 1: Embryonic Development as a Cascading Process

Human brain development can be summarized abstractly as a cascading process whereby undifferentiated tissue is made heterogeneous in response to asymmetrical exposure to environmental signals (Sanes, Reh et al. 2006; Lemke 2009). The general mechanism underlying this process can be described as follows. First, signaling molecules are secreted by an environmental source into a field of undifferentiated cells (i.e. the genetic material being expressed within the cell body is the same across all cases). Second, the molecular signals then bind to a corresponding receptor located on the cell wall of each undifferentiated cell. Next, the binding of the signal molecule to the receptor initiates a signal transduction pathway inside of the cell body of the receiving cell; a signal transduction pathway is simply an intra-cellular molecular signal that is released whenever a primary signal attaches to its corresponding receptor. During embryonic brain development, the primary role of these secondary messengers is to modify gene expression in the cell so that it will either develop new types of receptors, produce and secrete new types of extra-cellular molecular signals, or, especially in later stages of development, modify its physical structure.

The above process is defined as a cascade because the characteristics associated with each subsequent step of differentiation are enabled and constrained by the those associated with the differentiations occurring at previous steps; in other words, this means that the cellular differentiation occurring at time t serves as the foundation for differentiation occurring at time t+1; the differentiation occurring at time t+1, in turn, serves as the foundation for differentiation occurring at time t+2; etc. A step occurring in the cascade at time t is said to enable a step occurring at time t+1 because the differentiation occurring at time t provides the necessary receptors, secondary messengers, or structures needed to carry out the differentiation occurring at time t+1; likewise, differentiations occurring at time t+1 are constrained by differentiations occurring at time t because the processes unfolding at said time are only possible once the necessary inputs generated at time t are provided.

Importantly, this cascading process can unfold in one of two ways. In the first pathway, a biological structure located outside of a field of undifferentiated cells–called a signaling center– secretes a primary messenger that differentiates a subset of the undifferentiated cells in a *uniform* fashion; newly differentiated cells arising in this fashion are called organizer cells. In the second pathway, the specific type of gene expression induced by the signaling center is determined by the *concentration* of the molecular signal acting upon the receiving cell. Because the concentration of a molecular signal is reduced with each subsequent binding, those cells located closer to the signaling center receive greater concentrations than those cells located farther away. As a result of this, cascades unfolding in this manner differentiate a field of cells along a position-dependent gradient; a molecular signal operating in this fashion is called a morphogen or postional signal.

Section 1.2: Early Embryonic Development of the Human Brain: From Ectoderm to Neural Tube

Soon after fertilization the human embryo resembles a flat, disk-like structure divided into three layers of cells (Sanes, Reh et al. 2006; Lemke 2009). The top layer of cells is called the ectoderm, the middle layer is called the mesoderm, and the bottom layer is called the endoderm. Over the course of embryonic development, each of these layers will give rise to a different set of anatomical features; specifically, the endoderm will transform into the intestines, lungs, and liver; the mesoderm will eventually produce the kidneys, reproductive organs, bones, muscles, and vascular system; and the ectoderm will generate the epidermis (i.e. skin), the central nervous system, and the peripheral nervous system.

The cascade responsible for transforming the ectoderm into the central and peripheral nervous system is initially put into motion by two processes (Sanes, Reh et al. 2006; Lemke 2009). The first of these is called neural induction and consists of the ectoderm differentiating into epidermal and neural sections. During the neural induction process, a group of proteins-- called chordin and noggin-- are secreted by a mesodermic signaling structure—called the notochord—into the central axis of the ectoderm. Here, along the central axis, chordin, and noggin, bind with another signaling protein called bone morphogenic proteien (BMP). Because of this interaction, the BMP is unable to bind with the ectoderm tissue along the central axis and, as a result of this failure, the axial tissue transforms by default into the neural plate. In those areas of the ectoderm where chordin, and noggin are not secreted, BMP successfully binds and induces a signal transduction pathway that transforms the undifferentiated ectoderm tissue into epidermal cells.

The second of the initial transformative processes is called neurolation, which is defined as a three-step sequence whereby the neural plate is transformed into the neural tube (Sanes, Reh et al. 2006; Lemke 2009). As will be discussed in greater detail in the next section, the neural tube is the foundational template responsible for guiding the development of the central nervous system up until the point of birth. The first step of neuralation consists of the reshaping of the neural plate from a short and squatty structure into one that is long and thin. During the second step, the newly-narrowed neural plate is once again reshaped into a trench-like structure called the neural groove. This transformation involves the central axis of the neural plate furrowing to create a medial hinge point, and the surrounding epidermal ectoderm pushing up each side of the neural plate to form the walls of trench. The third step of neurlation consists of these two walls coming together and fusing to form the neural tube's titular shape. As the fusing of the neural tube is taking place, a small section of the neural groove is pinched off to from a structure called the neural crest; this structure will eventually give rise to the peripheral nervous system.

Section 1.3: Embryonic Development of the Human Brain: From Neural Tube to Birth

Embryonic development of the brain from the neural tube to birth occurs along three structural dimensions and at three levels of anatomical organization (Sanes, Reh et al. 2006; Lemke 2009). The three structural dimensions include: a longitudinal dimension that runs from top to bottom; a circumferential dimension defined by the 360 degrees covered by the interior wall of the neural tube; and a radial dimension that runs from the outer-wall to the inner-wall of the tube. The three anatomical levels include: the gross anatomical level involving the contortion and expansion of the neural tube into the primary and secondary vesicles and the spinal cord; the tissue level involving the parcellation of the internal cavity of the neural tube and spinal cord into functionally specific regions; and the cellular level involving the creation and placement of neurons, as well as the wiring of neural networks.

Section 1.3.1: Gross Anatomical Development along the Longitudinal Axis

Development occurring along the longitudinal dimension produces the basic gross-anatomical structure of the brain via the creation of two sets of ventricles (Nolte 2009). The first set of ventricles, called primary ventricles, divides the neural tube longitudinally into three discrete cavities; the top cavity is called the prosencephalon, or forebrain; the middle is called the mesencephalon, or the midbrain; and the bottom cavity is called the rhombencephalon, or hindbrain. The spinal cord, in turn, also develops at this point at the farthest end of the neural tube immediately behind the rhombencephalon. After this first set of ventricles form, the second sets forms by the upper-prosencephalon ventricle subdividing to produce two telencephalic ventricles and one diencephalic ventrical, and the lower-posencehpalic ventricle protruding out on both its sides to produce two optic ventricles. The hindbrain, in turn, further subdivides to create the metencephalon and the myelencephalon. Along with this series of subdivisions, gross-anatomical brain development involves the rapid volumetric expansion of the ventricle cavities. This expansion is driven by the fluid pressure exerted against the walls of each ventricle as they fill with cerebralspinal fluid. Arguably the most prominent consequence of this expansion can be seen in the telencephalic ventricles inflating to the point where they sit on top of the diencephalic ventrical.

Like the processes of neural induction and neuralation, the longitudinal regionalization of the neural tube involves signaling proteins turning on different genes in different parts of the developing brain (Sanes, Reh et al. 2006; Lemke 2009). In this case, the functional purpose of these proteins is to establish the boundary lines between each of the above regions. Also like neural induction and neuralation, these boundaries are established through a cascade whereby coarse-grained divisions are fine-tuned by subsequent steps. During the first step of this cascade, the initial boundaries of the forebrain and hindbrain are determined through the subdivision of the neural tube into an Otx2-gene expressing anterior section and a Gbx2-gene expressing posterior section. Once these two regions are in place, the initial boundaries of the midbrain and upper-hind brain are sketched out through the expression of the genes Otx1, Ent1, Ent2, Pax2, Pax 5, and Pax 8 along the Otx2/Gbx2 boarder. The boundary of the mesencephalon proper is then established by the differential expression of Wnt1 in the Otx2 portion of the midbrain, and the metencephalon emerges in response to the activation of Fgf8 on the Gbx2 portion. The boundary of the telencephalon, in turn, is carved out of the main anterior/Otx2 subdivision by the subsequent expression of Otx1, Emtx1, Emtx2, and BF1. Although the exact molecular mechanism has yet to be determined, the boundary of the diencephalon appears to be shaped by the expression of the genes Gbx2, Dlx2, and Pax6. Finally, the segmentation of the hind-most part of the rhombencephalon appears to be influenced by the secretion of FGF8, a protein called sonic hedgehog, and a morphogen called retinoic acid.

As embryonic development continues, all of the above ventricles will further differentiate to produce the various functionally-specific regions found in mature brain; for example, the telencephalic ventricles will give rise to the cortex and the olafactory bulbs, the diencephalon ventrical will transform into the hypothalamus, the mesencephalon will become the tectum and the tegmentum, and the rhombencephalon differentiate into the cerebellum, pons, and medulla. Although the basic boundaries of these future structures are established through the signaling processes described above, the vast majority of their development takes place along the circumferential and radial dimensions of the neural tube at the tissue and cellular levels of anatomy.

Section 1.3.2: Tissue Development along the Circumferential Axis

Development along the circumferential axis of the neural tube is commonly referred to as dorsal/ventral differentiation (Nolte 2009). In short, development occurring along this dimension involves differentiating the structural and functional characteristics of the tissue located at the top of the forebrain, midbrain, hindbrain, and spinal cord from the tissue located at the bottom of these same regions.

Within the hindbrain, circumferential differentiation involves the development of two grooves–called the sulcus limitans–on each side of the neural tube and down into the developing spinal cord. The emergence of the sulcus limitans divides the spinal into a top-half called the alar plate and a bottom half called the basal plate (Sanes, Reh et al. 2006; Lemke 2009). As embryonic development continues, the alar plate will transform into the interneurons responsible for carrying information about the body into the brain; likewise, the basal plate will further develop into the motor neurons and interneurons responsible for transmitting neural impulses from the brain to the muscles. The sulcus limitans also serves to divide the hindbrain section of the neural tube into an alar plate/sensory neuron and a basal plate/motor neuron section as well. In this case though, the fully developed specialized regions are involved in trafficking neural sensory and motor signals between the brain stem and the anatomy located within the head and neck. Although the sulcus limitans does not continue into the forebrain and midbrain, both of these regions develop dorsal-specific and ventral-specific interneurons. For example, in the ventral part of the telencephalon sonic hedgehog is responsible for transforming cells into GABAergic inhibitory neurons and Gli3 is responsible for transforming cells in the dorsal part of the telencephalon into glutamatergic excitatory neurons (Sanes, Reh et al. 2006; Lemke 2009).

Molecularly speaking, dorsal and ventral differentiation of both the hindbrain and the spinal cord occur in response to being exposed to different levels of the morphogens BMP and Sonic hedgehog, respectively. In the case of the differentiation of the dorsal region, BMP is secreted from a group of cells located at the top of the neural tube called the roof plate. Those cells located nearest to the roof plate receive the highest concentration of BMP and, as a consequence, are programmed to become a group of neurons called D1 interneurons; the next two sets of cells, being farther away from the roof plate and, thus, receiving less BMP, become instead D2 and D3 interneurons. The functional purpose of these dorsal neurons is to relay signals transmitted from the sensory neurons located throughout the body into the brain. In the case of the ventral differentiation, Sonic hedgehog diffuses up from a group of cells located at the bottom of the neural tube-- called the floor plate-- to trigger the development of motor neurons and three sets of ventral interneurons (V3, V2 and V1). The function of these neurons is to relay command signals from the brain to the various parts of the body (Nolte 2009).

Section 1.3.3: Cellular Development along the Radial Axis

As was discussed above, development and differentiation occurring along the longitudinal and circumferential axes focuses primarily on dividing the neural tube into an increasingly finer-grained grid of functionally specific tissue. In the case of the radial axis, development and differentiation involves the generation of individual neurons and the wiring of the neural networks they comprise. Also similar to the longitudinal and circumferential axes, radial development and differentiation unfolds in a series of steps at several sub-dimensional levels of anatomy.

The radial axis of the neural tube is defined as the wall separating the inner ventricles of the developing neural tube from the outer environment (Nolte 2009). Very early in development, this wall consists of only two layers of cells: the first, which lines the inside of the ventrical, is called the ventricular zone; and the second, which faces the outer environment, is called the marginal zone. The first developmental process occurring at along this axis is called cellular proliferation; in short, it consists of neural-embryonic stem cells located in the ventricular zone copying their genetic material and then dividing in two. During the next phase of development, called cell migration, a portion of the copied-cells slide upwards along a cellular scaffolding to form the cortical layers described in section xxx. Interestingly, these layers form inside-out, meaning that the first cells to leave the ventricular zone form cortex layer VI and subsequent departing cells form layers V, IV, III, II and I in that order.

Once a cell reaches its respective cortical level, the development process continues in a third phase called cellular differentiation(Sanes, Reh et al. 2006; Lemke 2009). During this phase, each neuron differentiates itself by preferentially establishing a synaptic link with a specific set of target neurons. Because the developing neuron reaches its cortical home possessing only a cell body, the first step of cellular differentiation involves the formation of the dendrite and axon. A key component of the developing axon is called the growth cone, which consists of several flat sheets of undulating membrane and several probing spikes; the combination of these two structures work together to pull the growing axon in the direction of a specific target neuron. An axon “knows” both the identity of its target neuron and the “roadmap” for getting there due to an interaction between a set of receptors located on the growth gone and a corresponding set of chemoattractant and chemorepellent guidance cues. A chemoattractant guidance cue consists of a diffusible molecule that emanates from the target cell and binds to the matching receptor on the growth cone. In a similar fashion to the molecular signals discussed in the previous section, the binding of the chemoattractant to the receptor promotes the growth of the axon along the concentration gradient leading back to the target cell. A chemorepellent, in turn, is a diffusible molecular signal that, upon binding to receptors on the growth cone, pushes a growing neuron in the opposite direction of its concentration gradient.

Part IV: Chapter Summary and Discussion

The focus of the first half of this chapter was to identify and describe the structural and functional characteristics of several key areas of the brain using three basic organizational principles. The main reason for this initial focus was to re-enforce the idea that the brain is a highly-organized in nature. A further goal in this section was explain what it means to say that a brain area is functionally involved in generating an experience or cognitive process. In short, the reason the occipital lobe is said to play a role in formulating visual sensory information is because the cellular circuits and processes discussed in Chapter 3 are located there. In the second half of the chapter I turned to examine how these structural properties of the brain are determined by a person's genes during embryonic development. Once again, the fact that the distribution of neuron cell types and the connections between regions is established by a person's genetic code during development strongly supports the argument that the structural and functional properties of the brain are hardwired.

Most importantly, though, the genetic determination of connections is not the full story of how the structural and functional characteristics of the brain are determined. An unusual outcome of embryonic and early post-natal development is the production of an excessive number of neurons and synaptic links; in short, this means that an organism's genetic code is programmed to create more nodes and more links between nodes than may be necessary for a neural network to carry out its assigned function. Indeed, according to estimates, between 30% and 50% of the synaptic links existing at the time of birth is eliminated by the end of adolescence (Lemke 2009). The purpose of this redundancy is to prepare the brain birth to perceive and respond to a very broad range of potential stimuli by creating several possible pathways for transmitting communicative signals. Continued post-natal development involves the restructuring of pathways in response to how the organism interacts with its environment. In this way, the species-specific nervous system developed during embryonic development is tailored by the accumulation of experience to efficiently meet the unique demands of a specific environment. Quite remarkably, the total number of synaptic links and the overall complexity of neural networks in the brain dramatically increase over this same time period (Fair, Dosenbach et al. 2007).

The structural topology of a neural network is refined considerably during early post-natal development through a process called activity-dependent synaptic elimination and reorganization (Bear, Connors et al. 2007). As the name suggests, the first step of this process involves the elimination of synaptic links that do not effectively contribute to the transmission of a signal; for the most part, the effectiveness of a transmission is determined by the strength with which presynaptic and postsynaptic activity are correlated. In those instances where this correlation is weak, the postsynaptic receptors and the presynaptic terminal are first disassembled and removed, and the axon branch is then retracted. Upon the completion of this removal, the axons of the remaining synaptic links are strengthened in response to being repeatedly used and eventually become permanent. Synaptic reorganization is defined as the process by which the number of connections between a set of nodes changes, and the total number of links within the set remains the same. For example, if the topology of a neural network was defined as four links between nodes A and C, and two links between nodes B and C, a synaptic reorganization would consist of redistributing the number of links between dyad AC and dyad BC in an equitable manner (i.e. three links per dyad). This of course would involve the elimination of one link in dyad AC and the creation of a new axonal link in dyad BC.

The synaptic reorganization of a neural network occurs in conjunction with two types of activity-dependent processes, called asynchronous and synchronous firing. Asynchronous firing is said to occur when the pre-synaptic neuron fires out of sync with the post-synaptic target (or vice-versa); synchronous firing, in turn, occurs when both the pre and post-synaptic neuron fire at the same time. For example, imagine a neural network consisting of four neurons labeled A-D and six synaptic links labeled AC1, AC2, AD1, BD1, BD2, and BC1; further, also imagine that the target neurons C and D require the input of at least two axons in order to fire. If neuron B were to fire, an electrical impulse would travel down axons BD1, BD2, and BC1 toward the target neurons D and C. But, because neurons D and C require the input of at least two axons before firing, only target neuron D would fire in response to neuron B’s signal. As a consequence of this, the pre and post neurons of the synaptic links BD1 and BD2 would fire in sync while the pre and post neurons of synaptic link BC1 would not; as a further consequence, the asynchronous link BC1 would be eliminated in accordance with the “delete the weak” principle noted above, and the topology of the network would thus be reorganized as AC1, AC2, BD1, and BD2.

Of course, the intra and inter-cellular processes underlying activity-dependent synaptic elimination and reorganization are the same as those described in Chapter 3 during my discussion of memory formation. As such, the neurological foundations of cognitive processes are in fact the product of a carefully orchestrated interaction within and between hierarchically-nested levels of organization.

Chapter 5: An Mm Analysis of how Graph Theory is used to Identify and Describe Intrinsic Connectivity Networks

Chapter Introduction

In Chapter 4 I examined how structurally and functionally distinct brain regions are formed through the aggregation of intra and intercellular processes. Along with these, I also noted that each distinct brain area is also defined, in part, by the unique set of afferent and efferent pathways it forms with other regions. The purpose of this chapter is to examine how graph theory can be used to describe these inter-connected brain areas, as well as capture the emergent properties that result from their topological properties. Toward this end, this chapter will be divided into two parts. In Part I I will conduct an Mm analysis that will define several analytical concepts developed by the mathematical field of graph theory. Part II will then explain how these analytical concepts being applied to neuroscience to objectively identify and describe the structural and functional characteristics of the neural networks connecting brain regions.

Part I: A Brief Review of Graph Theory and its Applications to Neuroscience.

For a little more than two decades, graph theory has been used to make sense of physical, technological, biological, and social systems comprised of highly complex relationships between large multitudes of component parts (Newman, Barabasi et al. 2006). The reason graph theory has proven so useful to such a broad list of scientific fields is two-fold: first, it is uniquely qualified to identify and describe the emergent properties of densely-connected objects; and second, because the mathematical techniques that define it-as well as the insights it offers- are completely agnostic to the content of what it is being applied to. Or, in other words, it does not matter if the units of analysis are genes, sexual partners, or societies; a network, is a network, is a network. In light of this, the purpose of this portion of the chapter is to briefly introduce what graph theory is and how it can be applied to neuroscience. Further, this portion will also serve as background for the terminology and ideas that will be discussed later in the chapter.

Section 1: What are Graphs and Networks?

Graph Theory is the name of the mathematical tool-set devoted to the formal analysis of graphs and networks. Although the two terms are often used interchangeably, it is important to keep in mind for methodological reasons that graphs and networks are not identical (Sporns 2011). A graph is an immaterial mathematical object comprised of a set of nodes interconnected by a set of edges. A network, in turn, is a real-world collection of interconnected parts that can be *represented* as a graph. In this case nodes and edges are the abstractions of interactions between concrete objects-- i.e. trade between countries, relationships between people, shared memberships between organizations, etc. The reason it is important to keep this distinction in mind is because information derived from or conditions applicable to graphs do not always hold true for their network counterparts. For example, one type of graph– called a random graph– is created by drawing an edge between two randomly selected nodes. Because each node is chosen at random, the probability that any two nodes will be connected to each other is equally distributed across the entire set. Knowing that a graph is a random graph is important to a researcher because said information provides interesting insights into the nature of its structural dynamics (Newman, Barabasi et al. 2006). Although one can easily construct such a graph in the abstract, constructing a random network involving concrete nodes and edges is much more difficult. For example, the edges defining a social network cannot be assigned by randomly selecting nodes; indeed, the probability that two people are socially connected is heavily influenced by their social statuses, their cultural backgrounds, and their physical locations. Indeed, it is much more likely that two working-class, white, Protestant males living in the same small town are socially linked than it is that a Columbian peasant and an Australian aborigine are. Despite this important difference, though, I will use the terms graph and network interchangeably throughout this chapter in order to simplify the discussion.

A first step in analyzing a graph is to identify its topology. The topology of a graph is the 'blue print' that specifies how each of the individual nodes is connected to one another by each of the individual edges. A common way to specify a graph's topology is called an adjacency matrix; here, the nodes of the graph are represented as the rows and columns of the matrix, and the edges are represented as matrix entries. An important part of specifying a topology is defining whether a graph's edges are directed or undirected, as well as binary or weighted. The difference between an undirected and a directed edge is this: an undirected edge simply specifies the existence of a link between two nodes; a directed edge, on the other hand, is one that specifies which of the two nodes it connects is the source and which is the destination. Graphs possessing directed edges are called "directed graphs;" graphs utilizing undirected edges are called undirected graphs. In terms of a concrete real-world example, the international trade network denoting the amount of total trade between countries is an example of an undirected graph; likewise, the international trade network denoting imports and exports explicitly is an example of a directed graph. Similarly, a binary edge indicates whether or not an edge exists between two nodes, while a weighted edge represents the quantity of the connection. In this case, graphs with binary edges are called binary graphs and graphs with weighted edges are called weighted graphs. Using once again the example of the international trade network, the edges comprising a binary graph would simply denote whether or not two countries engaged in trade; a weighted graph, in turn, would specify its edges in terms of the amount of trade taking place. Because the two categories of edges are conceptually independent, it is possible for graphs to be directed and binary, undirected and weighted, etc.

Section 2: Descriptive Statistics for Analyzing the Properties of Graphs

Specifying the adjacency matrix is a critical part of analyzing a graph's topology because it allows for the identification of several helpful descriptive statistics (Sporns 2011). Heuristically, these can be grouped into three sets: the first based on the concept of a degree; the second based on the concept of a path; and the third based on the concept of a clustering coefficient.

Section 2.1: Degree-related descriptive statistics.

Generally speaking, a degree is a measure that is assigned to each of a graph's nodes that identifies the number of edges it shares with the other nodes in the set. In the case of an undirected graph, the degree is calculated by summing the number of edges it possesses. Due to how their edges are defined, it is possible in the case of directed graphs to calculate three degree measures: one for the total number of incoming edges;

one for the total number outgoing edges; and one for the total number of overall edges. In the case of weighted graphs one can also calculate what is called the node strength, which sums the all the value of all of the edge weights connected to a node. Once a degree is assigned to each of the nodes comprising a graph, one can then calculate what is called a degree distribution. As its nomenclature suggests, a graphs degree distribution indicates how the edges are distributed amongst the individual nodes; e.g. do some nodes possess a larger number of edges while others do not? Or does each node possess relatively the same number of edges?

As Sporns and Tononi (2007) note, the functional interpretation of the degree measure is fairly straightforward. For example, in the case of weighted graphs a high in-degree value indicates that the node is influenced by a large number of nodes, while a low in-degree value indicates that the node is relatively isolated from the influence of other nodes. Likewise, a high out-degree value indicates that a node is highly influential, while a low out-degree value indicates that the node is relatively non-influential. Furthermore, one can also calculate the proportion of a node’s edges that are either outgoing or incoming in order to functionally classify it as a ‘sender’ (outgoing > .5) a ‘receiver’ (incoming > .5) or a ‘relay’ (outgoing = incoming) (Kotter and Stephan, 2003). As the respective nomenclature of each type suggests, sender nodes are functionally responsible for transmitting to other nodes in the graph; receiving nodes are responsible for collecting transmissions; and relay nodes are responsible for trafficking incoming and outgoing signals on to their final destinations.

Although the above measures are an important tool for understanding the structural and functional properties of graphs in very general terms, they are somewhat limited in their ability to offer finer grade observations (Costa and Sporns 2005). One example of this limitation is the fact that multiple nodes within a network can share the same node degree; likewise, there is an infinite number of network structures, all of which displaying different functional consequences that nonetheless possess identical degree distributions. As such, said measures are not sufficient for characterizing the uniqueness of local connectivity within and across networks in a discriminative way (Costa and Sporns 2005).

In order to deal with this limitation, researchers have recently developed a new measure called a hierarchical degree. The purpose of this measure is to take into consideration how a single node is connected to neighborhoods of nodes across several hierarchical levels. A hierarchically-nested neighborhood of nodes is defined as the set of nodes that can be reached from a single node in *d* number of steps (da Fontoura Costa and Silva 2006). This set of nodes is labeled as Rd(i), where:

R = the ring of nodes constituting the hierarchical neighboring nodes of node i
d = the number of steps
i = the reference node located at the center of the ring.

The first hierarchical neighborhood level consists of the set of nodes that are directly linked to the reference node i. In this case, the hierarchical degree and the node degree are capturing the same network properties. Once the initial set of neighboring nodes is defined, subsequent sets of neighbors can be calculated as Rd+k(i) where d+k equals steps d+1, d+2…d+3, d+k. Or, in other words, the second level hierarchical neighborhood consists of the set of nodes that can be reached by the reference node i in two steps; the third level, in turn, is comprised of those nodes that are located three steps from the reference node i; etc. In hierarchical terms, the hierarchical out-degree is defined as the number of edges directed from a lower-level ring (i.e. Rd(i)) to a higher-level ring (Rd+1(i)). Likewise, the hierarchical in-degree is defined as the number of edges directed from Rd+1(i) to Rd(i).

Somewhat like classifying individual nodes a sender, a receiver, or a relay, one can classify a reference node as either converging or diverging (Costa and Sporns 2005). This is done by calculating what is called a divergence measurement using the equation:

$$Dd\,(i) = \frac{nd+1\,(i)}{hd\,(i)}\,.$$

Where: Dd(i) = the measure of divergence between Rd(i) and Rd+1(i)
$nd+1\ (i)$ = the number of nodes in Rd+1(i)
$hd\ (i)$ = the number of edges between nodes in Rd(i) and nodes in Rd+1(i)

The value of this measure is that it can indicate the degree to which links leading away from a reference node are either converging or diverging as one moves across hierarchical neighborhoods. For example, if there are 4 nodes in $R2$, and 6 edges extend from $R1$ to $R2$, this indicates that some nodes in $R1$ connect to more than one node in $R2$. As such, the local connectivity found at R1 is converging onto fewer nodes in R2. If, on the other hand, there were 6 edges from R1 connecting to 6 nodes in R2, then the local connectivity would be said to be diverging as the distance from the reference node increases.

Section 2.2.: Path-related descriptive statistics

A path is defined as a connection between two nodes that is comprised of a finitely ordered sequence of unique edges and intermediate nodes. Or, in other words, where as an edge is a *direct link* between two nodes, a path is an *indirect link* between two nodes that is provided by a series of intermediaries. Using the concept of a path, one can calculate what is called a path length. In the case of binary graphs, the length of a path is coterminate with the minimal number of edges needed to connect the pair of nodes being considered. In weighted graphs, the shortest path length is equal to the summation of the edge weights with the largest quantitative value. Or in other words, the larger the value of the edge weight, the shorter the distance between the two edges. Further, a path that ultimately leads back to the starting node is called a cycle. Further still, a graph is defined as fully connected if all pairs of nodes comprising it can be linked by a path of finite length.

In the case of weighted networks, one can also take into consideration the direction of the associated edges comprising the paths between a set of nodes to identify what are called motifs. A motif is a descriptive statistic that categorizes clusters of nodes into typologies based upon the various combinations of directional values their connecting edges take on. For example, there are 13 different ways to connect three nodes in a directed graph; once these are known, it possible to then to deconstruct a network into the component motifs that serve as building blocks for the larger whole (Sporns and Tononi 2007). The benefits of identifying both type and frequency distribution of the motifs comprising a network stem from the fact that both of these measures can play a significant role in influencing the nature emergent properties arising from the dynamic processes taking place on the graph. Indeed, as both Prill and colleagues (2005) and Zigulin (2004) have recently shown, the periodicity and chaotic dynamics of biological systems are directly tied to both the presence and frequency distribution of specific types of motifs.

Section 2.3: Cluster-related descriptive statistics

A clustering-related statistics measure the degree to which a graph's nodes cluster into densely connected modules. Here, a module is defined as a set of nodes that share greater numbers of mutual connections within the set and fewer connections between other sets of nodes (Sporns 2011). A common indicator of this type is called the clustering coefficient. The local version of this measure is found by dividing the number of existing edges between an individual node and its neighboring nodes by the total number of edges that could hypothetically exist if the node was fully connected. Instead of pertaining only to a single node, the global clustering coefficient measures how densely connected the overall graph is; this measure is calculated by taking the average of the individual local clustering coefficients. As was the case with the degree measure for individual nodes, one can also calculate a hierarchical clustering coefficient (Costa and Sporns 2005; da Fontoura Costa and Silva 2006). This coefficient measures the amount of clustering existing within a hierarchical neighborhood and thus allows for the analysis of the clustering of nodes surrounding a node of interest.

The clustering coefficient is an important measure for several reasons. First, a densely connected set of nodes exhibit a considerable degree of robustness. In short, this means that it is possible for individual nodes or edges to be randomly deleted and the overall structural or functional properties of the network will remain intact (Bullmore and Sporns 2009). The reason for this is because the density of connections allows for the possibility of alternate pathways that can reroute an interaction to avoid 'dead ends.' An example of this property that is commonly cited in the literature is the internet; e.g. many servers and connections can fail, but the world-wide web continues on. Second, and especially in the case of biological networks, highly clustered nodes make it possible for functional specialization to occur (Barabási and Oltvai 2004; Yook, Oltvai et al. 2004; Chagoyen and Pazos 2010). Here, the term functional specialization refers to the ability of subnetworks of a larger graph to engage in interactions that are unique from those engaged in by other subnetworks embedded in the same larger graph. I will elaborate further regarding why this is the case below during my discussion of the application of graph theory to neuroscience.

Section 2.4: Degree and Path Measures Combine to form Measures of Hubs and Centrality

In section 2.1 I noted that high-degree nodes can exhibit a considerable amount of influence over other nodes in a graph; similarly, I noted in section 2.2 that short path lengths mean that it is possible to get from one node to another in a few number of steps. These two descriptive measures can be combined to form ~~a~~ concept called centrality. Generally speaking, the concept of centrality refers to the degree that a node exerts an influence over the flow of information within a network (Sporns 2011); e.g. highly central nodes exert a lot of influence, while low central nodes do not. One specific type of centrality is called closeness centrality; this measure is calculated as the inverse of the average path length between a node and all other nodes in a graph. In this case, high closeness centrality means that the associated node is able to exert an influence over any other node in the network through a relatively few number of steps. As such, a high closeness central node may functionally act as a proverbial orchestra conductor that coordinates the dynamics of an entire graph. Another type of centrality is called betweeness centrality; a node with high betweeness is one that a large proportion of shortest pathways must pass through on their way to their final-node destination. Functionally speaking, a high-betweeness node is one that is capable of controlling information flow due to the fact that is structurally serves as a gateway to other node. Following Bullmore and Sporns (2009), high closeness centrality nodes will be called provincial hubs and high betweeness centrality nodes will be called connector hubs.

Section 2.5: Classifying a graph's topology

The final aspect of graph theory that I want to discuss is how one can classify the topology of a graph as either a lattice, random or small-world based upon how it is constructed and the presence of different combinations of the above descriptive statistics (Barabási and Oltvai 2004). A lattice graph is characterized by a highly ordered pattern of connections between nodes. Arguably the most common examples of this type of graph are the ring lattice and the grid lattice. The former of these consists of a ring of nodes with each node connected to both its nearest and n+1 neighbor by a single edge. The latter gird lattice consists of a set of nodes arranged into a series of equal sized columns, with each node connected to its four cardinal neighbors. Due to these structural features, lattice graphs are characterized by completely homogenous degree distributions, high clustering coefficients, and long path lengths.

A random network is constructed by starting with a completely disconnected set of nodes and repeatedly drawing edges between pairs with a uniform probability (Barabási and Oltvai 2004). The reason that this graph is called random is because the probability that any two nodes will be connected is constant across iterations and is completely independent of previous selections. Unlike lattice graphs, random graphs are characterized by low clustering coefficients and short path lengths. Interestingly, a ring lattice graph can be transformed into a random graph by randomly selecting a node and rewiring its edge to another randomly selected node.

Finally, a small-world graph is characterized as having a high clustering coefficient and a short path length (Barabási and Oltvai 2004). Like random graphs, small-world graphs can also be created by rewiring a ring lattice graph. Indeed, if one were to create a continuum defined by the probability that a pair of nodes would be selected for rewiring, the lattice graph would represent one end of the continuum (where the probability equals zero) and the random graph would represent the other end (where the probability equals zero). The small-world graph, in turn, is formed when the probability is in between these two extremes. As a consequence of this rewiring a small-world maintains aspects of the highly-ordered lattice graph in the form of locally clustered modules, while also taking on features of the random graph in the form of a few long-distance connections between these modules. The former of these tendencies generates the high clustering coefficient and the latter generates the short path length.

As was noted in the introduction to this chapter, different types of graph topologies exhibit different types of emergent structural characteristics and dynamics. In the case of the small-world topology, there are four properties that I want to highlight. First, transportation networks possessing a small-world topology are extremely efficient at moving goods or transmitting information/signals between nodes (Li, Xiong et al. 2006; Jiang 2007; Jiang 2008). In other words, this means that these networks can move things across a network in a minimal number of steps; in those situations where there is an associated cost with 'wiring the network,' e.g. creating an edge between nodes, efficiency also refers to the fact that a small-world network topology are relatively cheap to construct. Second, the small-world typology allows for both differentiation and integration of biological-related structural-functional processes (Sporns 2006). As was noted above, structural-functional differentiation emerges as a consequence of the high-clustering/modularity of small-world networks, while the integrative capacity emerges as a consequence of the occasional long-distance link between modules. Third, in those situations where the nodes of a network are comprised of oscillators, a small-world typology greatly enhances the ability for the entire network of nodes to synchronize their oscillatory dynamics (Watts 2003). And finally, small-world networks are extremely robust to failure due to the random removal of nodes or edges; or, to put it another way, a small-world network can withstand a considerable amount of breakdown before the associated emergent properties disappear (Watts 2003). As will be discussed in the next section, small-world networks and their associated emergent characteristics are an important part of normal brain function.

Part II: The Applicability of Graph Theory to Neuroscience

In order to use graph theory to examine the human brain, one must first define in biological terms the content that will constitute the network's nodes and edges. In the case of large-scale brain networks, both of these measures can be defined in structural, functional, or effective terms (Bressler and Menon 2010; Sporns 2011).

Section 1: Defining Structural Connectivity Networks

In the case of structural connectivity, a "node" is defined as a specific brain region using the anatomical landmarks (e.g. fissures and gyri) and cytoarchitecture (e.g. neuron types, receptor density) discussed in chapter 4. For example, the dorsal medial prefrontal cortex, the amygdala, and the anterior cingulate cortex are all commonly labeled as nodes in neural network analyses (Sporns 2011). The edges of structurally defined connectivity networks, in turn, consist of the long-range axonal-fibers that transverse from one region of the brain to another that were also discussed in chapter 4. Because neurons only fire action potentials in a single direction, structural connectivity networks can be specified as directed graphs; e.g. the source node is the brain region that generates the action potential, and the destination node is the brain region that receives it.

The recent development of diffusion tensor imaging has greatly improved the degree to which one can determine the topological properties of structural connectivity networks (Sporns 2011). Diffusion tensor imaging uses magnetic resonance imaging (MRI) technology to map the neural connections between regions of the brain. This is done by tracing the diffusion of water molecules found in an axon's myelin sheath from the cell's source to its destination. DTI works by taking advantage of several atomic processes. First, hydrogen atoms will naturally align themselves in parallel with the gradient of a magnetic field. Second, a very small portion of hydrogen atoms will not align themselves in such a manner in the presence of a magnetic field. Third, this small portion of atoms can be forced to align in parallel if they absorb a sufficient amount of energy. Fourth, the small portion of atoms will release this energy and return to their original state once the magnetic field is removed. This released energy can then be detected as an electrical signal. And finally, atoms naturally diffuse in space; this tendency was already discussed in chapter 2. By generating a magnetic field around the brain, delivering a burst of energy, and then removing the magnetic field, it is possible for an MRI machine to 'tag' the location of hydrogen atoms in the brain. By repeating this process over time, one can then trace the 'tagged' hydrogen atoms as they diffuse along the myelin sheath. Because the myelin sheath runs parallel to the axon (see chapter 2), it is thus possible to 'trace' the axon from one brain region to another.

Section 2: Defining Functional Connectivity Networks

There are two ways one can define a functional connectivity network. In the case of the first, a 'node' is defined as a brain region that displays a significant change in biological activity *while an individual is engaged in cognitive acts* (Bressler and Menon 2010). Further, an edge is this first case is said to exist between two nodes if the changes in activity of each are statistically correlated with each other (Sporns 2011). Here, an unweighted network edge is defined simply by whether or not the correlation is statistically significant. Likewise, the edge of a weighted network is represented by the strength of the correlation (e.g. the stronger the correlation, the 'heavier' the weight). As an example of a functional network, recall from Chapter 4 that the prefrontal cortex and the amygdala co-activate whenever an individual attempts to deliberately suppress the experience of a negative emotion. Given this relationship, these two regions would be considered nodes in a functional network and the statistical significance of the co-activation would represent the edge.

In the case of the second definition of a functional connectivity network, *nodes* are defined as the totality of brain regions that demonstrate correlated *base-line metabolic activity* (Sporns 2011); functional networks of this type are called either resting-state functional connectivity networks, or intrinsic connectivity networks. The brain's base-line metabolic activity is defined as the constant and spontaneous changes in the membrane potential of neurons.[6] At the local level, current empirical and theoretical research suggests that this spontaneous activity is functionally responsible for establishing and maintaining a constant balance between excitatory and inhibitory input into a neuron. The importance of this functional balance, in turn, is related to the fact that it creates dynamic balance that can easily transition from rest to either full excitation or full inhibition when needed. At the more global level being discussed here, it is argued that synchronized base-line metabolic activity facilitates the rapid transition between different functional states underlying different cognitive processes (Bresller and Menon 2010). Like the first type of functional network, the edges of resting-state networks are defined by either the presence or strength of correlations.

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[6] Amazingly, despite representing only 2% of an adult's weight 16%-18% of the calories consumed per diem are used to fuel this constant activity, while roughly only 2% of these calories are used to fuel deliberately invoked cognitive tasks (Raichle, MacLeod et al. 2001)

Two important technologies for measuring functional connectivity are called electroencephalogram (EEG) and functional magnetic imaging (fMRI). An EEG works by recording the voltage generated by the electrical currents that flow during the synaptic excitation of dendrites (Bear, Connors et al. 2007). This is done by placing electrodes upon the scalp in key positions and measuring the change in activity in the brain underneath. As was noted in Chapters 2 and 3, a change in electrical activity is functionally related to sensory processing, memory, attention, etc. As such, it is argued, by measuring changes in electrical activity one is measuring the neurological correlates of consciousness, thinking, etc. as they unfold in real time. An fMRI in turn, measures changes in oxygen levels in the blood. According to current understandings, a transient increase in neural activity results in both an increase in the amount of oxygen consumed from the blood located in the regions surrounding the active cells and an the amount of blood being delivered to the same area (Cacioppo and Berntson 2005). Given this relationship, it is argued that a change in the ratio of deoxygenated-blood to oxygenated-blood in a brain region is strongly correlated with changes in neural activity. Further, because hydrogen in deoxygenated blood displays a different magnetic resonance than it does in oxygenated blood, it is possible to detect this change using the magnetic resonance imaging technology discussed in section 3.1. Once again, because changes in neural activity is theorized to underlay changes in sensory and cognitive processes, this measure, although an indirect indicator of neural activity, is argued to capture the neurological foundations of mental processes.

Section 3: Defining Effective Connectivity Networks

Finally, and in a similar fashion to functional connectivity, effective causality networks are comprised of nodes that represent brain regions displaying changes in activity and edges denoting statistically significant relationships. The important difference, though, is that effective networks further employ specialized modeling techniques to determine causality between nodes. One such technique is called Granger Causality, which uses time-lagged linear regression analysis to assess the amount of information about the future state of one brain region that is gained by taking into account the past states of other regions (Sporns 2011). Given that 'causes' must precede 'effects', this method establishes directionality by determining which nodes provide the highest predictability for others in the network.

Section 4: Integrating Structural, Functional, and Effective Definitions

Although one typically finds in the neuroscience literature a tendency for researchers to classify neural networks using only one of the above criteria, it is becoming increasingly popular to combine measures to create a more accurate and robust representation (Greicius, Supekar et al. 2009). For example, one could imagine a situation involving a functional connectivity network comprised of three nodes. Because all three of these nodes would be involved in generating the same cognitive process, the functional dynamics constituting each node would be statistically correlated with every other node in the network. It may be the case though that the three nodes are structurally connected as a linear chain whereby the first and last brain regions do not directly interact. Or, to put it another way, nodes 1 and 3 are statistically correlated because of a shared interaction with node 2. To clarify this situation, then, one could combine DTI and a functional measure to discern the structural typology of the functional network. Moreover, one could then further use Granger Causality to transform the undirected structural-functional network into a directed network. Doing this would in turn provide insights into the causal dynamics responsible for generating the cognitive processes under analysis. As a consequence of combining all three measures, then, one would produce a relatively complete large-scale anatomical and physiological model of the biological pathways in question.

Section 5: Examples of Graph Theory Applied to Brain Networks

Having established how one can state neurological systems in graph theoretical terms, I will now turn to discuss the biological significance of the network concepts of clustering, hierarchical clustering, hubs, and small-world typology. Toward this end, I will briefly review a handful of studies that have utilized graph theory to gain insights into the structural and functional organization of the brain.

The first of these studies was performed by Sporns et al (2007). In this experiment, the authors constructed a structural connectivity network of the macaque and cat cortex by treating physical markers of the brain as the nodes and the afferent and efferent fiber pathways as edges. After constructing each network they then calculated the node degree distribution, motif classes, betweeness centrality, and closeness centrality measures; once identified, they then used the combination of these measures to detect the presence and functional relevance of provincial and connector hubs. Regarding the general characteristics of the resulting neural networks, Sporns et al (2007) found that both the macaque and cat cortices were fully connected; contained a high fraction of reciprocal pathways; exhibited node degrees that varied over a very broad range of values; and possessed both the high clustering and short pathway lengths that characteristic of a small-world topology. Further, a cluster analysis of both species' neural networks revealed the presence of subgraphs that functionally corresponded to the visual, sensorimotor, auditory, and prefrontal regions.

The motif concept was already introduced in Chapter 3 at the level of the neural circuit to model the different ways neurons can structural connect to generate different functional responses. At the level of large-scale neural networks, motifs have been used to help understand evolutionary development of the vertebrate brain (Sporns 2011). Careful cross-species comparisons of neural structures and functions have revealed that the complexity of capacities attributable to mammals emerged by building and/or elaborating upon existing neural patterns found in simpler animals. Or, to put it another way, evolutionary processes did not create new nervous systems de novo for each new species; instead, more complex systems were developed by tweaking, rearranging, or expanding upon existing properties. In this context, a motif is defined as a specific network topology comprised of M nodes and a set of directed edges. A motif class is defined as a specific combination of directed links between the M-number of nodes. A motif frequency spectrum, in turn, is defined as the total number of possible structural combinations for a given set of M nodes. For example, there are 13 different ways one can connect 3 nodes using directed edges. Finally, a functional motif is defined as specific pathways within a single structural motif class that can be exploited communicate between edges.

Regarding the detection of motif fingerprints, Sporns et al (2007) found that the spectrum of motif types exhibited in the macaque and cat brain to be highly correlated (r^2 .88, p<10^-5); moreover, they also found an overabundance in both cases of the motif type M3/9. Here, the term 'overabundance' refers to the fact that, when compared to either random or lattice networks, the difference in the frequency of this motif class in the macaque and cat is statistically significant. Moreover still, they also found that the majority of the M3/9 motif type was located in the visual and polysensory association areas of both species cortices. Despite these strong similarities though, important differences existed as well; for example, the macaque cortex also exhibited an overabundance of M3/12, while the cat cortex showed an overabundance of m3/4, m3/8, and m3/11 motifs. Interestingly, the neural network of the roundworm C. elegans exhibits a very different motif frequency spectrum; indeed, although equally distinguishable from both random and lattice structural topologies, the neural network of this very simplistic animal exhibited instead an overabundance of motif classes M3/4 and M3/6. Moreover, the frequency of M3/9 motifs in the C. elegans did not significantly differ from the random and lattice network controls (Sporns and Kotter 2004).

Such a finding begs the following question: why is motif class M3/9 predominantly found in more evolved species and evolutionarily conserved across mammialian species? In an attempt to shed light on this question, Sporns et al performed a series of simulations to detect which structural motifs are most predominately found in network topologies that have been optimized to provide a large number of functional motifs with a minimal number of connections. According to their results, the M3/9 motif is one of a few motif classes that predominately occur as a consequence of these requirements. Given this, Sporns et al. (2007) argue that the M3/9 motif is heavily selected for due to its ability to provide a considerable amount of functional variety while minimizing the biological costs associated with wiring neurological networks.

Finally, Sporns et al. determined that the brain regions that are most frequently a part of M3/9 and, to a lesser degree M3/13motifs are also topological hubs. In the macaque cortex, these regions included areas found in the parietal cortex, dorsolateral prefrontal cortex, the posterior cingulate cortex, and the insula. Importantly, all of the areas have long been known to be functionally involved in polysensory or multimodal association areas. After identifying the hubs of each species' cortex, Sporns et al next classified each as being either a provincial hub or a connector hub; two results that devote particular attention to are the brain regions V4 and 46. According to their analysis, area V4 is a provincial hub due to the large presence of short, intra-modual connections between various aspects of the visual system; similarly area 46 was classified as a connector hub due to the vast majority of its connections being between multiple modules.

Importantly, the reason Sporns et al. (2007) chose to highlight these two brain regions is because there is a strong correspondence between their hub-type and the functional processes they engage in. Indeed, the V4 region in the macaque is functionally responsible for integrating different aspects of visual stimuli processed throughout the visual system into a coherent representation; e.g. binding the color, texture, and shape of an object into a unified experience. Similarly, area 46 is functionally responsible for gathering information about the organisms current state, the current state of the external environment, and the organisms current goals; maintaining this information in working memory; and using it to coordinate future actions and/or predict rewards. Given that the entirety of this information is located across multiple regions of the brain, it is clear why area 46 would structurally consist of a hub with a large number of inter-module links.

In summary, this first review highlights several key points. First, the overabundance of specific motif fingerprints indicates that the structure of the mammalian cortex, even in lower animals such as the cat and the macaque, is non-randomly organized. Second, many aspects of this non-random structural organization are strongly conserved across species within the mammalian class. Third, the non-random structural properties of neural networks are strongly related to the functional properties associated with the brain regions comprising the network. Fourth, the most common structural motifs found in the more biological and behaviorally complex animals are optimized to provide a large number of functional motifs with minimal wiring costs. And finally, differences in structural properties clearly distinguish between functionally distinct regions of the brain.

Motivated by the explanatory success achieved by animal models such as those just described, researchers soon turned to applying similar techniques to the human brai. In one such study (Hagmann, Cammoun et al. 2008) used diffusion and fMRI to construct an adjacency matrix of the neurological nodes and edges comprising the human cerebral cortex, and then calculated for each node the following network measures: degree, strength, betweeness centrality, and efficiency. Similar to the macaque and cat cortex, these initial descriptions showed that the human cortex exhibits the high-clustering and short path lengths that are characteristic of a small-world topology, as well as broad distribution of node degree and node strength values. Also like the macaque and cat cortices, the human cortex demonstrated the tendency for both provincial and connector hubs to be structurally located in areas known to play a functional role in monosensory and polysensory information.

An important component of the Hagmann and colleagues (2008) article is that the researchers used graph theoretical tools to identify a structural core of highly and mutually connected brain regions. To accomplish this task, Hagmann and his associates performed what is called a *k-core decomposition* of the human cortex adjacency matrix. A k-core is defined as the largest subgraph of a network that is completely comprised of nodes possessing a degree of at least k. K-core decomposition, in turn, is the process by which nodes possessing a degree less than k are removed until only the nodes with k degree remain. As a result of this analysis, Hagmann et al found the precuneus, the posterior cingulate, the isthmus of the cingulate, and the left and right paracentral lobules to be the brain regions that comprise the k-core of the human cortex. Along with performing the k-core decomposition, the researchers also performed what is called an s-core decomposition; this procedure is identical to the k-core decomposition, accept that it is based upon node strength and not node degree. In this case, the s-core was comprised of the posterior cingulate cortex, the precuneus, the cuneus, the paracentral lobule, as well as the superior and inferior parietal cortex as comprising the structural core.

After decomposing the cerebral network in the manners just discussed, Hagmann and colleagues next used *spectral graph partitioning* to identify intrinsic modules embedded within the larger neural network; this technique employs a specific algorithm that is designed to group collections of connected nodes in such a way that "optically matches the intrinsic modularity of the network (p1482)." The result of this partitioning produced six modules: four of these were located within the frontal and temporoparietal areas of each hemisphere; one centered on the posterior cingulate cortex; and another centered on the precuneus/pericalcarine cortex. Having established the connectivity patterns denoting the structural core and modules of the human cerebral cortex, Hagmann and colleagues completed their analysis by identifying which brain regions served as provincial and connector hubs. According to the authors, connector hubs were, without acceptation, located along the medial axis of the cortex; moreover, the vast majority of the connector hubs were found to be located in the posterior medial and parietal cortex. Provincial hubs, in turn, were located in the frontal, temporoparietal, and occipital modules. Interestingly, 70% of the total between-module edges pass through the two medial hubs.

Like the Sporns et al (2007) article, the importance of Hagmann and colleagues (2008) stems from its ability to demonstrate several key points. First, graph theory can be utilized to extract important information about the structural and functional organization of the human cortex. Second, the neural network comprising human cortex is structurally organized as a small-world topology. Third, this small-world topology allows for both the segregation and integration of functional processes. And finally, the small-world topology is evolutionarily conserved across species within the mammalian family. This last point raises the following question: given that the small-world topology in general and the combination of functional segregation/integration in particular is such a prevalent feature in the structural organization of the mammalian brain, what happens when this topology is altered due to physical damage or illness? Simulations have attempted to answer this question by selectively deleting nodes and edges from models of actual neural networks (Sporns 2011); generally speaking, these studies have revealed the following patterns: 1) As should be expected from a small-world network, the removal of randomly selected edges and nodes has little consequence on the global topological properties of a neural network; the targeted removal of hubs and bridges, though, rapidly degrade the topological organization of the brain; 2) the consequences that stem from the removal of a hub depend upon whether it is classified as provincial or connector; specifically, the deletion of connector hubs increases the small-worldness of the global topology by increasing the isolation of the densely connected clusters, while the deletion of provincial hubs reduces small-worldness by reducing the clustering modules; and 3) the removal of node and edges from modules located along the anterior-posterior midline axis significantly impacts the strength of connections between nodes located within and between other modules, while the effects of node and edge deletion in sensory/motor related modules remained within the affected region.

In an attempt to ground these simulation results in real-world data, a number of researchers have recently begun to investigate how changes in the structural organization of the human neural network correlates with changes in the functional capacities of patients diagnosed with neural degenerative illnesses and/or mental illness (Buckner, Sepulcre et al. 2009). Interestingly, many of the effects seen in the simulations are also observed in these empirical cases. For example, Zhou and colleagues (Zhou, Greicius et al. 2010) examined how behavioral variant frontotemporal dementia (bvftD) and Alzheimer's disease (AD) differentially degrade neural networks in the human brain, as well as how each respective pattern of degradation differentially affects patient's cognitive capacities. BvftD is a degenerative disease that primarily attacks a network comprised of the anterior cingulate cortex, the frontoinsula, the amygdala, and the striatum; according to emerging research, this network is significantly involved in the generation, detection, and processing of self-conscious emotions, moral emotions, and empathizing with the emotional states of others. AD, in turn, targets a posterior hippocampal-cinculo-temoral-parietal network involved in episodic memory, visualspatial imagery, and navigation. As will be discussed in greater detail below, these two networks are functionally anti-correlated; in short, this means that the activation of one decreases activity in the other. Although the exact details remain to be fully elucidated, early studies indicate that shared connections play a role in these dynamics.

According to Zhou and colleagues analysis, patients diagnosed with bvftD displayed reduced connectivity between the nodes of the emotion-related network; in terms of psychological effects, this structural alteration resulted in degraded self-representations of emotion and emotion related social behaviors. The researchers postulate that this effect is due in particular to reduced connectivity between the frontoinsula and other nodes in the network; the reason for this is because this brain region is believed to act as a critical hub that "anchors subjective awareness through multichannel integration of contextual, hedonic, homoeostatic, and interoceptive processing streams" carried out by the other nodes of the emotion network. Along with this, Zhou and colleagues also report that bvftD patients displayed an increase in the strength of connections within the anti-correlated posterior hippocampal-cinculo-temporal-parietal network. Moreover, this increase in connectivity strength positively correlated with an increase in the associated psychological processes related to visuospatial imagery. And finally, although Seeley et al do not categorize the frontoinsula hub as a connector hub, it is interesting to note that damage to this brain region resulted in an increase in the small-worldness of the over-all topology of the brain network.

In the case of AD the effect was the mirror opposite; here, the progression of the disease decreased connectivity in the posterior hippocampal-cingulo-temporal-parietal network and increased connectivity in the frontoinsula emotion-related network. At the psychological level, this pattern of degeneration resulted in the degredation of capacities related to episodic memory, navigation, and visulspatial imagery, as well as an increase in emotion detection, emotional self-representation, and emotion-related social behavior. Once again, although Seeley et al did not classify the typology of the hubs located in this brain region, it is important to note that damage to this area decreased the small-worldness of the overall brain network.

Part III: Summary and Conclusion

The goal of this chapter was to explain how graph theory can be applied to the brain regions and pathways discussed in Chapter 4 in order to identify the sui generis properties that emerge out of interactions between brain regions. Interestingly, an increasing amount of emerging empirical research is demonstrating that structural, functional, and resting-state definitions of neural networks are all capturing different dimensions of the same thing. In other words, brain regions that co-activate during cognitive tasks are also correlated in the resting-state and, moreover, are either directly or indirectly connected through afferent or efferent pathways. Given this pattern, researchers have largely concluded that structural and functional connectivity patterns observed in the resting-state, as well as during the performance of a task, represent biologically distinct networks that are functionally responsible for carrying-out specific kinds of processes. Generally speaking, networks such as these are called intrinsic connectivity networks. In Chapter 6 I will examine how the functional responsibilities of three of these networks are directly related to the vast majority of microsociological theory.

Chapter 6: An MDA Analysis of Three Types of Intrinsic Connectivity Networks

Chapter Introduction

According to current empirical evidence, the adult brain possesses between 6 and 10 distinct intrinsic connectivity networks (Deco and Corbetta 2011; Deco, Jirsa et al. 2011). In this chapter I will examine in detail the structural and functional characteristics of three types of ICNs that are commonly referred to as task-positive networks, task-negative networks, and salience-related networks (Deco and Corbetta 2011). The reason that I want to focus on these in particular is because, they collectively represent the neurological foundations of several cognitive processes that micro-sociological theory has identified as important to social interaction (Turner 2002; Burke 2006).

Part I: A Brief Overview of Attention-Related Research

The concept of 'attention' has long played an important role in the philosophical, psychological, and sociological consideration of how humans interact with their physical and social environments (Raz and Buhle 2006). In the early stages of these respective analyses, attention was defined in very general terms as the mental act of selecting aspects of the environment for explicit conscious processing (Posner 1990). Largely beginning with William James, though, modern research has increasingly recognized the analytical and empirical existence of a spectrum of attention types ((Posner 1990; Raz and Buhle 2006). For example, it is now common-place to see in the cognitive psychology and cognitive neuroscience literature distinctions between exogenously-focused attention and endogenously focused attention (Fox, Snyder et al. 2005; Golland, Bentin et al. 2007). The former of these involves an organism selecting aspects of their external environment for explicit conscious processing (i.e. objects, sounds, temperatures, etc.); variants of this type of attention are the hallmark of task-positive networks. The latter, in turn, involves the explicit conscious processing of stimuli located in the organism' s internal environment (i.e. thoughts, memories, emotions, visceral sensations, etc.); variants of this type of attentional processing are the hallmark of task-negative networks and will be discussed in Part II.

Other classes of attention are traditionally referred to as alerting, orienting, and executive (Raz and Buhle 2006). Generally speaking, alerting-type modes of attention are functionally responsible for increasing and sustaining response readiness in preparation for an impending stimulus. Orientating attention, in turn, is defined as the ability to overtly or covertly select specific information from among multiple sensory stimuli for explicit consideration. Here, overt orientating attention consists of moving one's eyes until the desired object is within one's field of view. The covert orienting of attention involves the shifting of one's focus to an object without moving one's eyes. A common example, of covert attention would be attending to something one's peripheral vision while keeping one's eyes looking straight ahead. And finally, executive attention is the 'ability to monitor and control the information processing necessary to produce voluntary action (Fernandez-Duque, Baird et al. 2000).' One example of this form of attention include the ability to monitor for and resolve conflict and errors during planning and decision making; executive attention also facilitates the accomplishment of novel or unrehearsed actions; the successful accomplishment of difficult tasks; and tasks that require overcoming habitualized responses to stimuli (Raz and Buhle 2006).

Along with investigating differences in types of attentions, researchers have also recently begun to examine the functional role played by attention during the specific cognitive and behavioral acts of emotional regulation, self-regulation, effortful control, inhibitory control, and working memory. Specifically, research focusing on emotional regulation examines how attention can interact with emotion-related processes to reduce, enhance, or maintain the phenomenological experience of feelings such as fear, anger, happiness, guilt, shame, disgust, pain, or pleasure (Ochsner 2010).

Similar to emotional regulation, research on self-regulation, effortful-control, and inhibitory-control examine how attention enables individuals to reduce, enhance, or maintain constant the probability that an individual will or will not engage in particular cognitive or behavioral acts . In terms of the field of psychology, research examining will-power, addiction cravings, and the inability of certain mental illness diagnoses to control negative thoughts are strong examples of these processes. Further, and although their postulated mechanisms are not typically framed in terms of attention, sociological and criminological research that focuses on the relationship between a lack of self-control and a willingness to engage in deviant acts is an excellent example of these particular attention-related processes as well.

Finally, working memory is defined as the ability to maintain and manipulate information 'online' in the absence of incoming sensory or motor stimulation (Corbetta and Shulman 2002). Functionally speaking, working memory has been repeatedly shown to be positively correlated with general intelligence due to its involvement in accessing goal-relevant information as needed to support complex cognition (Broadway and Engle

2010). Or, in other words, higher-capacities for working memory are positively related to levels of general intelligence due to the formers ability to provide greater 'mental processing power' to the kinds of activities measured by the latter. According to extensive psychological research, attention is meaningfully related to working memory to the degree that it maintains access to stimuli and goals that may not be currently present, as well as provide a buffer against distractions or habits that could disrupt working-memory related processes (Broadway and Engel 2010).

In tandem with this theoretical development, there also occurred an evolution in the methodological techniques used to study attention as well. In the early days of attention research, the primary methodology employed was called chronometry (Posner 2005; Raz and Buhle 2006). In short, chronometry is an experimental design that purported to measure and assign reaction times to the neurological activity underlying cognitive processes. By controlling both the nature of the stimulus and the response, it was believed that one could detect variations in the cognitive processes involved by detecting differences between the application and the stimulus. For example, one of the original applications of this technique involved applying a small electrical shock to the right foot of a participant and then instructing them to lift their right hand as soon as the sensed it (Donders 1969). This initial test would serve as the baseline measurement. The researcher would then instruct the participant to raise the hand that corresponds to the foot that is shocked; unlike the first test run, the participant is not told a priori which foot will be shocked. In other words, they must first mentally evaluate which foot was shocked and then raise their hand. By subtracting the second response time from the first, then, it was argued that a researcher could calculate the processing time underlying the mental act attentively deciding which foot was shocked and which hand to lift. Although some methodological advancements were made over time (like, for example, adopting more rigorous mathematical models to calculate changes in reaction time), this technique was by and large the methodology for studying attention up until the beginning of the 1950s (Raz and Buhle 2006).

With the development of single-cell electrical recording techniques in the early 1950s, it became possible to directly measure neurological responses to stimuli in the brains of both anesthetized and awake laboratory animals (Raz and Buhle 2006). In short, this methodology involved presenting an animal with a sensory stimulus and then mapping which neurons in the brain changed their activity in response. For example, by subtly changing various characteristics of a visual stimulus, i.e. its size, shape, color, direction and speed of movement, it was possible to chart which parts of the visual system are responsible for representing which aspects of the visual environment. Moreover, researchers could also measure the role of attention and awareness during the processing of sensory stimuli by altering the level of anesthetization of the laboratory animal or by removing portions of the brain. For example, if a brain region responds to a stimulus when an animal is both fully awake and fully anesthetized, then this brain region more than likely does not play a role in generating an awareness of the stimulus. But, if a brain region only responds to a stimulus when an animal is fully awake–and variation in the level of this activity is strongly correlated with the quality of a response– then there is a higher probability that it plays a meaningful role in attention-related sensory processing

(Raz and Buhle 2006). Along with mapping the structure of brain regions involved in attention-related processes, this technique also allowed for the ability to discriminate between ‘bottom-up’ and ‘top-down’ processing of stimuli by determining whether low-order sensory areas or higher-order association areas became active first. Knowledge that higher-order activity could precede lower-level sensory processing provided important insights into how attention, goals, and a priori knowledge of proceeding events can significantly influence if and how sensory information is processed (Raz and Buhle 2006).

Due to the invasive nature of single cell recording, though, it wasn’t until the development of the imaging techniques discussed in Chapter 5 that similar methodologies could be applied to humans. Despite the difference in technology, much of the methodology is the same. In other words, a baseline measurement of an intrinsic connectivity network in the resting state is made; the participant is asked to perform a task; new measurements are taken of the brain areas comprising the network while the participant engages in the task; and finally, differences in activity-levels between the two measurements are compared and functional responsibilities are assigned based upon the observed patterns of activity. These responsibilities are determined by carefully designing tasks that require specific cognitive acts at very specific moments. For example, during the Stroop Switching Task participants show words such as: blue, green, orange, yellow, etc. On certain trials, the participant is told to read the word; on other trials they are told to specify the color of the word; and on still other trials they are alternately instructed to read the word or specify the color. In this case, the need to keep in mind the instructions measures working memory, while the need to override the tendency to read the word when asked to state the color measures self-regulation and response inhibition.

Part II: Structural and Functional Properties of Task-Positive and Task Negative Networks

A major advance in attention related research that has stemmed from the incorporation of neuroimaging technologies is the discovery that discrete intrinsic connectivity networks are functional responsible for different types of attention, or different dimensions of a single form. For example, researchers have repeatedly demonstrated the existence of two sets of attention-related brain regions displaying anti-correlated neural activity (Fox, Snyder et al. 2005). The first of these sets is called task-positive brain regions; the characteristic feature of these areas is that they exhibit increased neural activity during cognitive tasks that require participants to deliberately focus their attention on events occurring in the external environment. In other words, task-positive brain regions are those that play an active role in generating the orienting and executive types of attention discussed above. Brain regions that are commonly identified as comprising the task-positive set include the dorsolateral prefrontal cortex (DLPFC), inferior parietal sulcus (IPS), inferior parietal lobe (IPL), ventral intraparietal sulcus (vIPS), the frontal eye field (FEF), the inferior precentral sulcus, the supplemental motor area/pre-supplemental motor area (SMA/pre-SMA), the MT+, and the insula/frontal operculum (Fox, Snyder et al. 2005; Cole and Schneider 2007). The second set is commonly referred to as task-negative brain regions (Fox, Snyder et al. 2005); unlike their task-positive counterpart, these brain regions exhibit increased brain activity when a participant is allowed to remain unfocused. Generally speaking, this consists of relaxing quietly with their eyes closed and letting their mind wander (Raichle, MacLeod et al. 2001). As such, this network is often called the default mode network because it becomes most active when an individual is not actively engaging with the external world; i.e. it is the default state of activity the brain returns to after engaging in a deliberate attentive task. Although subsequent research has since refined this list, the brain regions originally identified as comprising the task-negative network include the posterior cingulate cortex (PCC), retrosplenial cortex, medial prefrontal, lateral parietal, superior frontal, parahippocampal, and inferior temporal gyri (Fox, Snyder et al. 2005).

Task-positive and task-negative networks are described as anti-correlated because, by-and-large, the level of neural activity in one set is negatively correlated with the level of neural activity in other. In other words, this means that an increase in the amount of attention one pays to the external world is strongly correlated with a decrease in the amount of neural activity found in the task-negative brain regions. Likewise, an increase in the level of neural activity in the task-negative areas is strongly correlated with a decrease in the level of neural activity observed in the task-positive brain regions. It is important to point out, though, that the task-positive and task-negative labels are somewhat misleading for the following reason. Subsequent research occurring after the initial discovery of the task-negative brain regions revealed a subset of areas that increase their neural activity during cognitive tasks involving internally focused attention (Buckner, Andrews-Hanna et al. 2008; Spreng, Mar et al. 2009). Examples of this kind of activity include thinking about one's current physical or mental state; thinking about the physical or mental state of other people; retrieving episodic memories; and envisioning possible future scenarios. Further still, recent research has demonstrated that the task-positive set of brain regions can also be divided into subnetworks according to the specific type of processes they engage in.

Section 1: Structural and Functional Properties of Top-Down and Bottom-Up Attention

Extensive research involving behavioral, neuroimaging, lesion, and electrophysiological technologies has demonstrated that two interacting intrinsic connectivity networks are functionally responsible for two distinct forms of orientating related attention (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). The first of these is called the dorsal attention network and is structurally comprised by the right and left IPS, FEF, SMA/pre-SMA, and MT+ (Fox et al 2006). Because the dorsal attention network demonstrates increased neural activity after the presentation of cues indicating where, when, or to what a participant should direct their attention (Fox et al 2006), the network is argued to be responsible for generating and controlling top-down orientation of attention to external stimuli based upon previous knowledge, expectations, or current goals (Corbbeta and Shulman 2002). Moreover, the dorsal attention network also demonstrates increased neural activity in response to the presentation of highly-salient, but behaviorally irrelevant stimuli (Corbetta, Patel et al. 2008).

According to empirical evidence, the dorsal attention network perfomrs this function by generating, maintaining, and actively employing 'attentional sets' (Corbetta and Shulman 2002). As defined by Corbetta and Shulman (2002), this is a combination of a perceptual set, which consists of the neurological patterns of activity associated with the stimulus (See Chapter 3), and a motor set, which consists of the neurological patterns of activity that are associated with the behavioral response to be directed toward the stimulus once it is detected. Importantly, different aspects of top-down attentional control are carried-out by different regions of the dorsal attention network. For example, in humans, the dorsal PPC appears to be functionally responsible for assembling the associative links between the physical properties of an expected stimulus and the required behavioral response and for dynamically altering these associations at will (Corbetta and Shulman 2002). Similarly, activity in the FEF and the IPS has been shown to be significantly correlated with activity in the visual system, which, in turn, is correlated with the perception of anticipated stimuli. In short, it is believed that these two nodes send a signal to the visual system that alters the alpha rhythm in the area of the visual field where the stimulus is expected to be presented in such a way that biases the visual system in favor of its selection. Recall from Chapter 3 that alpha rhythms gate the flow of visual stimuli into the brain and that the desynchronization of alpha rhythms is strongly correlated with the conscious awareness of stimuli.

A recent experiment performed by Capotosto and colleagues (Capotosto, Babiloni et al. 2009) provides an excellent illustration of the neurological mechanism underlying how attentional sets are utilized. In the first step of their analysis, Capotosto et al. used EEG to record neural activity in the FEF, the IPS, and the occipital cortex (e.g. the visual system) as they performed to tasks. For the first task, the participants were asked to stare at a small white cross located in the center of an otherwise black computer screen. The participants were then instructed that a small rectangle would appear on either side of the fixation cross as a cue for which of the two sides one of four possible stimuli would appear. These stimuli included the letter T, the letter L, an upside down version of the letter T, and an upside down version of the letter L. The participant was then told to press a button with their left hand when they saw either version of the letter T, and to press a button with their right hand when they saw either version of the letter L. Finally, EEG was used to record neural activity in the FEF, the IPS, and the occipital cortex while the participants carried out the task. As expected, the presentation of the cue resulted in the increased activity in both the FEF and the IPS; moreover, this increased activity was strongly correlated with the desynchronization of alpha activity in the area of the visual system that codes for the portion of the visual field where the stimulus was expected to appear; and finally, the level of preparatory activity and desynchronization was strongly correlated with the speed and accuracy of stimulus detection. In the second step of their analysis, Capatosto et al. used transcranial magnetic stimulation (TMS) after the cue and before the presentation of the stimulus to disrupt the neural activity occurring in the FEF and the IPS. The introduction of the TMS had two effects. First, the disruption of neural activity in IPS resulted in a weakened desynchronization of alpha activity in the visual system. Second, the disruption of neural activity in the FEF was correlated with the ability to distinguish right-side-up T's from upside-down L's (and vice versa). Taken together, these results were interpreted to empirically confirm that the IPS is functionally responsible for preparing the visual system to receive anticipated neural signals, while the FEF is responsible for specifying the content of the signal that the visual system should anticipate.

The second intrinsic connectivity network related to external-orientating attention is called the ventral attention network. Generally speaking, the ventral attention network is functionally responsible for detecting and initiating the reorientation of attention to behaviorally relevant stimuli that are currently outside of an individual's attentional focus or appear infrequently (Corbetta and Shulman 2002; Corbetta, Patel et al. 2008). The structural core of this network is comprised of the right ventral frontal cortex (VFC) and the right temporal-parietal junction (TPJ) (fox et al 2005); peripheral components of the TPJ portion of the core include the posterior sector of the superior temporal sulcus (STS), the superior temporal gyrus (STG), and the ventral part of the supramarginal gyrus (SMG). Peripheral components of the VFG portion of the core include parts of the midle frontal gyrus (MFG), inferior frontal gyrus (IFG), the frontal operculum, and anterior insula (Corbetta et al 2008).

Like its dorsal counterpart, the component parts of the ventral attention network exhibit distinct functional responsibilities. For example, Shulman and colleagues (Shulman, Astafiev et al. 2009) used a shift-stay target detection task to determine the unique functional responsibilities of the TPJ and the VFG during bottom-up driven reorientation. A shift-stay target detection task involves the following sequence of events. First, a participant is shown a visual target image and told that they must correctly press a button whenever this image appears on the screen. They are then told that the image will appear in one of two groups of other items that are physically separated from each other by a small white cross. Further, the participant is also told that a cue consisting of a red square will occasionally appear to indicate which group the target will appear. In other words, if the red square appears on the right side of the cross, then, until otherwise indicated by a new cue, the target will eventually appear within the group of items located on the right side of the cross. The subsequent appearance of the cue on the left side of the cross will indicate that the target will then only appear within the group located on the left side of the cross. Finally, participants were told that a 'switch cue' indicating that the target will now begin appear on the opposite side from that which was previously indicated will appear frequently (86% probability), infrequently (14%), or with equal probability as a 'stay cue' (50% probability). After being given these instructions the experiment is then run while fMRI is used to record changes in brain activity.

According to Shulman and colleagues' analysis the TPJ exhibited increased neural activity whenever a 'switch cue' was presented, while the VFG only exhibited increased activity when the presented 'switch cue' was unexpected (e.g. only appeared with a 14% probability). In light of extensive other experiments demonstrating similar results, it was interpreted that the TPJ is functionally responsible for disengaging current attentional focus and resetting the dorsal attention network in preparation to orient attention to another spatial location. The increased activity in the VFG, in turn, was interpreted as acting as a circuit breaker for the behavioral responses being maintained 'online' by the dorsal attention network. The further, Shulman et al argued that the reason the VFG only acted as a behavioral response circuit breaker during low-probability switches is because the behavioral response involved required to carry-out the switch was already being kept online in the higher probability scenarios.

While Shulman and colleagues (2009) conclusion is largely due to inferences from the activation patterns they observed, a similar study by Asplund and colleagues (Asplund, Todd et al. 2010) suggests an actual causal mechanism by which the ventral attention network disrupts the current orientation of the dorsal attention network. In short, their analysis demonstrated that, during periods of top-down attentional control, neural activity in a portion of the VFG is positively correlated with neural activity in the FEF and IPS and negatively correlated with the TPJ. But, as soon as the TPJ increased activity in response to an unexpected stimulus, the VFG disengaged from the FEF/IPS and instead became more functionally integrated with the TPJ. In light of this pattern of activity, Asplund and colleagues (2010) concluded that the ventral attention network 'circuit breaks' the dorsal attention by withdrawing an important contributor to its functional dynamics. Much like the application of TMS discussed above, this disruption, in turn, allows for alternate signals to be processed and, thus, the shift in attentional control.

Section 1.1: Structural and Functional Properties of Task-Control Networks

Beyond facilitating the deliberate orientation of spatial attention, subsequent research has discovered how portions of the dorsal attention network interact with other externally-focused brain regions to establish, maintain, and adjust the control of attention over the course of carrying-out a task. In one such line of research, Dosenbach and colleagues (Dosenbach, Fair et al. 2008) used a mixed-block/event related experimental design to determine these control-related processes. A mixed-block/event-related design is divided into a serious of task-block and control periods. During the task-block period measurement of neural activity are recorded as a participant is presented with three types of stimuli (Visscher et al 2003). The first is called a sustained stimulus and is presented uninterrupted over the entire period. The second is called a transient stimulus; it is only presented intermittently at varying time intervals throughout the task-block period. And finally, the third is called a combined stimulus; it consists of the presentation of both sustained and transient stimuli over the entire task-block. The control block, in turn, consists of the participant engaging in a period of activity that is unrelated to the task being empirically evaluated.

The combination of mixed-block/event-related design and fMRI is an important research methodology because it allows investigators to tease out neural signals that may only participate in a cognitive event at specific moments or for limited periods of time from those that play a functional role throughout the entire period. This ability, in turn, allows researchers to further divide intrinsic connectivity networks into functionally distinct subgraphs that may otherwise be indistinguishable from the functional dynamics generated by the larger whole.

Employing the above experimental technique in combination with fcMRI revealed that two dynamically interacting top-down networks are functionally responsible for performing task-sets. The first of these is called the fronto-parietal control network and is made up by the dorsolateral prefrontal cortex (dlPFC), intraparietal sulcus (IPS), inferior parietal lobule (IPL), precuneus, dorsal frontal (dF), and midcingulate (Fair 2007:13507). Specifically in regard to the task signals identified above, it was found that the dF, IPS, precuneus, and midcingulate regions comprising the frontal-parietal network increased activity in response to the start-cue to initiate the task set; while its IPL and dlPFC portions demonstrated increased activity during the generation of error related/adjustment signals. Importantly, this control network exhibited little-to-no-neural activity related to set maintenance.

The second proposed network, called the cinguloopercular network, is argued to consist of the dorsal anterior cingulate/medial superior frontal cortex (dACC/msFC), bilateral anterior insula/frontal operculum (aI/fO), anterior prefrontal cortex (aPFC), and thalamus. In contrast to the above patterns of neural activity, the dACC/msFC, bilateral aI/fO, and (to a lesser extent) the aPFC portions of the cinguloopercular network demonstrated increases in all three types of task-related activity over the entire duration of the set. Based upon this different pattern of neural activity, it is hypothesized that the fronto-parietal control network is functionally responsible for initiating attentional control in response to indicators for the commencement of a task-set, as well as performing rapid, adaptive adjustments to behavior in response to error-related feedback. Because the associated neural activity is so short lived, it is believed that the error-related information handled by this network is used to make adjustments from one trial to another, or across a limited number of trials (Dosenbach, Fair et al. 2008). In regard to the cinguloopercular network, it is hypothesized that it is responsible for initiating cognitive control at the onset of a task, as well as for processing task-related information across the sequence of iterative trials comprising an entire task epoch (Dosenbach, Fair et al. 2008). This conclusion was based on the fact that its component parts were the only to maintain sustained neural activity.

Section 1.2: Structural and Functional Properties of Working Memory

In a recent empirical study, Cole and Schneider (Cole and Schneider 2007) investigated the ICN network involved in working memory while performing a task. According to the exiting literature at the time, the following brain regions were believed to dynamically interact during an externally focused task that required both working memory and executive control: dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex/pre-supplementary motor area (ACC/pSMA), the dorsal premotor cortex (dPMC), anterior insular cortex (AIC), the inferior frontal junction (IFJ), and the posterior parietal cortex (PPC). The first step of their analysis employed functional connectivity MRI to determine if the often cited brain regions noted above comprise a single functional connectivity network. According to their results, the resting-state neural activity of all six regions showed greater correlation with each other than with other regions in the brain; subsequent analysis further showed that these regions also demonstrated higher-correlations amongst each other during task-related activity than with other regions of the brain. Along with these correlative patterns, distance-based cluster analysis further revealed that the regions comprising this functional connectivity network are more tightly coupled with each other than they are with other regions.

The second step utilized fMRI to measure changes in neural activity while participants engaged in two versions of an experimental technique called a visual search task. During the first phase of a visual search task a participant is shown a screen with a line that is located in one of four boxes and oriented at either 45 or 135 degrees and told to remember the line’s orientation. In the second phase the participant is shown 1 new screen with a different orientated line every second for 10 seconds and is asked to press a button whenever what is seen on the screen matches what they were asked to remember during the first phase. The possible orientations the participant is shown are 0, 45, 90, and 135 degrees. According to the logic of the experiment, 0 and 90 degree orientations are considered distracters because their presence never requires the participant to react. If the target stimulus, e.g. the orientation that requires a response, is 45(135) degrees, then the 135(45) degree orientation is considered a "foil" because it is similar enough to the target to incorrectly cue a response from the participant. The third phase consists of a 32 second period during which the probability that an oriented line would be displayed on the screen ranged from 5% at the beginning of the phase and 55% at the end. In other words, this period consisted of long periods of time during which nothing was displayed. Finally, the last phase consisted of 10 seconds of simply staring at a small cross in the center of the screen. The second version of the visual search experiment is much like the first, but with one small difference; specifically, the participant is shown two oriented lines during the first phase and told that they will need to push a button whenever they see either line. Further, they are also told that the removal of a small cross in the center of the screen will indicate which of the two orientations they need to look for when the next screen appears. Beyond these differences, the two types are identical.

For reasons that will be made clear in a moment, it is important to highlight how each phase utilizes a different type of executive function. The first phase requires the ability to effectively encode into working memory which orientation is the target and what the proper location is, as well as prepare oneself to respond appropriately when the target is seen. The second and third phases require the ability to effectively maintain this information in working memory, use it to evaluate the characteristics of incoming stimuli, deploy the appropriate response, and withhold responses to distractor and foil stimuli. It is also important to note that the second version of the visual search task is more cognitively demanding than the first due the need to keep multiple targets in mind and correctly respond to each individually at the appropriate time.

The fMRI analysis of the participants as they engaged in each version of the visual search task revealed several interesting patterns. First, and as would be expected from a coherent neural network, the entire executive system was involved in carrying-out the empirical task. As was also expected, the brain regions comprising the executive system showed greater activity, and, thus, greater cognitive effort, during the more cognitively demanding version of the task. Second, individual brain regions demonstrated unique periods and lengths of activation; specific combinations of these were determined to reflect different functional contributions to the larger, over-all process. For example, the DLPFC was active during the beginning of the third phase of the task (e.g. the 32 second period of irregular presentations of stimuli); decreased activity during the middle of the second part of the third phase; and then increased activity in the last portion of the third phase. Based on this pattern, as well as other technical details that will not be discussed here, the researchers concluded that this brain region is functionally responsible for converting the visual stimuli associated with encoding the target into a sustainable memory trace, as well as for converting this memory trace into “actionable representations for task performance.” In a similar fashion, the ACC/pSMA only demonstrated an increase in activity immediately before the presentation of a screen during second phase of the switching version of the task. Once again, this and other technical details suggest that the ACC/pSMA is involved in the preparation of the actual motor response. Finally, the DPMC, lateral PPC, and the AIC showed increased activity throughout the entire task; this pattern was interpreted to indicate that these regions are functionally involved in the constant maintained of the related information needed to correctly perform the task.

Part III: Structural and Functional Properties of Default and Internally-Focused Networks

The default network is comprised of eleven brain regions: the anterior medial prefrontal cortex (aMPFC), the posterior cingulate cortex (PCC), the dorsal medial prefontal cortex (dMPFC), the temporoparietal juction (TPJ), the lateral temporal cortex (LTC), the temporal pole (TempP), the medial temporal lobe (MTL), the ventral medial prefontal cortex (vMPFC), the posterior parietal lobule (pIPL), the retrosplenial cortex (Rsp), the parahippocampal cortex (PHC), and the hippocampal formation (HF+) (Buckner and Carroll 2007; Hagmann, Cammoun et al. 2008; Buckner, Sepulcre et al. 2009; Andrews-Hanna, Reidler et al. 2010; Sporns 2011). Topologically speaking, the structural connectivity of the default network is defined by two central hubs (the aMPFC and the PCC) and two sub-networks. The first of these sub-networks consists of the dMPFC, TPJ, LTC, and TempP, and is called the dMPFC system. The second is called the MTL system and is defined by the MTL, vMPFC, pIPL, Rsp, PHC, and HF+ (Leech, Kamourieh et al. 2011).

The DMN network *as a whole* has been empirically demonstrated to be functionally responsible for generating and controlling three broadly defined cognitive states and processes (Stawarczyk, Majerus et al. 2011). The first of these is commonly referred to as the default state. Stated in sociological terms, this state consists of what Alfred Schutz (1967) called duration: a “continuous coming-to-be and passing-away” of undirected thoughts, which is phenomenologically experienced as the constant transition from a “now-thus” to a “new now-thus.” The reason that this mental state is referred to as ‘default’ is because the associated pattern of neural activity is what the brain ‘defaults’ to whenever not engaged in a cognitively effortful task (Raichle and Gusnard 2005; Preminger, Harmelech et al. 2011). The second DMN-related process is sometimes referred to as the sentinel-hypothesis (Buckner, Andrews-Hanna et al. 2008; Stawarczyk, Majerus et al. 2011). This specific pattern of activity is believed to represent a state of ‘watchfulness’ (Gilbert 2007), whereby the brain engages in the general and unfocused monitoring of an individual’s internal and external environment for salient or potentially relevant stimuli. And finally, the third DMN-related cognitive process is called endogenously-focused attention (Fox, Snyder et al. 2005; Buckner and Carroll 2007; Buckner, Andrews-Hanna et al. 2008) . This pattern of neural activity is associated with the deliberate generation and effortful control of internal cognitions; phenomenologically, these internal cognitions are experienced whenever an individual covertly thinks, deliberates, ruminates, recalls, considers, or fantasizes about something in their ‘mind’.

Section 6: Structural and Functional Properties of the DMN subsystems

The internal cognitions generated by the DMN can be divided into two subtypes based upon their content and structural-functional connectivity patterns (Leech, Kamourieh et al. 2011). The first subtype of internal cognitions consists of episodic memory, autobiographical memory, imaginary scenario construction, and prospection. Here, episodic memory is defined as an individual's memories about objects, places, events, people, and situations that were directly experienced from the first-person perspective. Autobiographical memory, in turn, is a form of episodic memory that involves the specifics of events that one has lived through (Buckner, Andrews-Hanna et al. 2008). For example, a person's knowledge of how to get from their place of work to their home is an episodic memory because they learned that information through the first-person perspective. A person's recollection of a specific conversation that they had with their spouse during a specific drive home from work is an autobiographical memory. Imaginary scenario construction, in turn, is defined as the ability to imagine with great detail fictitious or hypothetical events (Buckner and Carroll 2007; Buckner 2010). And finally, prospection is defined as the ability to view oneself from a future perspective; e.g. thinking about themselves making dinner later that evening, or taking a trip the following weekend (Buckner and Carroll 2007; Buckner 2010). As a whole, this subtype of cognitive processes is largely performed by neural activity occurring in the MTL subsystem of the DMN (Leech, Kamourieh et al. 2011).

The second set of internal cognitions is predominantly generated by the dMPFC subsystem and involves the processes of self-reflection and mentalizing (Leech, Kamourieh et al. 2011). Self-reflection is the ability to make oneself an object of one's attentional focus for the purpose of evaluating ones current physical or emotional state; appraising ones characteristics or abilities; or thinking about ones current goals, desires, or plans of action (Fox, Snyder et al. 2005). Mentalizing, in turn, is the ability to infer the emotional and physical states of being of other people; to infer their goals, desires, or plans of action; as well as to engage in reflected appraisals (e.g. thinking about what another person may or may not think about oneself) (Corbetta, Patel et al. 2008).

Section 6: The neuronal activity patterns associated with the self are generated by coordinated interactions between the DMN, Cortical Midline, and Subcortical brain regions.

Just like the mental acts of *thinking about oneself* from different temporal and situational contexts, the patterns of neuronal activity involved in *being a self*-consist of several inter-related processes generated by reciprocally interacting sub-networks (Northoff and Bermpohl 2004; Northoff, Heinzel et al. 2006; Northoff, Duncan et al. 2010). Unlike the MTL and dMPFC subsystems though, these sub-networks are comprised of both DMN and non-DMN brain regions (Northoff, Duncan et al. 2010). Generally speaking, these regions include what are commonly called the cortical midline structures (Northoff and Bermpohl 2004), as well as several subcortical areas. Specifically, the CMS consist of the medial orbital prefrontal cortex (MOFC); ventromedial prefrontal cortex (VMPFC); pre and subgenual anterior cingulate cortex (PACC); the supragenual anterior cingulate cortex (SACC); dorsal medial prefontal cortex (DMPFC); medial parietal cortex (MPC); posterior cingulate cortex (PCC); and the retrosplenial cortex (RSC) (Northoff et al 2006). The subcortical regions include the periaqueductal grey (PAG); superior colliculi (SC); mesencephalic locomotor region

(MLR); the preoptic areas; the hypothalamus; and the dorsomedial thalamus (DMT). The totality of these brain regions are collectively referred to as the subcortical-cortical midline system (SCMS) (Northoff 2011).

The SCMS is functionally responsible for enabling self-related processing (Northoff 2011), which is defined as the dynamic coordination of interoceptive and exteroceptive stimuli with an individual’s goal-directed activities. As the term is used here, interoceptive stimuli refer to those sensations the emanate from inside an organism; specifically, they include such experiences as feeling tired, thirsty, or hungry; the visceral sensations associated with emotion; and the awareness of the position of one’s body, or parts of one’s body, in physical space. Exteroceptive stimuli are the sensations one receives from the external environment; i.e. sights, sounds, tastes, scents, etc (Kandel, Schwartz et al. 2000). Furthermore, the term dynamic coordination means that homeostatic information; information about what is currently located or occurring in the environment; and information about how these external properties relate to the current condition or location of the organism’s body are combined into a single representative pattern of neuronal activity (Northoff, Heinzel et al. 2006).

It has recently been proposed that this representative state of ongoing neuronal activity is the foundation from which the various dimensions of an individual’s self are constructed (Preminger, Harmelech et al. 2011). According to this argument, the subcortical regions of the SCMS integrate the extensive amount of exteroceptive and interoceptive information that they receive from the various sensory regions of the brain into what has classically been called either the ‘physical self’ or the ‘proto-self’ (Northoff and Bermpohl 2004). In short, this dimension of the self is simply a stable nexus point that demarcates a certain class of stimuli (e.g. those that originate from inside the organism) from another (e.g. those that emanate from outside the organism), as well as relates both these classes to a set of signals that may be potentially generated (e.g. the set of behavioral responses that may be enacted given the current state of and relation between an organisms internal and external environment).

This 'proto' state of neuronal activity is argued to then be combined with a second pattern of activity that is generated by the cortical midline portion of the SCMS (Northoff, Duncan et al. 2010). The emergent dynamics that result from this combination are classically referred to as either the 'mental self', or the 'core self' (Northoff and Bermpohl 2004); as a whole, these dynamics are said to generate the 'temporally extended sense of relatedness' that characterizes the feeling of *being* a self. Deeper insights can be garnered into the nature of this dimension of the self by recognizing that the VMPFC and Rsp of the cortical midline portion of the SCMS are also a part of the the MTL subsystem that is responsible for generating prospection and episodic/autobiographical memory. Indeed, in light of this overlap it is argued that the CMS portion of the SCMS is specifically responsible for integrating neuronal activity about current interoceptive and exteroceptive conditions with information about both previous and potentially future interoceptive states and environmental conditions (Northoff, Duncan et al. 2010).

Importantly, these first two dimensions of the self are largely conceptualized as being pre-reflective; e.g. they are ongoing and stable processes that occur independent from an individual’s deliberate efforts (Northoff, Duncan et al. 2010). A third dimension that is classically referred to as either the ‘spiritual self’ or the ‘narrative self’ is argued to represent those aspects of the individual that emerge when they engage in self-reflection; e.g. when they deliberately and actively reflect upon their current state; the relation of these states to past, present, and future environments; or past and potentially future states in isolation (Northoff and Bermpohl 2004). It is again possible to gain insights into the underlying mechanism that enables this dimension of the self by recognizing that the DMPFC component of the SCMS overlaps with the DMN. Recall from above that the neuronal activity associated with the DMPFC subsystem is functionally responsible for enabling self-appraisals, reflected-appraisals, and role-taking. Given this link, it is suggested that this third dimension of the self is temporarily activated through the functional coupling of the ‘proto’, ‘core’, and DMPFC subsystem’s neuronal activity; and deactivates when these regions are decoupled (Northoff, Duncan et al. 2010).

To summarize, neither mental acts nor the self are substantive things lodged in the brain; instead, both are dynamic, complex, and self-organized patterns of neuronal activity that unfold within and across multiple layers of aggregation. At the upper-echelons of this aggregate, subsystems of the default network are responsible for generating the self; episodic and autobiographical memory; self-appraisals; reflected appraisals; role-taking; and imaginary/future orientated cognitions. The fact that multiple-- yet related-- cognitive processes are generated within the same neural network is illuminating in terms of how the above micro-sociologically relevant processes are created. For example, Addis and colleagues (Addis, Pan et al. 2009) empirically demonstrated that the MTL system is comprised of two subsystems: one that enables the cognitive act of remembering, and another that enables the cognitive act of imagining. But, when Addis and colleagues (2009) compared the neural activity underlying each system during a series of tasks they found several interesting details. First, acts of remembering and acts of imagining share a common set of neural nodes. And second, imagined events are constructed by recombining existing episodic memories in a novel way to represent 'new' or hypothetical situations. Lombardo and colleagues (Lombardo, Chakrabarti et al. 2009) demonstrated a similar finding in the case of the dMPFC subnetwork. Confirming a significant amount of other empirical research, it was shown here that the neurological subnetwork that is functionally responsible for enabling self-appraisal and mentalizing about the physical and mental states of others strongly-overlap. Although the exact significance of this result is still being determined, it appears to suggest that the dMPFC extrapolates from the current state of the self to simulate what the other is or may be thinking. While similar uncertainties still remain, emerging research suggests that the MTL and dMPFC subsystems interact during mentalizing as well. Here, the empirical evidence appears to suggest that episodic memory is employed along with the current state of the self to imagine another's situation. In short, this means that, at least in part, individuals are able to understand the actions and experiences of others by recombining elements from their own past and present experiences and using this as a basis of inference.

Part IV: Structure and Function of the Salience Network

The last intrinsic connectivity network I will discuss is commonly referred to as the Salience Network (Seeley, Menon et al. 2007). Like those already discussed above, the Salience Network can be structurally divided into a core--which is comprised of the anterior insula, the anterior cingulate cortex, and the ventrolateral prefrontal cortex-- and a periphery-- which consists of the amygdala, the substantia nigra/ventral tegmental area, and the thalamus (Seeley, Menon et al. 2007; Menon and Uddin 2010). Unlike the other intrinsic connectivity networks already discussed, though, the Salience Network is unique to the degree that it forms a 'homeostatic afferent pathway' to the autonomic nervous system vis-a-vis the brain stem and the spinal cord (Menon and Uddin 2010).

Although the exact responsibilities of the Salilence Network have yet to be fully determined, it is generally agreed that it is significantly involved in gathering information about an organism's external and internal environment and then delivering it to the regions of the brain that are involved in the generation of higher-levels of cognition (!?!). In regard to this, Seeley and colleagues (2007) say the following:

> The nervous system is continuously bombarded by internal and extrapersonal stimuli. A leading priority is to identify the most homeostatically relevant among these myriad inputs. This capacity requires a system that can integrate highly processed sensory data with visceral, autonomic, and hedonic “markers,” so that the organism can decide what to do (or not to do) next. We propose that the salience network described here is well suited for this purpose (p2353-54).

The basis for this opinion is derived from examining the functional and structural connectivity patterns of its component parts (Menon and Uddin 2010). For example, functional neuroimaging studies have consistently shown that the right portion of the anterior insula plays an important role in generating an individual’s subjective awareness of both positive and negative feelings such as sexual arousal, anger, and disgust (Menon and Uddin 2010). Along with these more basic emotions, the anterior insula and the anterior cingulate cortex have been found to play a role in processing more complex social emotions such as those underlying the evaluation of the trustworthiness of others; the admiration of another's skill or virtue; the feeling of compassion for the physical or psychological suffering of others; and the planning of malevolent or deceitful acts (Menon and Uddin 2010).

Further, several lines of research have demonstrated that the core of the Salience Network is also involved in emotional decision making. For example, Levens and Phelps (2010) found that the anterior insula facilitated 'interference resolution' in working memory by biasing attention to emotionally relevant characteristics. Here, interference in working memory refers to an inability to recall a specific piece of information from a larger set due to the presence of some commonality that makes distinguishing details difficult e.g. remembering a particular person's name after being rapidly introduced to a group of people. Similarly, others have reported the influence of insular activity during decision making involving the calculating the perceived reward, risk, and fairness of outcome in economic exchange (Xue, Lu et al. 2010). Specifically, Xue and colleagues (2010) report that increases in insular activity also correlate with the subjectively-experienced urge to both continue to play, and increase the size of ones bet after either winning or nearly winning in a gambling task. Hence, not only does the core of the Salient Network aid decision making by heightening relevant information (as in the case of interference resolution), but it also motivates certain decisions by modulating the sense of urgency to make certain choices over others.

Given the involvement of the Salience Network in memory, self, and attention related process, it would seem plausible that this network interacts in a significant way with the Attention, Control, and Default Networks discussed above. And, recently, several empirical studies explicitly demonstrated this to be the case. Motivated by the existence of several 'shared nodes'--e.g. the thalamus, anterior insula, and anterior cingulate cortex, Sridharan and colleagues (Sridharan, Levitin et al. 2008) used a combination of fcMRI and Granger Causality to examine if and how the Salience Network and Attention Control networks interact during tasks. According to their analysis, the Salience Network acts as a central hub that directs bottom-up salient information to the control network in order to activate top-down attentional control. Interestingly, they also found that the Salient Network was negatively correlated with portions of the Default Mode Network as well. Based upon these results, Sridharan et al (2008) concluded that the Salient Network acts as a switching mechanism to simultaneously activate the externally focused Attention Network and deactivate the internally focused Default Mode Network in order to maximize the salience of events occurring in the environment.

Interestingly, Mohanty and colleagues (Mohanty, Gitelman et al. 2008) showed that the Salience Network is preferentially involved when a cued visual target is related to the homeostatic state of the individual. Specifically, it was found that fasting for eight hours significantly increased the subjective feeling of being hungry. Further, the degree to which an individual experienced hunger increased the amount of neural activity in the Salience Network. This increase in neural activity, in turn, influenced the speed with which the dorsal attention network was able to relocate attention to a spatial position. Importantly though, this influence was only seen when the target to which the individual was to locate their attention was a food item and when they were hungry. Or, in other words, the Salience Network did not influence the dorsal attention network when food targets were presented to satiated participants, or when non-food targets were presented to hungry participants. Based on these findings, it appears that the Salient Network can be distinguished from other networks that influence top-down processing--e.g. the ventral attention network-- to the degree that it is most responsive to stimuli that are most relevant to and current individuals homeostatic state.

In regard to the effect of the Salient Network on the Default Mode Network, Spreng and colleagues (Spreng, Stevens et al. 2010) demonstrated that portions of the two networks dynamically interact when individuals make future plans that involve the self. Specifically, the researchers asked participants to create a list of life goals, indicate the necessary steps to accomplish those goals, as well as indicate potential obstacles that may hinder their achievement. For example, common goals cited included doing well in college; getting married; paying off debt; etc. In the case of the school-related goal, often cited steps-to-success included studying hard and going to class. Also in regard to school, common obstacles included not having enough time to study, not having enough money to pay tuition, and poor previous performance. Although this study did not examine the effect of the Salient Network in great detail, the fact that its nodes are active during emotionally salient and self-related planning strongly suggests that it influences the content of future plans by providing the Default Mode Network with current or potential visceral reactions to the achievement of goals.

Part IV: Summary and Conclusion

The goal of this chapter was to identify and describe the structural and functional characteristics of three sets of intrinsic connectivity networks called the task-positive, task-negative, and salience networks. As was discussed above, these three networks are functionally responsible for generating many of the psychological concepts that sociological social psychology theories are built upon. Importantly, the biological processes underlying the associated activities of each network are the outcome of the totality of structural and functional processes discussed in chapters 2-5. As such, the totality of these chapters clearly illustrates how it is that the interactions between ions that generate the action potential ultimately give rise to the intrinsic connectivity networks responsible for generating cognition.

Chapter 7: Applications of Neuroscience to the Theoretical Framework of Alfred Schutz

Chapter Introduction

I noted in Chapter 1 that supporters of the biosocial perspective argue that the incorporation of biological insights can assist sociological theory by: 1) increasing the explanatory power of the social sciences' micro-level theories by replacing philosophical assumptions about human nature with more empirically informed insights; 2) improving the accuracy and precision of micro-level theories by sharpening the epistemic relationship between abstract concepts and their physical referents; 3) increasing the internal validity of social science research by improving the operationalizability of concepts and proposed causal mechanisms. In this final chapter I will explicitly illustrate these points by applying the insights outlined in Chapters 2-6 to the sociological theory of Alfred Schutz (1967).

Part I: Mu analysis of Shutz

The *Phenomenology of the Social World* (PSW) was written by Alfred Schutz in response to his long standing concern with the philosophical assumptions (or, more accurately, the lack there of) underpinning Max Weber's Economy and Society (Schutz 1967). Schutz's dissatisfaction with Weber stems from two sources. First, it is Schutz's opinion that Weber's concept of "the meaningful act of the individual" is not the theoretical primitive that Weber claims it to be. Instead, argues Schutz, Weber's term is a "mere label for a highly complex and ramified area" in much need of further elaboration (ibid: 7-8). This is problematic for Schutz because he interprets the meaning of an action as varying in relation to the spatial and temporal vantage point from which it is perceived.

Indeed, in Schutz's opinion there is a radical difference between the meaning-structure used to interpret one's own behavior, the behavior of immediately experienced consociates, and the behavior of indirectly experienced contemporaries and predecessors (ibid: 8). As such, Schutz concludes that Weber's analytical model is too blunt of an instrument to be usefully employed in sociological research.

Second, Schutz argues that Weber's analytical approach fails to specify how individuals are able to understand the meaningful actions of others, as well as how it is that meanings are built-up and transformed within and across various vantage points. Schutz believes the reason for this stems from the fact that Weber was not interested in rigorously investigating the ontological and epistemological presuppositions undergirding his analytical scheme; indeed, in the opening lines of Chapters 1 and 2 of Economy and Society, Weber notes it is not his goal to formulate a new theoretical understanding, but instead to merely state existing concepts in more exact terms. As such, and because it is readily apparent from every day experience that inter-subjective agreement occurs, Weber took the existence of these processes for granted and paid them no further mind. For Schutz, though, such reliance upon common-sense assumptions is dangerous because they can unknowingly introduce biases or errors into an otherwise scientifically-sound analysis. Specifically, this can occur through "equivocations creeping into basic concepts," or through "a failure to see that apparently diverse phenomena are really of the same type (ibid: 9)." In either case, Schutz believes the remedy to such problems can only come from penetrating beyond superficial appearances to the root causes of social phenomena.

Given the above, the PSW represents Schutz's attempt to rectify Weber's shortcoming by first deconstructing the concept of "meaning" to its phenomenological core; and second, by demonstrating how this "core" gives rise to an entire spectrum of meaning-types. Regarding his first aim, Schutz asserts that the true primary concept underlying sociological analysis is the individual's inner time-consciousness. In terms of his second goal, Schutz argues that the spectrum of meaning-types alluded to above are carved out of this inner time-conscious via the individual's attentional gaze, with each type corresponding to a particular motivational attitude. Importantly though, Schutz is not content with articulating a mere typology of inter-related concepts. Instead, Schutz also wishes to explicate the exact mechanisms by which each conceptual construct operates, as well as delineate how his primary and low-order concepts processually give rise to their conceptual decedents.

Ironically, Schutz recapitulates Weber’s limitations by incorrectly assuming that his concept of inner-time consciousness is as much of a primitive as he thinks it is. Indeed, as was outlined in Chapters 2-6, modern neuroscience has penetrated deep beyond the superficial appearances inherent to a purely philosophical analysis of mind to the molecular, cellular, and neuro-circuitry of human cognition. In so doing, neuroscience has revealed that Schutz's primary concepts of inner-time consciousness, duration, reflection, etc. are in fact mere labels for highly complex and ramified areas of analysis in much need of further empirical elaboration.

Following the logic Schutz used in his analysis of Weber, the goal of this Mu analysis is to demonstrate how Schutz's concepts and arguments can be more accurately specified using insights derived from modern neuroscience. Also mirroring the order in which Schutz presented his own argument, section 1-3 will be devoted to analyzing the biological foundations enabling the constitution of meaningful lived experience in the constitutor's own stream of consciousness. Specifically we will examine here Schutz's theory of consciousness, action vs. behavior, and the formation of stocks of knowledge on hand. Building upon this analysis, I will then turn in section 4 to articulating the neurological correlates of inter-subjective understanding.

Section 1: Consciousness According to Schutz

The cornerstone of Schutz's theoretical edifice is his concept of inner-time consciousness. According to Schutz, inner-time consciousness is defined as the phenomenological process by which individuals subjectively experience both their internal thoughts and their external environments. Following James, Husserl, and Bergeson, Schutz defines inner-time consciousness as a dynamic system that vacillates between two distinct states called duration and attention to life.

The conscious state of duration (also called stream of consciousness) is defined by the individual passively experiencing life as a continuous flow. In terms of the individual's internal environment, duration is experienced as mind-wandering: i.e. the undirected, unintentional, waxing and waning of thoughts, remembrances, ideas, etc. Likewise, an individual experiences their external environment in the context of duration as an equally continuous flow of sensory stimuli; here sounds, sights, and smells wash over and through the senses, but no single one is selected out for special consideration.

Instead, the totality of individual sensations is experienced as an undifferentiated sensuous background.

According to Schutz duration manifests itself as a seamless flow of experiences through a process called "retentional modification." The first step of this process consists of the individual perceiving an object located within their internal or external environment as a primal impression; or, in other words as a stimulus that is sensed at a preconscious level of experience (i.e. as a ray of light hitting the retina or a sound wave hitting the eardrum). Once this sensory event has occurred, the primary impression is then simultaneously transformed into a "primary remembrance" called retention, and an "immediate anticipation" called protention. Much like the resonating gong of a just-struck bell, retention is simply the echo created by the primary impression that continues to be temporarily experienced. Unless otherwise acted upon by the consciousness of the individual via reflection or reproduction (to be discussed next), this retention will simply trail off out of the immediate consciousness of the individual and into their storage-bin of past experiences. A protention, on the other hand, is like a radar signal emanating from the primary impression into the future to anticipate the next primary impression. Thus, the gap between primary impressions is bridged by the protentions and retentions of each linking-up the sequence into a continuous whole.

Schutz defines the conscious state of attention to life as an individual intentionally "turning back against the stream of consciousness" in order to mentally "hone in" on a particular experience. In the case of the individual’s internal environment, this state can be described as purposefully selecting out of the stream of consciousness a particular thought, idea, memory, etc. so as to deliberately mull it over, work through it, or recollect it. Regarding the external environment, an example of this second state would be an individual explicitly directing their attention to a single stimulus located within the otherwise undifferentiated background; i.e. by looking at *that* object *there*, or listening to *the* chirp of *that* bird of *that* flock.

The processual dynamics that generate attention to life are called reflection and reproduction. As Schutz uses the term, reflection refers to the act of attention being directed at an experience that is still undergoing the process of "retentional modification;" i.e. the experience had occurred within the very recent past. Reproduction, on the other hand, consist of the attentional gaze being directed by the individual into the storage-bin of their now-expired retentions in order to call-forth or recreate the associated experiences in the here-and-now.

Section 1.2: Neurological Foundations of Duration, Attention to Life, Protention, Reflection, and Reproduction.

In light of the arguments presented in Chapter 6, I argue here that the default mode network represents the neurological correlates of Schutz's concept of duration. Recall that the default mode network is functionally responsible for 'default activity'—defined as the continuous coming-to-be and passing-away of undirected thoughts that is experienced by the individual as the constant transition from a fluid stream of consciousness---as well as sentinel activity, which is defined as the general and unfocused monitoring of an individual's internal and external environment for salient or potentially relevant stimuli. This relationship is solidified by two points: 1) both Schutz and the initial discovers of the default mode network directly reference James' concept of ‘stream of consciousness’ as a psychological equivalent; and 2) both Schutz and the associated neuroscience literature define duration and default activity respectively as the passive experience of reality that occurs outside of deliberately focused attention.

For similar reasons, I argue that the task-positive network and the internally-focused attention processes generated by the default mode network are the neurological correlates of Schutz’s concept of attention to life. A major connection between Schutz and these intrinsic connectivity networks lies in his argument that the attention to life process involves the ‘carving out’ of duration a specific experience for explicit consideration. As was noted in Chapters 3 and 6, psychological processes related to the focusing of attention involve the amplification of certain stimuli over and above others located in the same stream of experience. Specifically, this is done by increasing the synchronization within the cell assembly of the neural signal to which attention is being devoted and decreasing the synchronization of the neural signals that are to remain outside of the field of attention.

Along with this connection, the dynamic properties of cell assemblies further represent the neurological correlates of Schutz’s concepts of protention and retention. Recall from Chapter 3 that a cell assembly is defined as a discrete network of strongly mutual excitatory neurons that is capable of acting briefly as a closed system, and that the phrase 'strongly mutual excitatory neurons' refers to the high probability that an action potential generated by an intra-assembly-presynaptic-neuron will trigger an action potential in an intra-assembly-postsynaptic-neuron. Further, also recall that the fact that the entire assembly representing a stimulus can be triggered by only a subset of neurons becoming active; as was noted in Chapter 3, this is how individuals are able to recognize a complete circle from only a partial presentation. To use Schutz's terminology, the initially firing neurons of the assembly that begin to fire during the 'now-thus-experience' 'call-out' to subsequent cells in the assembly that represent the 'new-now-thus-experience' to the degree that the activity of the former puts the later into motion.

For similar reasons, I argue that the neurological concepts of working memory and memory in general represent the biological correlates of Schutz's concepts of reflection and reproduction. As was noted in Chapter 6, working memory consists of the continuation of a cell assembly's neural activity after the associated stimulus is no longer present; the important characteristics here are the fact that working memory requires the deliberate application of attention (as does Schutz's concept of reflection), and the fact that the neural activity associated with working memory occurs immediately after the occurrence of the initial stimulus. As was discussed in Chapter 4, the memory of a stimulus involves the re-activation of the neural activity of the cell assembly representing it; moreover, as was discussed in Chapter 6, the neural activity associated with a memory can be deliberately activated by the attention network and the internally focused default mode network. Both of these conditions are of course the hallmark of Schutz's concept of reproduction.

Section 2: Meaning, Stocks of Knowledge

Having articulated how individuals *experience reality,* Schutz next turns to discuss his theory of how said experiences become *meaningful*. Following Hussrl once again, Schutz argues that experiences are not inherently meaningful; instead they must be made so through the application of the individaul's attentional gaze. Or, to put it another way, the meaning of an experience is co-terminate with the interpretation assigned by the individual after apprehending it in their attentional gaze. In the most general sense, the process by which an experience becomes endowed with meaning is called the *constitution of meaningful lived experience.*

For Schutz, conceptualizing meaning as a *constituting process* is useful because it specifies the mechanism by which individuals are able to construct, combine, and configure experiences into a multitude of interpretations called *configurations of meaning* or *meaning-contexts*. Formally speaking, a configuration of meaning is defined as a series of experiences, E1, E2,…En, that, once lived through as a series of separate steps, can be cognitively synthesized by the individual into a single, unified, object of attention. Once created, this single, unified, object of attention can be combined with other unified objects of attention into a new, higher-order object of attention. Indeed, the sequence of experiences associated with hitting each individual key on the keyboard can be combined into that object of attention: "I typed the sentence." In turn, a collection of "I typed the sentence" objects can be combined with the object, "I clicked the send button" to create the higher-order object "I sent the email." etc. etc. etc. The totality of an individual’s configuration of meanings, i.e. the sum of their meaningful lived experiences, is called their *stock of knowledge on hand.*

According to Schutz, a stock of knowledge possesses two very important characteristics. First, the configurations of meaning constituting a stock of knowledge can be either "taken-for-granted" or "problematized," depending upon the attitude motivating the individual's attentional gaze. To say that a configuration of meaning is "taken-for-granted" means that an individual can effectively interact with it at its then perceived order of constitution without needing to call attention to the constituting experiences underlying its construction. Or, put in terms of an illustrative example, an individual can understand the meaning of the constituted object: "I sent an email" without having to cast their attentional gaze to the constituting objects: "I typed the first sentence", "I typed the second sentence", "I hit send", etc. Contrarily, a configuration of meaning is said to be problematized when an individual becomes motivated to use their attentional gaze to deconstruct it into its constituting parts in order to understand the processes of its production. Once again, in terms of an illustrative example, problematizing the constituted object “I sent an email” would involve breaking it down to its constituting objects: “I type the first sentence, etc., etc.” The process by which the meaning of an experience is modified in response to a change in the motivation driving the attentional gaze highlighting it is referred to as an *attentional modification of meaning*.

A second important characteristic associated with a stock of knowledge is the fact that it can be organized into categories called *schemes of experience*; i.e. subsets of meaning configurations that are combined into categories based upon a common theme. Or, to put it another way, a scheme of experience consists of the meanings and experiences associated with a specific kind of object or situation. Importantly, Schutz argues that said themes can be attributed to either abstract or concrete “objects,” located in either the external or internal environment; for example, in this quote he says:

> “man in the natural attitude "has," therefore, a stock of knowledge of physical things and fellow creatures, of social collectives and of artifacts, including cultural objects. He likewise "has" syntheses of inner experience. Among these are to be found judgment contents (or propositional contents) which are the result of his previous acts of judgment. Here also are to be found all products of the activity of the mind and will [as well as] the ordering procedures of both theoretical and applied science and the very rules governing these, such as the rules of formal logic. To these we should add his experience of all sorts of practical and ethical rules (Schutz 1967: 81).

Functionally speaking, schemes of experience are responsible for enabling the possessing individual to interpret the meaning of objects and situations in their environment; the actual act of using a scheme of experience in this manner is called a *synthesis of recognition*. According to Schutz, the performance of a synthesis of recognition involves taking the lived experience that is to be classified, referring it back to the schemes on hand, and interpreting its meaning based upon this comparison. Interestingly, Schutz says that a synthesis of recognition is also what enables an individual to interpret the meaning of symbolic signs; in this case, the perceived sign is matched to the image of the signifier stored in a scheme of reference (or vice-versa). In either case, though, the process of categorizing lived experience under schemes by means of synthetic recognition is called t*he interpretation of the lived experience.*

Now, the totality of concepts Schutz develops in this portion of his argument culminate in his specification of what he calls the natural attitude. According to Schutz, the natural attitude is characterized by at least three fundamental assumptions; first, that reality substantively exists as it is perceived (i.e. the sun rising in the east and setting in the west is a real, naturally occurring phenomenon and not an elaborate illusion constructed by a malevolent demon); second, that reality is both stable and predictable (i.e. the defining characteristic s of the objects and processes constituting reality do not arbitrarily change from one moment to the next); and third, that one is able to take-for-granted both of these assumptions when either interacting with an object or process, or when planning to do so in the future (i.e. once the underlying properties of an object or process are established, they do not need to be continually re-confirmed). In regard to this concept, he says the following:

> The ordinary man in every moment of his lived experience lights upon past experiences in the storehouse of his consciousness. He knows about the world and he knows what to expect. With every moment of conscious life a new item is filed away in this vast storehouse. At a minimum this is due to the fact that, with the arrival of a new moment, things are seen in a slightly different light. All of this is involved in the conception of a duration that is manifold, continuous, and irreversible in direction. It can, however, be demonstrated not only deductively but by examination of one's own consciousness as one lives in the natural standpoint, grows older, and accumulates knowledge. Now, to the natural man all his past experiences are present as ordered, as knowledge or as awareness of what to expect, just as the whole external world is present to him as ordered. Ordinarily, and unless he is forced to solve a special kind of problem, he does not ask questions about how this ordered world was constituted (Schutz 1967: 81).

Section 2.1: Neurological correlates of stocks of knowledge, synthesis of recognition and the natural attitude

If we accept that the activation of cell assemblies represents the neurological correlates of duration and reproduction, then it logically follows that declarative memory in general– and episodic, semantic, and autobiographical memory more specifically– are the biological correlates of Schutz's concept of stock of knowledge. Recall from Chapter 4 that the totality of an individual's experiences or knowledge about the world that can be consciously accessed is called declarative memory; further, recall from Chapter 6 that the default mode network draws upon declarative knowledge to–in Schutz's terminology–

"construct, combine, and configure" knowledge about the self and the world in order to interpret and imagine past, present, and future experiences. Further still, also recall from Chapter 6 that the default mode network is capable of deconstructing a memory into increasingly finer detail by devoting a greater amount of attention to the recollection.

Along with the above, it also logically follows that Hebbian learning is one of biological mechanisms underlying Schutz's concept of the configuration of meaning. Recall from Chapter 4 that Hebbian learning is the process by which collections of neurons that repeatedly fire during an experience strengthen their connections to form the cell assembly that represents that experience. Because this process is not accessible to conscious experience, Hebbian learning arguably represents the automatic process by which experiences are grouped and categorized into meaningful schemes; processes that employ the default mode network, in turn, explain how stocks of knowledge are deliberately manipulated.

Finally, how the sentinel state of the default mode network employs declarative memories represents Schutz's concepts of synthesis of recognition during the natural attitude. A strong example of this applicability can be seen in how environmental stimuli are coded by the brain as self-relevant. Recall from both above and from Chapter 6 that 'sentinal' default mode activity involves the brain engaging in the general and unfocused monitoring of an individual's internal and external environment for salient or potentially relevant stimuli. Researchers have repeatedly shown that the cognitive and neurological content of sentinel processes is heavily imbued with self-relevant information

(Smallwood and Schooler 2006; Buckner, Andrews-Hanna et al. 2008; Christoff, Gordon et al. 2009; Spreng, Stevens et al. 2010). This means that when the mind wanders, it tends to think about autobiographical memories, future plans and goals, and other self-related thoughts. Likewise, the sentinel state of activity involves a constant cycling through episodic and semantic knowledge that may need to be recalled to address a situation in the environment. In a certain sense, the sentinel state of activity represents a constant simulation of the external environment based on the brain's previous experiences. Translated into Schutz's terminology, this means that the psychological process of duration involves a constant synthesis of recognition of self-relevant stimuli vis-à-vis the comparison of the meaning of said stimuli to meanings stored in the individual's stock of knowledge.

Recently, Rameson and colleagues used fMRI to compare and contrast the patterns of neural activity associated with the implicit and explicit perception of self-relevant stimuli (Rameson, Satpute et al. 2010). In this study, a group of participants were asked to rate how well the adjectives "athletic" and "scientific" applied to their self-concept, as well as rate how important each concept was to their sense of self. Participants that indicated that 'athletic' was both an accurate description of themselves and an important part of their self-concept were coded by the researchers as possessing an athletic identity. Likewise, participants that indicated that 'scientific' was both an accurate and important description of their self-concept were coded as possessing a scientific identity.

Following this, each participant was shown a stream of 88 emotionally neutral images of athletic and scientific-related situations and asked to identify for each one whether or not a human being was present in the scene. The requirement to detect a person in the image was used to divert the participant's conscious attention away from the 'athletic' or 'scientific' theme that underlined each scene. The goal of this task was to determine if non-consciously processed stimuli are 'tagged' by the brain as being self-relevant; and, if so, which areas of the brain are responsible. After performing this task, the participants were then shown 40 athletic and 40 scientific-related adjectives and asked to quickly respond with either 'me' or 'not-me'. Here, the goal of the task was to determine which brain regions were involved in the explicit evaluation of the self-relevance of a stimulus.

According to Rameson and colleagues' (2010) results, the implicit and explicit detection of self-relevant stimuli are largely processed by the same brain regions. Specifically, these regions include the medial prefrontal and ventral medial prefrontal cortices, the amygdala, the subgenual anterior cingulate cortex, the posterior cingulate/precuneus, and the ventral striatum. Further, the strength of neural activity generated by a brain region during the explicit performance task is significantly correlated with the strength of the neural activity generated during the performance of the implicit task. For this reason, Rameson and colleagues (2010) conclude that processing self-relevant information engages roughly the same neural structures regardless of whether it is done in an implicit or explicit manner.

Importantly though, Rameson and colleagues are careful to note that the dorsal medial prefrontal cortex was observed to be uniquely involved in the explicit perception of self-relevant stimuli (Rameson, Satpute et al. 2010). Following a theoretical model proposed by Northoff and Bermpohl (2004), Rameson and colleagues interpret this pattern of neural activity to mean that the ventral medial prefrontal cortex is functionally responsible for tagging and representing incoming stimuli as self-relevant at the preconscious level; the dorsal medial prefrontal cortex, in turn, is functionally responsible for consciously evaluating this relevance. Accordingly, this is why the ventral medial prefrontal cortex is involved in both implicit and explicit tasks; e.g. regardless of the task type, incoming stimuli must be tagged and internally represented before they are consciously reflected upon.

Because the neurological representation of a perceived stimulus and the memory of said stimulus are identical (Iacoboni, Molnar-Szakacs et al. 2005; Squire and Kandel 2009), and because the ventral medial prefrontal cortex is a part of a larger neural system that is constantly cycling through memories of past stimuli, Northoff (2011) argues that the ventral prefrontal cortex detects self-relevant stimuli by matching the incoming signal to the corresponding pattern of neural activity stored in memory. This ‘matching process’ is exactly what Schutz calls a synthesis of recognition. Further, the distinction between the functional role of the ventral and dorsal prefrontal cortices mirrors Schutz’s distinction between the natural attitude and the deliberate focusing of one’s attention on the meaning of a stimulus; e.g. the automatic processing of the former represents the natural attitude, while the deliberate processing of the later represents the process of attention to life.

Section 3: Distinguishing between Behavior and Action: A question of Ascribed Meaning.

The penultimate set of concepts Schutz develops in this part of his analysis are intended to explain how it is individuals assign meaning to their behaviors, formulate courses of action, and achieve their goals. By turning to this topic, Schutz transitions from describing the general/abstract process by which individuals experience and interpret reality to the more specific/concrete process by which individuals experience and interpret themselves as active participants in said reality. Despite this change in focus, though, it is important to highlight that Schutz does not formulate this new set of concepts de novo; instead, he explicitly derives them from the concepts he formulated to identify and describe the general processes underlying experience and meaning in the abstract. As such, Schutz's discussion of behavior should not be seen as a qualitatively new argument, but as an elaborative application to a new realm of experience.

Toward his goal of explicating the above, Schutz introduces three new concepts: spontaneous activity, behavior, and action. As do both behavior and action, spontaneous activity consists of the stream of bodily movements that individuals engage in as they go about their daily lives. What distinguishes spontaneous activities from behaviors and actions though, is the fact that they involve bodily movements that occur outside of the individual's "attention to life." In other words, spontaneous activities represent the physical correlate of the mental process of duration; i.e. they exist as a steady stream of physical experiences that are generated by the individual, but occur outside of their deliberate attention. Because an individual's "attention to life" is the fountainhead from which meaningful-experiences ultimately arise, the fact that spontaneous activities exist outside this conscious awareness means that they lack meaning; i.e. they, like the mental processes occurring in duration, exist at a prephenominal level of experience.

As was just intimated, both behavior and action consist of a set of bodily movements that have been carved out from the larger stream of spontaneous activity by an indivdual's attentional gaze; moreover, both sets of movements are further distinguished by the fact that they are made 'meaningful' by the meaning-endowing properties inherent to the 'attention to life' dimension of consciousness. In short, this means that behaviors and actions are not necessarily characterized by the fact that an individual's body is engaged in a *qualitatively different type of movement*, but by the fact that their "ego-ray of attention" has carved out from the duration of their movements *a specific set of activities for deliberate consideration*.

Now, the key characteristic that distinguishes action from behavior, in turn, is the temporal vantage point from which the individual's attentional gaze establishes the associated set of activities as meaningful. Indeed, according to Schutz a behavior is the process by which the individual's attentional gaze *looks back* into the now-just-passed stream of spontaneous activity to bring a *just-occurred* movement into conscious awareness; as such, behaviors can be more specifically defined as meaning-endowing processes of consciousness that specify for the individual "that which they have already carried out." Actions, on the other hand, are defined as bodily movements that have been endowed with meaning by the demands of a yet-to-be completed act. In this case, the meaning-endowing process involves the individuals 'attention to life' projecting into the future and imaging some desired state of affairs. From this future perspective, the attentional gaze then looks back and proscribes the series of movements needed to bring this hypothetical state into fruition. As such, actions differ from behaviors to the degree that the former ascribe meaning to movements before they are completed, while the latter only do so after the fact.

Section 3.1: Projects and Acts: the meaning-context concept applied to physical activities.

Recall from above that Schutz followed his discussion of the meaning-endowing capacities of the ego-ray with an analysis of how sets of individual experiences can be configured into a single meaning-context; and, once formulated, this set of configured meanings could be viewed as a single object of attention; recall, too, that Schutz also argued that any configured object of attention could be deconstructed by the ego ray back into its constituting individual experiences. Because the ego-ray of attention is causally involved in the transformation of spontaneous activities into meaningful actions, this (de)configuration process applies-by logical definition- to the domain of physical movements as well. Moreover, so to do the related concepts of stocks of knowledge, schemes of experience, and the synthesis of recognition. As such, the purpose of this section is to investigate how Schutz applies these cognitive concepts to the realm of physical activity.

In his general discussion of meaning-configuration, Schutz specified the underlying process as the individual experiences E1, E2,… En being collapsed into a single object of attention. The reason this was possible, he claimed, was because of the logical relationship that existed between sets of individual experiences created a web of meaningful connections that tied the parts together into a unified whole. In the case of actions, the unifying force that ties the individual activities into a single object of attention is the imagined final state of affairs that the sequence of activities is teleologically working to bring about. Or, to put it another way, the individual's overall expectation that the series of individual actions, when brought together in a specific sequence, will bring about the desired consequence, is what makes it possible collapse the entire sequence into a single object of attention. As it relates to an individual's physical activities, an object of attention constituted in this manner is called either a *project* or an *act.*

The fact that Schutz defines the individual's expectation as a project's unifying force begs the following question: how or why is an individual able to expect that a sequence of actions is capable of producing a desired end? Posing this very question himself, Schutz answers it by stating that the source of the expectation stems from an individual's previous experiences; i.e. an individual expects action sequence A1, A2,...An will produce a desired state because it has successfully done so in the past. Deducing from the fact that the application of past experiences to present situations functionally involves an individual’s stock of knowledge, Schutz argues that acts, like general constituted objects of attention, can be stored in an individual's stock of knowledge as "stocks of experience" for how to accomplish specific tasks. Indeed, in regard to this point, Schutz (1967:91) says the following:

> The means-end sequence itself is in fact a context of past experiences, experiences involving the successful realization of certain ends by the use of certain means. Every in-

order-to motivation presupposes such a stock of experience which has been elevated to an "I-can-do-it-again" status.

Along with this, Schutz further argues that- like stocks of knowledge- stocks of experience can be either 'taken-for-granted" or "problematized." In this context, a sense of taken-for-grantedness arises to the degree that an individual gains competency in performing a sequence of actions, or, to the degree that the invocation of the sequence has successfully generated the desired state in the past:

> The more cases there are of such acts and the better their rational principles understood, the more are they "taken for granted." This explains why practice and exercise increase efficiency. The more a given action-a technical accomplishment, for instance-is exercised, the less noticeable to the actor are its separate steps, although in the beginning he had to proceed in one-two-three fashion. From this it is easy to see that how broad the span of the project is depends precisely on how "accomplished" the actor is. Therefore, generally speaking, the more commonplace the project, the greater its breadth, for we will be more likely to have an automatic "knowledge" of how to run through the component steps (Schutz 1967:90).

Regardless of the reason though, it needs to be kept in mind that the defining factor that characterizes the action sequence's taken-for-grantedness is the absence of the need for the ego ray to actively guide the carrying out of the act.

An act can be problematized, in turn, by an individual applying their ego ray of attention to it in order to highlight each of the individual actions comprising the associated sequence. According to Schutz, hitherto taken-for-granted acts can become problematic for a variety or reasons. In some instances it is because the objects needed to carry-out a specific action of the sequence is not available; in others, the motivational need driving the original formulation of the project has either dissipated or changed. Again, regardless of the reason, Schutz argues that the problematization of the act causes the individual to re-apply their ego ray of attention to the situation and intentionally interact with it.

Section 3.2: Neurological correlates of spontaneous activity, behavior, action, and stocks of experience.

As was discussed in Chapter 4, the neurological signals enabling the sequence of motor acts that underlie a behavioral response are stored as cell assemblies in the supplementary motor and primary motor cortices as non-declarative memories. The performance of a motor act consists of the re-activation of the corresponding cell assembly; moreover, the cell assembly constituting a motor act is formed through Hebbian learning as the performance of the motor act is repeated over time. Following the arguments I made in Section 2.1 above, I argue that the cell assemblies underlying the non-declarative memories associated with a learned motor act represent Schutz's concept of stocks of experience. Given this, then, spontaneous activity is simply motor acts that occur outside of Ego's attentional gaze; behavior is simply an already-performed motor act that has been brought to Ego's attention by the processes of self-reflection generated by the default mode network. Likewise, action is simply the motor acts that are activated in the premotor and supplementary motor cortices by the default mode network during the imagining or planning of possible future actions.

Section 4: Schutz's General Thesis of how Ego experiences The Other from the vantage point of Ego's Natural Attitude.

According to Schutz, the mental processes that enable the individual Ego to experience the "The Other" are in many ways very similar to those that enable them to experience the rest of reality. Consequently, this means several things. First, it means that the existence and activities of other human beings are experienced in duration as a continuous flow of non-differentiated moments. Second, it means that specific experiences of others can be brought into 'sharp relief' by the individuals ego ray of attention, and, thus, endowed with meaning. Third, said object of attention can be filed away within the individual Ego's stock of knowledge/experience as a meaningful experience of/with "The Other." Fourth, the individual can use the totality of their stock of knowledge (i.e. both those portions that are and are not directly related to "The Other) to interpret the meaning of "The Other's" activities. And fifth, once constituted, Ego's experiences of "The Other" can be either taken for granted and accepted in toto, or, problematized and broken down into their constituting parts for further analysis.

At the same time though, Schutz recognizes that the experiences entering into an individual's duration that stem from the activities of other humans are not identical to those emanating from inanimate objects. In short, this is because the engendering source of these experiences is itself a conscious agent that is capable of both behavior and action. Or, in other words, experiences emanating from other human beings are already endowed with meaning before they become the focus of another individual's ego ray. As such, in order for an individual to *fully interpret* the meaning of Other-based experiences, they must somehow engage in a synthesis of recognition from both their own standpoint as an agent perceiving reality and from the vantage point of the original agent that endowed the observed activity with meaning. Further, when interpreting the object of attention from the vantage point of "the other", the observing Ego must also correctly identify the motivational context for why the other engaged in said activities.

According to Schutz, an individual conveys information to others about the meaning of his or her activities and subjective states in three ways. The first of these is through *expressive movements*, which are defined as the spontaneous activities performed by Alter that are observed by Ego. Recall from above that Schutz defines spontaneous activities as the physical movements performed without any deliberate motive; e.g. they occur outside of the individual's ego ray of attention and without deliberate intent. Specific examples of expressive movements that Schutz notes include 'the gestures and facial expressions which, without any explicit intention, enter into every conversation.'

The second way Alter conveys information to Ego is through what I will refer to here as *expressive indications*. An expressive indication differs from an expressive movement to the degree that the former involves Ego observing the *behaviors* performed by Alter. Recall from above that Schutz defined behavior as deliberately performed physical movements—e.g. they are part of a project-- occurring outside of an individual's ego ray of attention. Here, Schutz gives the example of Ego observing a woodcutter chopping wood; the physical movements involved in the project of chopping are deliberately performed, but the woodcutter does not focus his attention on each action as it occurs. The defining characteristic, then, is that the physical movement in question is meaningful to both the performer and the observer.

The last way Alter conveys information to Ego is through the use of signs. According to Schutz, a sign is a physical gesture, vocal utterance, or object that is deliberately injected into the environment by Alter for the explicit purpose of expressing a subjective experience to Ego. Importantly, Schutz argues that the act of communicating with signs is same as the physical act of planning and performing a project; in other words, an individual begins with a picture in his or her mind of a desired outcome and then performs a series of activities to bring this imagined state into fruition. In the case of deliberate communication, though, the series of activities consists of the purposive selection of specific signs in order to convey the content of a subjective experience or desire.

Of course, communication requires more than simply the conveyance of information; it also requires the deciphering, interpretation and understanding of what this information means as well. Accordingly, Schutz specifies two ways Ego is able to understand the meaning of Alter's behaviors and actions. The first of these is called acts of explication and the second is called genuine understanding. For Schutz, an act of explication involves an individual deliberately focusing his or her ego ray on the expressive movements, expressive indications, and significant symbols displayed by Other and comparing this experience to the schemes of experience stored within his or her stock of knowledge. An explication is successful if and when Ego is able to achieve a synthesis of recognition. Importantly, Schutz argues that said synthesis of recognition is limited to identifying the meaning context of the movement, indication, or symbol in-of-itself; for example in the case of Other speaking German to Ego, an act of explication involves Ego recognizing that the symbols being employed by Other are German symbols, as well as recognizing the colloquial definition of those symbols.

In the case of genuine understanding, though, Schutz argues that Ego focuses her attention on the subjective experiences of Other *in order to explicate his reason for* *performing a behavior or employing a symbol.* Or, to put it another way, genuine understanding involves Ego attempting to explicate *why* or *for what* purpose Other is doing or has done something; for example, in the case of Ego listening to Other speaking german, Ego's genuine understanding of Other's actions requires that Ego asks herself such questions as "What does this person mean by speaking to me in this manner, at this particular moment? What is this person's in-order-to motive? What does the choice of these words indicate (Schutz 1967:113)?"

Importantly, Schutz further identifies a very specific mechanism whereby Ego is able to achieve a genuine understanding of other:

> Taking this interpretation of our own perceptual data as a starting point, we can plot out in our mind's eye exactly how *we* would carry out the action in question. Then we can actually imagine ourselves doing so. In cases like this, then, we project the other person's goal as if it were our own and fancy ourselves carrying it out. Observe also that we here project the action in the future perfect tense as completed and that our imagined execution of the action is accompanied by the usual retentions and reproductions of the project, although, of course, only in fancy. Further, let us note that the imagined execution may fulfill or fail to fulfill the imagined project. Or, instead of imagining for ourselves an action wherein we carry out the other person's goal, we may recall in concrete detail how we once carried out a similar action ourselves. Such a procedure would be merely a variation on the same principle. In both these cases, we put ourselves in the place of the actor and identify our lived experiences with his. If, however, I as the observer wish to avoid an inadequate interpretation of what I see another person doing, I must "make my own" all those meaning-contexts which make sense of this action on the basis of my past knowledge of this particular person (Schutz 1967:115-116)."

Section 4.1: Neurological correlates of Schutz's concepts of Expressive Movements, Expressive Indications, Acts of Explication, and Genuine Understanding.

In light of the above discussion, I argue here that somatosensory mirror neurons represent the biological correlates of Schutz's concept of expressive movements. Recall from Chapter 4 that somatosensory mirror neurons are a special kind of neuron that enables an individual to experience the somatosensory sensations felt by others. For example, Ego seeing Alter being pricked on the back of his right hand generates the same perception of pain in Ego's somatosensory cortex as the actual experience of being pricked does in Alter's somatosensory cortex. Similarly, somatosensory neurons located in Ego's insula generate similar feelings of disgust, pain, and joy when they are being expressed by observed others (Wicker, Keysers, et al 2003; Niedenthal 2007; Jabbi, Bastiaansen and Keysers 2008; Jabbi and Keysers 2008). Because the facial reactions occur automatically during the experience of these emotions (e.g. the associated facial movements are not deliberately imbued with meaning by Other a priori), and because the simulation of Alter's emotional state in the brain of Ego communicates to him information about Alter's current experience, the functional definition of somatosensory mirror neurons is identical to Schutz's definition of an expressive movement.

Using a similar logic, I argue that motor mirror neurons represent the biological correlate of Schutz's concept of expressive indications. Recall from Chapter 4 that motor mirror neurons generate the neural activity underlying a motor act in the brain of Ego when she observers said motor act being performed by Other. Because physiological properties associated with the performance of a motor act (e.g. the shape, position and vector of the hand and arm) are strongly correlated with the act's intended goal, a simulation resulting from the observance of said act indicates to Ego the reason Other is engaging in the associated behavior. Importantly, the motor act generated in Other's premotor cortex is deliberately created in order to carry-out the desired goal; in Schutz's terminology, it is an *in order to* behavior. Because of this meaningfulness to Other, and the fact that this meaning can be transmitted to Ego vis-à-vis observation, I argue that the concept of mirror motor neurons is a strong fit to Schutz's concept of expressive indications.

It is absolutely critical to qualify the type of understanding that Ego is able to garner about Other from the simulations generated by mirror neurons. As was noted in Chapter 6, the psychological processes of self-reflection and 'mentalizing'–e.g. consciously reflecting upon the physical, emotional, and mental states of oneself and others– are enabled by the default mode network. For this reason, this network represents the neurological foundations of Schutz's concepts of act of explication and genuine understanding. The fact that mirror neurons are not located in the default mode network means that the simulations they generate do not play a direct role in these forms of understanding. Given this, what kind of understanding do mirror neurons generate? The answer to this question is two-fold. First, the fact that both the neurological activity generated by Other and simulated by Ego occurs outside of the either's directed attention means that it is experienced by Other and Ego as *duration*; as such, mirror neurons enable Ego to understand Other's experiences by recreating in Ego his duration. Or, in other words, Ego understands Other's experiences because Ego's phenomological experience of duration is identical to Others. Related to this then, the phenomological feeling generated by mirror neurons is the experience of duration that Ego's default mod network directs his *attention to life* upon. Or again, in other words, the 'durational understanding' generated by mirror neurons is the content from which a 'genuine understanding' or an 'act of explication' is derived.

Part II: Summary and Conclusion

Alfred Schutz is no doubt one of micro-sociology's influential classical theorists. Despite this influence, though, Schutz heavy reliance on Husserl's phenomenological philosophy has hinder the empirical testability of his theories and the integration of his ideas into other micro-sociological frameworks. The integration of neuroscience in the manner discussed above greatly improves this situation in two ways. First, it demonstrates that the basic skeleton of Schutz's framework can be effectively stated in biological terms and without any reference to Husserl's phenomenology; in so doing, the above sections make possible an epistemic break between turn of the century philosophy/psychology and early 20th century sociological theory. Second, the incorporation of neuroscience into Schutz's framework allows for the application of the neuroimaging technologies discussed in Chapter 5 to the analysis of his concepts and theories. A strong example of this that was discussed above was the use of fMRI to identify which brain regions are functionally involved in the detection of self-relevant stimuli. In terms of Schutz's theories, the use of fMRI in this case explicated how a synthesis of recognition takes place during duration, as well as how the brain shifts to carve out stimuli from duration during attention to life.

Chapter 8: Overall Summary and Conclusion

The goal of this dissertation was to formulate a meta-theoretical framework that could address a set of criticisms that are frequently leveled against the emerging biosociological perspective. Recall from chapter 1 that these criticisms are as follows:

1. The biosocial perspective fails to properly explain how it is biological processes influence the psycho-social phenomena that they are shown to statistically correlate with.
2. Researchers reporting a statistically significant correlation between "*Biological Process X"* and "*Psycho-Social Phenomenon Y,"* often fail to explain the step-by-step mechanism by which process *"X"* is believed to cause phenomenon *"Y*."
3. The biosocial perspective fails to explain how the various biological correlates of psycho-social processes correlate with each other. For example, although "*Gene X"* and "*Neurological Process Y"* can both be shown to correlate with *"Mental Process Z"*, it is never explained if, how, or why, "*Gene X"* is correlated with "*Neurological Process Y*." Because of this, the biosocial perspective fails to present a cohesive argument for how biological processes act *in toto* to generate a mental process.
4. The biosocial perspective is overly inductive due to a lack of theoretical support explaining *a priori* why a biological process should be related to a psychological or social phenomenon.
5. It is not clear how or why the results generated by the biosocial perspective are applicable to the larger body of social research.

To conclude this dissertation, I will briefly summarize how the information presented in Chapters 2-7 is able to address these critiques.

The first three criticisms were largely addressed in chapters 2, 3, 4, and 5. In chapter 1 it was specifically shown that a gene codes for a specific protein; this protein is then embedded in the cell membrane as a neurotransmitter receptor. The biological function of this transmitter is to enable the transmission of an electrochemical signal from one neuron to another. In chapter 3 it was shown how the structural topology of a dense aggregate of neural circuits transforms the action potentials of individual neurons into a complex dynamical system of coordinated neural activity. Finally, chapter 4 and 5 illustrated how the dynamic neural activity that is localized within specific brain regions is then combined through higher-order topologies of neural connections to form the intrinsic connectivity networks responsible for generating cognitive activity.

The fourth criticism was addressed in Chapter 6. Specifically, a sociologist can assume *a priori* that a certain biological process is associated with a certain psychological or social process if a neuroscience has already demonstrated it to be the case. In other words, if neuroscience research has already shown that the default mode network is functionally involved in enabling an individual to take the role of the other, then a sociologist is safe to assume that the default mode network plays a role in enabling individuals to take the role of the other during a specific social process. Similarly, if neuroscience research has demonstrated that certain alleles of the DRD4 gene alter the structural or functional connectivity of the dorsal attention network, then a sociologist can assume that this allele may influence social processes that involve the top-down control of attention.

Regarding the fifth criticism, I argue that neuroscience can aid sociological theory in four ways. First, it provides sociological theory the capacity to define its concepts with greater precision. Because concepts are merely symbolic constructs created by the researcher, their ability to accurately reflect the phenomena they represent is limited by the observational power of the research technologies available (Collins 1994). As such, a single concept can erroneously be used to refer to two sets of unrelated phenomena simply because the characteristics that distinguish them occur at an inaccessible level of analysis. A similar problem can occur with hypothesized theoretical statements when a single process is argued to describe two empirically distinct phenomena. If two competing or seemingly unrelated psychological concepts can be shown to possess the same neurological substrate, then these two concepts can be combined into a single concept. Likewise, if a single concept can be shown to refer to two distinct biological processes, then this single concept can be split into two distinct concepts.

Second, neuroscience can identify elements of an identity process that may be occurring below the social, behavioral or cognitive level of analysis. This is an important contribution because a failure to account for these influences will increase the probability that a theory will fail to correctly predict or accurately explain the outcomes of social interactions. To illustrate this point, consider the following proposition: *A change in Cognitive Variable X is positively related to a change in Environmental Variable Y.* According to this proposition, a researcher should expect to see an increase in *Variable X* whenever they observe an increase in the value of *Variable Y*. Let us now assume though that in reality, *Environmental Variable Y* is only positively related to *Cognitive Variable X* if and only if *Neurological Variable Z* is above some threshold *k*. Under these circumstances, the proposition would only appear to be correct if *Variable Z* happened by chance to be above threshold *k* at the time the theory was applied. In short, a failure to consider the input of the neurological level of analysis may result in an accurate theory *by chance*, but its rightful incorporation can result in a correct theory *by design*.

Third, an understanding of the biological foundations of social behavior can help sociologists specify the scope conditions of their theories with greater accuracy. Simply stated, scope of conditions are defined as the set of circumstances under which a theoretical claim is expected to hold (Cohen 1989). Accurately specified scope conditions are important because they can aid researchers in diagnosing why a proposition failed to explain or predict a phenomenon of interest. On the one hand, said failure can stem from the fact that the relationships between the variables specified in the model do not accurately reflect the "real" nature of the processes they are meant to represent. On the other hand, it could also be that the "correct" theoretical explanation was applied to the "correct" set of phenomena, but not under the "correct" conditions. Knowing the relevant scope conditions of a theory can help discern between these two possibilities by allowing researchers to determine if the observed deviations from the expected outcome are attributable to conditions exogenous to the model. For this reason, then, more precisely stated scope conditions are better than their less precise counterparts because they provide a greater degree of accuracy when diagnosing the sources of "theory failure."

Finally, neuroscience research can help ‘grow’ sociological theory in new directions. According to Berger, Zelditch, and Wagner (Wagner 1984; Wagner and Berger 1985; Berger, Wagner et al. 1989; Berger and Zelditch 1993; Wagner 2007), sociological theories grow in a variety of ways. One of these ways is called proliferation. Formally stated, theoretical proliferation is defined as the following: “We say of two theories, T1 and T2, that T2 is a proliferation of T1 if T2 enlarges the range of application of the concepts and principles in T1 to social phenomena beyond the original domain or the original set of problems within a domain addressed by T1 (Berger and Zelditch 1993)." I argue that the ability to specify the neurological referents of sociological concepts allows for sociologists to proliferate their theories into new domains of analysis by illuminating hitherto unrecognized correspondences. For example, I have recently argued that identity related processes are carried out by the dorsal and ventral medial prefrontal cortex. These same regions are negatively impacted by mental illness. Given this, it may be possible to apply the explanatory power of identity theory to the sociology of mental illness to understand how anxiety, depression, bipolar disorder, etc. negatively impact the ability of diagnosed populations to form and maintain positive identities. It is easy to imagine similar proliferations occurring with other theories into other fields as well.

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