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The Human OFC, vmPFC, and ACC: Development and Evolution

A Thesis submitted in partial satisfaction of the requirements
for the degree of Master of Arts

in

Anthropology

by

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2014

The thesis of Linnea Lorene Wilder is approved and it is acceptable in quality and form for publication on microfilm and electronically:

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University of California, San Diego

2014

TABLE OF CONTENTS

LIST OF FIGURES

ABSTRACT OF THE THESIS

The Human OFC, vmPFC, and ACC: Development and Evolution

by

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Master of Arts in Anthropology

University of California, San Diego, 2014

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The prefrontal cortex is made up of several subdivisions. I will consider

three of these, the orbitofrontal cortex, the ventromedial prefrontal cortex, and the

anterior cingulate cortex. These areas make up the agranular and dysgranular

portion of the prefrontal cortex and have extensive connections with the

neocortex as well as several subcortical structures. They play a critical role in

emotional/social regulation, reward based learning, attention and error correction.

Through these functions they contribute to decision making processes. Here I will discuss the anatomy, functions, development, and evolution through reviews of comparative studies of great apes.

Introduction

The prefrontal cortex has been a focus of human evolutionary studies due to its role in higher order social and cognitive skills that are uniquely human. The human cortex as a whole has been greatly expanded relative to body size compared to other mammals and it has been suggested that the prefrontal cortex in particular has been differentially enlarged. However, it has now been shown that the prefrontal cortex appears to have scaled as expected for an ape brain of human brain size. There is evidence that it has undergone reorganization of specific areas over the course of hominid evolution, contributing to uniquely human cognitive skills.

The dorsolateral portions of the prefrontal cortex have been implicated in abstract rule learning and memory functions, allowing humans to plan and generate complex goals (Passingham and Wise 2012). Less is known about the orbitofrontal and ventromedial prefrontal cortices. These areas, along with the anterior cingulate cortex, are highly interconnected with other areas of the prefrontal cortex and may play a role in cognitive aspects of social and emotional regulation crucial to behavioral inhibition (including social inhibition, necessary in species with large social groups), performance monitoring, and action selection (Ridderinkhof et al 2004).

These areas have been considered more conserved than other regions of the prefrontal cortex, as they are present even in prosimian primates. In contrast dorsomedial, mid-lateral and ventral areas are present only in anthropoid primates (Passingham and Wise 2012). However, these areas show evidence of

reorganization in humans potentially contributing to human learning and decision making skills (Kringelbach 2005; Allman et al 2010).

In this thesis I will examine the functions, development, and evolution of three regions of the prefrontal cortex. Specifically, I will examine the orbitofrontal, ventromedial, and anterior cingulate cortices which make up the agranular and dysgranular portions of the prefrontal cortex (although the orbitofrontal cortex has a granular division as well).

In chapter I I begin with a discussion of the basic anatomy and connectivity of these regions. Chapter II describes the functions of these regions, detailing their role in reward learning, emotional regulation, and decision making. Chapter III discusses how abnormalities in structure and function in these regions contributes to psychiatric disorders including schizophrenia and anxiety disorders. In Chapter IV I discuss general development of the human brain and how neurological development contributes to the cognitive and behavior changes observed in childhood and adolescence. Chapter V briefly discusses what is known about evolution of the human brain through studies of comparative primate neuroanatomy. I conclude with a general summary of what is known about the orbital and medial prefrontal cortex.

I conclude that these regions have been altered in the course of hominid evolution and are critically involved in the development of reward learning and decision making processes. Understanding the development of these regions in humans as well as nonhuman primates can shed light on the changes in

developmental processes and timing that may have occurred in hominid

evolution.

Chapter I: Anatomy and Connectivity of the OFC, vmPFC, and ACC

I focus here on the orbitofrontal, ventromedial prefrontal, and anterior cingulate cortices, three subregions of the prefrontal cortex. In order to understand the functions and development of the OFC, vmPFC, and ACC I will first introduce the anatomy and connectivity of these regions. This includes the basic architecture of these regions as well as the extensive connections these regions have both with other cortical regions, and subcortical structures.

Prefrontal Cortex

The prefrontal cortex (PFC) is the anterior portion of the neocortex on the frontal lobe of the brain. It consists of Brodmann's areas 8, 9, 10, 11, 12, 13, 32, 44, 45, 46, and 47 (Fuster 1997). The PFC does not represent a uniform sector of the neocortex. Instead it is made up of multiple sections that are distinct in terms of cytoarchitecture, patterns of connectivity, and function (Passingham and Wise 2012).

The PFC can be divided into dorsal, orbital, and mesial sectors. The most superior of these is the dorsal sector which will not be discussed in depth here. It is divided from the orbital sector by the frontomarginal, lateral orbital, and circular sulci (Semendeferi et al 1997). The orbital sector is located immediately below the dorsal while the mesial sector encompasses the area from the gyrus rectus to the end of the mesial surface (Semendeferi et al 1997)(see Figure 1).

At a more specific level the mesial and orbital sections of the PFC can be divided separate sectors based on clusters of similar connectivity and physical location within the PFC and encompass the orbitofrontal, ventromedial, and anterior cingulate cortices (Passingham and Wise 2012). These regions will be the focus here.

The PFC displays the six layer cortex typical of the neocortex. Occasionally referred to as the granular prefrontal cortex, it can be distinguished from the rest of the frontal lobe (which is largely made up of the PFC and motor cortex) by the presence of a well-developed internal granule layer, layer IV of the cortex, a major target of projections from the thalamus. This layer contains mainly small Golgi type II granule cells, neurons which possess no or very short axons. The most common type of these found in layer IV of the PFC is stellate cells. These consist of a short dendrites which branch out in every direction and short axons which remain in the cortex and form connections with neighboring cells (Fuster 1997).

Layer I of the neocortex is cell sparse, containing mainly Cajal-Retzius cells, an important cell during development of the cerebral cortex, and the occasional stellate cell. Layers II and III, the supragranular layers, mainly contain pyramidal cells, so called due to their triangular cell bodies. They are the primary excitatory cell of the neocortex and typically have a number of branching basal dendrites and a single apical dendrite oriented toward the pial surface. These layers form connections primarily with other cortical areas are a responsible for corticocortical communication (Lewis and Melchitzky 2013).

The infragranular layers, V and VI, also contain mainly pyramidal cells. Cells in these layers project mainly to subcortical targets such as the amygdala, striatum, and thalamus. In layers III and V pyramidal neurons display a size gradient, being slightly larger near the boundaries of layer IV (Lewis and Melchitzky 2013). The second class of neurons commonly found in the PFC is inhibitory interneurons (Lewis and Melchitzky 2013).

Neurons are not located randomly in the cortex; they tend to form orderly radial units known as minicolumns. The minicolumn is considered a basic unit of organization in the neocortex and is shaped by and has possible implication for development and evolution which is discussed further in later chapters. Minicolumns traverse layers II through IV; they consist of 80 to 100 neurons and form a network within which the specialized cells of each layer can communicate. The size of minicolumns in homologous areas of the cortex in different species does vary but average size of minicolumns is relatively conserved across mammals, typically ranging from 40 to 60 microns. However, even small size differences can significantly alter the circuitry of a column and provide significantly more room for synapse, leading to greater potential connectivity, so the small difference in average size should not be ignored or treated as trivial (Buxhoeveden and Casanova 2002).

Although it is distinguished by the presence of a granular layer, the PFC includes both granular and agranular subdivisions. The density of layer IV, and thus the granularity of the PFC, increases in a caudal to rostral gradient. The most caudal sectors are agranular or dysgranular while the rostral-most sectors

contain a dense, well defined layer IV. This is of particular relevance here as the regions to be discussed in depth compromise the majority of the agranular sector of the PFC. The anterior cingulate cortex lacks a granular layer IV entirely while the orbitofrontal and ventromedial prefrontal cortices include both granular and agranular divisions (Passingham and Wise 2012).

Connectivity of the PFC

Across the entire mammalian Class the PFC is distinguished by the projections it receives from the mediodorsal nucleus of the thalamus (Price and Drevets 2012). The PFC is highly connected both within itself, with neighboring regions, and with other cortical and subcortical regions (Barbas 2007). Most of these connections are reciprocal; with the PFC sending projections back to the majority of structures it receives information from. The connections of the anterior cingulate cortex as well as the orbitofrontal and ventromedial regions of the PFC will be discussed below.

Orbitofrontal Cortex

Located on the ventral surface of the brain is the orbitofrontal cortex (OFC) occupying portions of Brodmann's areas (BA) 10, 11, 12, 13, 14, and 47 (Price 2006a)(see Figure 2). It extends from the olfactory areas to the frontal pole of the brain and displays a strong posterior to anterior gradient of granularity (Barbas and Zikopoulos 2006).

At the most posterior extent of the OFC lays the agranular insular cortex. As the name suggests, this area is agranular, lacking a layer IV. Price (2006a) labels area 47/12 as lateral OFC, which is marked by weak myelination, although

others see this area as part of the ventral PFC (Price 2006a; Passingham and Wise 2012). BA 13 forms the central portion of the OFC. This is a heterogeneous, region, ranging from completely agranular, lacking layer IV in the caudal portions, to dysgranular with a thin, poorly defined layer IV in its more rostral areas (Price 2006a).

Price includes areas BA 14, 25, and 32 as areas on the ventromedial and caudal medial wall of the OFC. Others however view these as being distinct from the rest of OFC and consider them a separate, ventromedial division of the prefrontal cortex (Price 2006a; Passingham and Wise 2012).

The rostral most portion of the OFC, comprised of BA 11 and 10, extends to the frontal pole of the PFC. Unlike the more caudal areas these areas are granular, this granularity increases near the frontal pole with weaker granularity in BA 11 compared to BA10. These areas are fully laminated with the traditional six layer structure, with each layer represented (Price 2006). It is in this area that the greatest differences between humans and monkeys is seen (Price 2006).

Connectivity of the OFC

The OFC is the portion of the prefrontal cortex (PFC) that receives input from the magnocellular medial nucleus of the mediodorsal thalamus (Price 2006b). The OFC is very polymodal, receiving projections from every sensory modality. This is particularly true of the posterior OFC (Barbas 2007).

Agranular portions of the OFC receive input from both the olfactory and gustatory cortices as well as visceral signals from the brainstem and thalamus. These agranular portions in turn project this information to the granular OFC.

Visual and somatosensory information is projected to BA 13. BA 13, along with

BA 14, receives some limited auditory input, but it has been argued that these

connections are part of the medial frontal rather than orbitofrontal network (Price

2006b). This fits with the evidence that the OFC is important for processing and

integrating sensory information related to food, which lacks an auditory

component (Passingham and Wise 2012).

Most sensory information, gustatory, visual, auditory, and somatosensory,

reaches the OFC through the thalamus. The connections to the olfactory bulb are

unique however. The olfactory bulb projects to the olfactory cortex which is

located directly behind the OFC. The olfactory cortex in turn projects directly to

the OFC, mainly to the posterior, agranular areas (Price 2006b). Sensory

information is sent through cortico-cortical connections from the posterior OFC to

the anterior OFC where it can be further processed (Price 2006b).

The OFC also has substantial connections with the limbic system

including the amygdala, entorhinal cortex, hippocampus, and parahippocampal

gyrus (Price 2006b). The medial and caudolateral OFC receives unreciprocated

projections from the hippocampus. This area of the OFC also receives input

from entorhinal cortex and the parahippocampal cortex (Price 2006b). There are

particularly strong reciprocal connections between the amygdala and the OFC.

Fibers from the amygdala project to the junction of layers I and II and to layer V

in the medial and caudolateral areas of the OFC. These same areas of the OFC

project to the amygdala from layers II, III, and V. The amygdala projects most

strongly to the posterior OFC, which in turn projects most strongly to the posterior

amygdala (Barbas 2007).

The posterior, agranular areas of the OFC also project to the lateral

hypothalamus and there are strong, reciprocal connections between the

magnocellular part of the mesiodorsal nucleus of the thalamus and the OFC

(Price 2006b). The OFC additionally projects to the central part of the striatum.

This region of the striatum projects the ventral pallidum and globus pallidus which

project to the medial part of the mediodorsal nucleus of the thalamus which,

completing a loop, projects to the OFC (Price 2006b).

The OFC is a sensory integration site which also sends and receives

information from many other cortical and subcortical brain areas. This suggests

a significant role in emotional processing and decision making (Barbas and

Zikopoulos 2006).

<u>Ventromedial Prefrontal Cortex</u>

The ventromedial prefrontal cortex (vmPFC) is located on the ventral

surface of the medial portion of the PFC. It mainly occupies parts of Brodmann's

areas, 14, 25, and 32 (Naqvi et al 2006)(see Figure 2). It extends from the sub-

cortical septal region posteriorly to the frontal pole anteriorly (Mackey and

Petrides 2010).

Similar to the OFC the vmPFC displays a caudal to rostral gradient in

granularity. The most posterior area, BA 24, is agranular and entirely lacks layer

IV. Layer IV begins to emerge in BA 32, which is dysgranular with a thin, faint

layer IV which increases in thickness and density in the more anterior BA 14 (Mackey and Petrides 2010).

All areas of the vmPFC have a dense layer Va which becomes denser in the more lateral portions of the vmPFC. The density of layer Va forms a gradient that is the inverse of the density of layer IV. Layer Va is most dense in BA 24 and least dense in BA 14 with BA 32 displaying intermediate density (Mackey and Petrides 2010).

Connectivity of the vmPFC

The vmPFC projects strongly to subcortical structures, in particular the lateral hypothalamus and periaqueductal gray region. These connections are very orderly, with the medial wall of the vmPFC projecting to the dorsolateral periaqueductal gray region and the anterior and ventromedial hypothalamus and the portion of the vmPFC on the medial surface of the OFC projecting to the ventrolateral periaqueductal gray region and lateral hypothalamus (Naqvi et al 2006). Projections have also been found from the vmPFC to the amygdala and brainstem. These connections suggest that the vmPFC may play a role in visceral functions and decision making (Naqvi et al 2006).

Anterior Cingulate Cortex

The cingulate cortex is a component of the limbic system situated around the corpus callosum. It can be seen on the medial surface of the brain and is composed of the cingulate sulcus and cingulate gyrus (Vogt et al 1995). There is a great deal of variability in the gross morphology of the cingulate cortex. In some

individuals there is a single cingulate sulcus, in others the cingulate sulcus splits into dual sulci (Vogt et al 1995).

The anterior portion (the ACC) is comprised of Brodmann's areas 24, 25, 32, and 33 (Allman et al 2001)(see Figure 3). The ventral portion of the ACC (BA 24a, 24b, and 25) is found on the cingulate gyrus while the dorsal portion (BA 24c and 32) occupies the cingulate sulcus (Paus 2001). The ACC can be distinguished from the posterior cingulate cortex (PCC) by the number of neurofilament containing neurons. These are found in large numbers is the PCC, particularly in layer III and are nearly absent from the ACC (Vogt et al 1995).

As with much of the OFC and vmPFC, the ACC is agranular, lacking layer IV of the cortex (Allman et al 2001; Devinsky et al 1995; Vogt et al 1995). The ACC is characterized by a prominent layer Va, which is thinnest in BA 33 and 25. BA 33 has poor lamination, without definite borders between layers II and III, and very thin layer VI. BA 25 has a well-defined layer V with a weak border with layer VI. However, layers II and III are more distinguishable than in BA 33 (Vogt et al 1995).

Brodmann's area 24 makes up much of the ACC and can be further subdivided based on cytoarchitecture. BA 24a is located adjacent to BA 33. It has a clear boundary between layers II and III and a thin, but well-defined layer Va. Layer Vb in this area has a high density of von Economo neurons (VENs) (Allman et al 2001; Vogt et al 1995). Von Economo neurons (VENs) have a distinct spindle shape, formed by the presence of a single apical dendrite and single basal dendrite (Allman et al 2001)(see Figure 4). It has been suggested

that these cells may be an adaptation for large brains to allow rapid communication (Allman et al 2010). This layer also contains clumps, or aggregations, of pyramidal cells (Vogt et al 1995).

Rostral and dorsal to BA 24a is BA 24b. This area has a very thick layer Va which contains large pyramidal cells. VENs and aggregations of pyramidal neurons can be found in layer Vb, although the density of VENs in this area is less than in BA 24a (Vogt et al 1995). Area 24c is generally located on the ventral bank of the cingulate sulcus, due to the variability of segmentation of the cingulate sulcus on some individuals parts of it extend to the surface of the cingulate gyrus. The supragranular layers II and III area as thick as or thicker than the infragranular layers. As with other portions of BA 24, layer Va is prominent in BA 24c and contains many small and medium-sized pyramidal cells. The density of VENs in layer Vb is less than in BA 24a or 24b, as a result this layer is more cell sparse and thus aggregations of pyramidal neurons are more prominent in this area (Vogt et al 1995).

BA 32 has been referred to as a transitional area of the ACC as it possesses features typical of the ACC as well as the rest of the frontal cortex (Devinsky et al 1995). It has a prominent layer Va, however this layer is not as thick or dense as is found in BA 24. It has a clearer layer III which contains large pyramidal neurons deep in this layer forming layer IIIc. Unlike the rest of the ACC it is dysgranular, with a thin, sparse layer IV which becomes more attenuated in more caudal portions of BA 32 (Vogt et al 1995).

Connectivity of the ACC

Bush and colleagues propose that the ACC is made up of two subdivisions, each of which has a distinct pattern of connectivity. The cognitive division is comprised of dorsal sectors of BA 24b, 24c, and 32. This area plays a role in a number of cognitive functions involving attention, error detection, and memory. It has reciprocal connections with BA 46/9 of the lateral PFC as well as the parietal cortex and both premotor and supplementary motor areas (Bush et al 2000).

The affect division is made up of rostral areas of BA 24a, 24b, 24c, and 32 as well as BA 25 and 33. These areas play a role in assessing emotional information and regulating emotional responses. The affect division of the ACC has strong connections to the amygdala, periaqueductal gray, nucleus accumbens, hypothalamus and hippocampus. In addition to these subcortical connections this area also projects to the anterior insula and OFC (Bush et al 2000).

The ACC also receives input from a wide variety of thalamic regions including the anteromedial, paraventricular, parafascicular, parataenial, paracentral, central and centolateral, reuniens, limitans, mesidorsal, and ventral anterior nuclei (Devinsky et al 1995). In addition to the thalamus the ACC has reciprocal connections with the brainstem nuclei (Paus 2001; Vogt et al 1995). The ACC also has reciprocal projections with the PFC which originate from layer V of the ACC. Layer V neurons from the ACC project to the superficial layers of

the dorsolateral PFC. The PFC in turn projects to motor areas in the ACC (Paus 2001).

The prominent layer V neurons of the ACC project to the motor cortex and spinal cord. This suggests that it plays a role in motor control and integrating cognitive information from the PFC with emotional and arousal information from the amygdala and brainstem nuclei (Paus 2001).

Conclusion

The OFC, vmPFC, and ACC comprise the agranular and dysgranular portion of the PFC. The OFC, located on the orbital surface of the brain, also includes a fully granular portion. The OFC is a major sensory integration site and has connections with the limbic system and amygdala which may allow it to process rewarding information and receive information about the current state of the individual (Barbas and Zikopoulos 2006). The vmPFC lacks a fully granular region, but is similarly interconnected with the amygdala. This region also has connections with the brainstem, periaqueductal gray region and lateral hypothalamus, which indicate possible visceral functions (Naqvi et al 2006). The ACC is the most posterior region of these three and is largely agranular but possesses a rare cell type, VENs, which may relate to the fast communication required in a large-brained social species (Allman et al 2001).

Chapter II: Functional Specializations of the OFC, vmPFC, and ACC

In this section I discuss proposed functions of the OFC, vmPFC, and ACC. I consider evidence from lesions, functional imaging studies as well as electrical stimulation of these regions. Each of these techniques presents unique benefits and limitations. Electrical stimulation provides very robust information about the effects of targeted activation in a particular area, however due to the invasive nature of this method its use for research is largely restricted to nonhuman (and non-ape) animals. It has been used in a number of monkey studies however, these results may or may not generalize to humans. Functional imaging is noninvasive and can safely be performed on both apes, including humans, and monkeys although the required stillness may be hard to achieve in nonhuman subjects and often requires special training or sedation which may alter the patterns of activation or produce activation that is unrelated to the given task. Additionally, although imaging methods do show the activation present in the brain during cognitive tasks, which can be compared to at rest activation or activation in another task, it can only show what areas are active at a certain time. Functional imaging cannot determine whether a particular area of the brain is necessary for a certain function as lesions studies can (Passingham and Wise 2012).

By studying impaired functioning in lesioned brains, with lesions occurring either as a result of natural injury or created surgically, areas of the brain necessary for a particular function can be identified. However, in many cases of

naturally occurring lesions in the human brain, multiple areas may be damaged

outside of the area of interest. Lesions that involve the OFC, vmPFC, and ACC

often include other regions of the PFC and thus altered functioning cannot be

attributed with certainty to one particular area (Damasio and Van Hoesen 1983).

Surgically created lesions provide more precise, targeted evidence for the

functions of a single region, however they are limited to nonhuman primates and

humans with some impairment (a brain may be lesioned to alleviate certain

conditions).While examination of altered function after surgically created lesions

does provide precise data, localized to a specific brain region, the results may

not generalize to healthy human brains (Passingham and Wise 2012).

Additionally, while a lesioned area may demonstrate the necessity of that area for

a certain function, it does not reflect the limits of all the areas that may be

involved, illustrating the need for functional imaging studies in conjunction with

lesion studies.

<u>Orbitofrontal Cortex</u>

The OFC has been implicated in many reward based functions. It

integrates information from nearly every sensory modality and represents the

reward value of taste which may play a role in stimulus reinforcement learning

(Rolls 2004). It may also play a role in regulation of emotion. Humans with OFC

damage often display euphoria, irresponsibility, and impulsivity (Damasio 1994).

Lesion Studies

Macaques with OFC lesions suffer impairments in their ability to select

rewarding stimuli. They often have trouble with go/no-go tasks, reversal learning

and extinction tasks. They will often continue to respond to stimuli even after it has stopped being rewarded (Rolls 2004). In one early study by Butter and colleagues (1963) macaques with OFC lesions were trained to press a lever for food, which both the lesioned macaques and normal controls were able to do equally well. In the extinction phase of the task the behavior was no longer rewarded, yet the OFC lesioned subjects continued respond more often than controls. This suggests that perhaps OFC lesions caused slower extinction of the habit, or difficultly inhibiting the impulse to press the lever, even when it is no longer rewarded (Butter et al 1963).

Later studies have refined these results. Meunier and colleagues (1997) tested macaques with OFC lesions on a number of tasks including delayed nonmatching to sample (DNMS) and an object reversal task. In the DNMS task the monkeys were presented with two objects, one of which was rewarded, after a delay the subjects were shown both the rewarded object and a new one, and were rewarded for choosing the novel object. Macaques were tested on this both pre and post-surgery; after receiving their lesions they took five times as many trials to successfully perform this task. In the object reversal task subjects were again shown two objects, one of which was rewarded. After they learned to reliably choose the initially rewarded object, the contingency was reversed. The macaques with OFC lesions did eventually perform this task above chance, but remained impaired compared to controls (Meunier et al 1997). Another object reversal study by Rudebeck and Murray (2008) demonstrated similar results. The OFC lesioned macaques were able to learn the initial contingency as well as

controls, however after the reversal they tended to make significantly more errors than controls. This was seen even after a correct trial, the lesioned subjects seemed to benefit less from rewards than controls (Rudebeck and Murray 2008).

These results are supported in a study by Izquierdo and colleagues (2004). Macaques with bilateral OFC lesions were tested to see if they would change their choice of objects as the value of the reward associated with them changed. After being fed to satiety the reward value of a food decreases and controls shifted their preference for the object associated with the non-devalued food. Monkeys with OFC lesions did not display this shift in preference (Izquierdo et al 2004).

Across all of these studies it appears that monkeys with OFC lesions seem less able to use reward information to flexibly adjust their stimulus-reinforcement associations. Neurons in the OFC respond to objects and learn which are rewarded and reverse the visual stimuli they respond to when the reward is reversed. It appears that this ability is lost in the macaques with OFC lesions (Rolls 2004).

Lesion studies in humans have produced similar results. Hornak and colleagues (2004) tested patients with surgical OFC lesions on a gambling task where they were presented simultaneously with two stimuli, one of which caused the subject to win money, the other to lose money. After the subjects reliably learned through trial and error which pattern to choose to win money the contingency was gradually reversed and the subjects had to monitor and keep in mind which pattern was currently rewarded. Normal controls were able to shift

their performance to continue winning money while patients with bilateral OFC lesion lost money after the reversal. This impairment was not seen in patients with unilateral OFC lesions (Hornak et al 2004).

Impairments in humans with OFC lesions include difficulties with go/no-go task, where subjects are told to respond to every stimuli presented except in some pre-specified condition, such as responding to every letter except X, as well as reversal learning and extinction tasks (Kringelbach 2005). Impairments in these tasks appear to be location specific within the OFC. Difficulties in go/no-go tasks are seen more with lateral OFC lesions whereas difficulty with reversal learning and extinction tasks is more associated with damage to the caudal OFC (Rosenkilde 1979).

Emotional changes in humans have been observed after damage to the OFC. This is often seen as euphoria, irresponsibility, and lack of affect. Humans with early life OFC damage been show to never develop an understanding of normal social conventions and suffer from behavioral problems throughout life (Kringelbach and Rolls 2004). It has been suggested that emotions may be tied to processing rewards and punishments which could explain the role of the OFC in the emotional changes observed in lesion patients (Kringelbach and Rolls 2004).

Functional Imaging Studies

The OFC may also respond to pleasing physical stimuli. FMRI studies in humans have shown that it is more active in response to a light pleasant touch, such as the feel of velvet, than to a stronger, neutral touch (Rolls 2004). Imaging

studies in human subjects have demonstrated the OFC responds not only to physical rewards such as food and touch, but there is also activation in the OFC the corresponds to abstract rewards and punishments such as money won or lost in a game. A gambling task identical to that used by Hornak et al (2004) in lesion patients was used in an fMRI study by O'Doherty and colleagues (2001). This study demonstrated that bilateral activation of the medial OFC was associated with monetary gains, while lateral OFC activity was associated with loss of money.

Electrical Stimulation

The secondary taste cortex, which receives projections from the primary taste cortex, is located within the caudolateral portion of the OFC. In the macaque OFC neurons in this region respond to the taste of food only until the monkey is fed to satiety, at which point they stop responding. Monkeys will work to obtain electrical stimulation in this area, but only while hungry. It is suggested that these neurons are representing the reward value of taste, with that value being higher the hungrier the subject is (Rolls 2004). Taste can serve as both a powerful reward and punishment and may play a role in the learning functions of the OFC.

Ventromedial Prefrontal Cortex

The ventromedial prefrontal cortex is thought to play a role in social function, depression, and decision making. Damage to the frontal lobe, especially in the orbitofrontal or ventromedial regions, has often been linked with euphoria, inappropriateness, irresponsibility, difficulty learning from the past, and

a lack of concern for future consequences (Bechara et al 2000; Kringelbach and Rolls 2004). Both the dlPFC and vmPFC are implicated in regulating depression.

Lesion Studies

The Iowa Gambling task (IGT), a task in which subjects choose cards from one of multiple decks, and variations of it are frequently used to test impaired functions in patients with vmPFC lesions. The original task consists of four decks, two of which were advantageous with low initial gains and low eventual losses while the other two were disadvantageous with high initial gains but higher eventual losses (Bechara et al 1994). Normal controls avoid the disadvantageous decks and choose the low risk, low reward advantageous decks and produce an anticipatory skin conductance response before a selection that is disadvantageous. Patients with vmPFC lesions lack this anticipatory skin conductance response and tend to choose the decks with high initial rewards and do not shift from these decks despite the high losses (Bechara et al 1994).

Bechara and colleagues(2000) tested patients with bilateral vmPFC lesions on two variations of the IGT to discover what was leading these individuals to make ultimately disadvantageous decisions. They hypothesized that this behavior could be explained by a general apathy about future consequences, rather than insensitivity to punishments or hypersensitivity to reward. In this version of the IGT the decks began with either high punishments (advantageous decks) or low punishment (disadvantageous decks) with rewards coming later. As in the traditional IGT, patients with vmPFC lesions chose whatever deck appeared to be initially more advantageous or less

disadvantageous, regardless of future consequences. This suggests that these patients are not insensitive to punishment, as they avoided the deck with initial high penalties, or hypersensitive to reward, as they did not switch to the high gain decks. Additionally, the skin conductance responses of the lesion patients after receiving either a reward or punishment were not significantly different that those of controls. This suggests that an insensitivity to future consequences, rather than heightened sensitivity to reward or decreased sensitivity to punishment, influences the decisions of these patients (Bechara et al 2000).

Fellows and Farah (2005) tested patients on a variation of the IGT task to determine whether their poor performance could be due to a more general reversal learning deficit. They hypothesized that the IGT is a type of reversal task where subjects must shift their preference for initially profitable decks as the contingencies change and they become disadvantageous. In this variation the decks were shuffled so the subjects encountered losses first and gains later in the game, and thus did not develop an initial preference for disadvantageous decks. In this task vmPFC lesion patients did perform as controls, supporting the idea of a deficit in reversal learning contributing to poor performance on the IGT, however these results are also consistent with the idea that this is caused by insensitivity to future consequences (Fellows and Farah 2005; Bechara et al 2000).

In a gambling task where the probability of winning was explicitly stated and subjects could choose the amount to bet, both healthy controls and patients with vmPFC lesions choose advantageous bets (those with 50% or higher odds

of winning) and increased the amount of their bets as the odds increased in their favor. However, lesioned patients bet much higher amounts on average, which resulted in more bankruptcies, suggesting a lack of concern for potential loss, or perhaps as Bechara et al (2000) suggest, a lack of concern for future consequences (Clark et al 2008).

Lesions to the vmPFC also result in emotional disturbances which may lead to deficits in rational decision making. Koenigs and Tranel (2007) tested individuals with vmPFC damage on the Ultimate Game, a task where two players interact to split a sum of money. One player proposes an amount to give to the other while they keep the rest, the other player can choose to accept the offer (in which case they both get paid) or reject it (in which case no one gets paid). Very low offers are often rejected, even by control subjects, perhaps due to an emotional reaction. The rejection rate for those with vmPFC lesions are higher than controls for unfair offers, suggesting that successful emotional regulation aids in rational decision making (Koenigs and Tranel 2007).

Damage to the vmPFC can lead to profound emotional and social disturbances. A case study of a 50 year old male patient with a right frontal vmPFC lesion demonstrates these deficits. While the patient retained normal intellectual abilities, he displayed severe deficits in social functioning. He had difficulty relating to others and lacked an emotional reaction in response to stimuli generally thought to be disturbing. He was socially uninhibited and his speech was frequently obscene, graphic, violent, and sexual. He was also highly distractible and had difficulty staying focused. Prior to this lesion he did not

display these characteristics. It appears that this lesion affected his social function through a decrease in inhibition (Dimitrov et al 1999).

Interestingly, patients with left vmPFC lesions have not shown these dramatic changes in social behavior or personality. They also perform as normal controls of decision making tasks such as the IGT. Patients with right unilateral lesions had deficits on this task, similar to those with bilateral lesions. They were also much more likely to display personality changes and deficits in emotional processing. This suggests that vmPFC functions may be lateralized. The right vmPFC appears to be necessary for normal social and emotional behavior as well as decision making (Tranel et al 2002).

Functional Imaging Studies

Individuals who suffer from clinical depression have demonstrated higher than average levels of dlPFC activity and low levels of vmPFC activity compared to healthy controls. Koenigs and Grafman (2009) suggest that this imbalance of activity within the PFC may contribute to depression. These results are supported by studies of patients with bilateral vmPFC damage who have been shown to have much lower levels of depression compared to individuals with intact frontal lobes. Damage to the vmPFC may also alleviate depression in those that suffer it chronically. It is thought that the vmPFC may play a role in negative emotions through its connections to the periaqueductal grey (PAG), hypothalamus, and amygdala. It may also play a role in self-awareness as individuals with vmPFC lesions often show a decrease in shame and guilt (Koenigs and Grafman 2009).

Anterior Cingulate Cortex

The ACC seems to play a role in a variety of motor, emotional and cognitive functions. These include a possible role in self-control, error recognition, voluntary movements, reward learning, and visceromotor control (Allman et al 2001). It has been suggested the ACC can be divided into two distinct areas based on functions, a dorsal, cognitive division, and a rostral-ventral, emotion division (Bush et al 2000).

Lesion Studies

While it is often argued that the ACC contributed to decision making processes by detecting and correcting errors, Kennerley and colleagues (2006) claim that this process is less straightforward and choices are guided by a more complete history of actions and outcomes, many of which are not strictly correct or incorrect, simply more or less advantageous than the alternatives. They tested macaques with ACC lesions on reversal learning and dynamic foraging tasks. In the reversal learning task they were trained to perform two behaviors, one of which was rewarded. After they had reliably learned to perform the correct action the contingencies were reversed. The lesioned subjects took much longer to learn the reversal and made fewer correct responses, even following a correct, rewarded trial. They did not however perform worse than controls of trials following an error and they were able to correct errors and respond to consistently rewarded stimuli. However, they were unable to sustain this and took much longer than controls to respond consistently to stimuli that had a high probability of reward if it was not rewarded on every trial. Kennerley et al (2006)

suggest that the second task, dynamic foraging, is a more ecologically valid task representative of real life decision making. In this task there were two actions that the monkeys performed, but they were rewarded probabilistically, with one action being favored over the other. The lesioned monkeys took significantly more trials than controls to approach the optimal ratio of responses to maximize payout. This could be due to an inability to form a history of choice-outcome relations and use that history to assign value to each choice, which may be the mechanism through which the ACC guides decision making (Kennerley et al 2006).

The ACC also appears to play a role in emotional regulation. Humans with ACC lesions demonstrate drastic emotional changes including increased apathy, impulsivity, disinhibition, aggression as well as decreased anxiety and obsessive behavior (Devinsky et al 1995). While it has been shown that a reduction of anxiety and obsessive behavior can result from bilateral ablations to BA 24 without any damage to surrounding areas, most of these dramatic behavior shifts are seen more prominently in patients with other frontal lobe damage, such as damage to the OFC. This makes is less clear what role exactly, the ACC is playing in these changes (Devinsky et al 1995).

There also seems to be an affective component to the ACC functions. Subjects with lesions to the ACC often display apathy as well as reduced spontaneity of speech and actions. The ACC appears to play a role in the affective component of pain. A study of 18 chronic pain sufferers who received a cingulumotomy to relieve their suffering reported that their pain is still present, but that it no longer bothered or worried them (Cohen et al 1999).

Functional Imaging Studies

Activation of the ACC has been observed in many tasks involving response conflict. A study by Pardo and colleagues (1990) measured regional cerebral blood flow (rCBF) during a classic Stroop task where subjects had to report what color a color word was written in. They found more robust activity in the ACC in incongruent trial (such as the word blue written in orange) than in congruent trials (the word red written in red) (Pardo et al 1990). MacDonald and colleagues (2000) reported similar results in an fMRI study with the ACC showing greater activation on conflict trials than congruent trials. Additionally, greater conflict (longer reaction times) was associated with greater ACC activation (MacDonald et al 2000).

Braver and colleagues (2001) tested subjects on three choice discrimination tasks while brain activity was monitored through fMRI. These included a go/no-go task where subjects were told to respond to every letter except X (17% of the stimuli presented), an oddball task, where the subjects were told to respond only to the letter X (17% of stimuli presented), and a response selection task where subjects had to respond to every stimuli, using their left hand for X and their right hand for all non-X stimuli. The ACC was activated in each of these tasks, suggesting a role as a general conflict detector (Braver et al 2001).

The ACC is thought to play a role in decision making by adjusting behavior to optimize rewards, potentially through reward learning and error detection during cognitive tasks. The ACC receives dopaminergic innervation from cells in

the ventral midbrain. Blood flow to the ACC increases while receiving a reward, even an abstract reward such as money. Interestingly, in Parkinson's disease, which involves damage to dopaminergic cells, this activation does not occur in response to reward, which supports the thought that they play a role in reward processing (Allman et al 2001). Additionally, there are neurons in the ACC which activate in response to a decrease in reward. Activation of these neurons corresponds with a switch in behavior to a more rewarding task (Allman et al 2001).

It has been suggested that through detecting and correcting errors, the ACC can help shape future decisions. As discussed above, Kennerley and colleagues (2006) propose a different explanation; that rather than simply monitoring error, the ACC plays a role in decision making through learning to respond to generally rewarded stimuli or stimuli that are over the long term rewarding. This explanation may be more valid as errors in reality do not often resemble those that occur in many laboratory cognitive tests. Actions are often not simply correct or an error, but are differentially advantageous or disadvantageous and the ACC may monitor the history of errors and rewards to evaluate the value of certain actions (Kennerley et al 2006).

Electrical Stimulation

The ACC also plays a role in visceromotor control and movement execution. Electrical stimulation in the macaque leads to changes in respiratory and cardiac rate as well as blood pressure. Additionally, it causes vocalizations that seem to express an internal emotional state. Stimulation also leads to certain

primitive motions such as rubbing, kneading, and sucking (Devinsky et al 1995).

Akinetic mutism can result from bilateral ACC lesions, although this is temporary

unless these lesions occur in tandem with lesions to the supplementary motor

area or other areas and pathways involved in motor control, so while the ACC

may play some role in movement, it is not the sole area of the brain with that

function (Devinsky et al 1995).

There does seem to be a strong role of the ACC in affect and emotion

however. Electrical stimulation of different section of the ACC can elicit different

emotions and cingulate lesions without other frontal lobe damage do lead to

apathy and placidity in humans (Devinsky et al 1995).

Conclusion

As we have seen the OFC, vmPFC, and ACC are involved in a large

number of cognitive and behavioral functions. The OFC is highly involved in

reward learning and representing the reward value of reinforcers (Rolls 2004).

The ACC appears to uniquely monitor error and adjust performance to fit context

(Kennerley et al 2006) The vmPFC seems to play a large role in emotional

regulation as well as decision making abilities (Bechara et al 2000). These

functions are not unique to the vmPFC, as both the OFC and ACC seem to play

a role in them as well.

These regions have important roles in both emotional and social

regulation as well as reward based learning functions which both contribute to

rational decision making processes as well as allow individuals to be successful

in a highly social species. These functions are significantly impaired in subjects

with lesions and dysfunction in these regions can lead to profound social,

emotional, and decision making impairments.

Chapter III: Pathology in the OFC, vmPFC, and ACC

Abnormal structure and functioning in the OFC, vmPFC, and ACC has been implicated in a number of psychiatric disorders. These include, but are not limited to, anxiety disorders such as PTSD and OCD as well as schizophrenia as well and neurodevelopmental disorders such as Down's syndrome and Autism Spectrum Disorder.

Anxiety disorders

Both post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) are disorders involving exaggerated and inappropriate anxiety. PTSD has a clear etiology, presenting after a single (in the case of classic PTSD) or multiple (complex PTSD) traumatic events (Thomaes et al 2010). The etiology of OCD is less clear, however there have been reported cases of individuals developing OCD like traits following damage to the frontal lobe (Ogai et al 2005; Kim and Lee 2002). These disorders present very differently, however it has been proposed that both involve dysfunction of the amygdala along as well as portions of the PFC, specifically, the OFC (Milad and Rauch 2007).

Classic PTSD is characterized by re-experiencing the traumatic phenomena, avoidance, numbing, and hyper-arousal. Patients with complex PTSD typically present all of these classic symptoms, as well as impairments in affect regulation in the form of anger and impulsivity (Thomaes et al 2010). Classic PTSD is associated with reduced volume of the ACC as well as hypoactivity of the ACC during symptom provocation situations. Thomaes and colleagues (2010) analyzed MR images of 31 adult females with complex PTSD

following childhood abuse and compared the volume of the ACC and OFC with the volumes of these structures in healthy controls. They found a reduction of gray matter volume in the right dorsal ACC, which supports previous findings in individuals with classic PTSD.

In addition to reduced ACC volume Thomaes and colleagues (2010) also found a reduction of gray matter volume in the right OFC, which has not previously been demonstrated in classic cases of PTSD, except in cancer survivors (Thomaes et al 2010). The OFC plays a role in both extinction of conditioned fear as well as regulation of emotion and impulsivity and thus may be related to symptoms of PTSD. However, given the history of childhood abuse as well as the associated symptoms (anger, impulsivity) these individuals suffered from, it would be premature to conclude that the reduction of gray matter volume observed in the OFC is truly related to PTSD and not an associated condition (Thomaes et al 2010).

Milad and Rauch (2007) have proposed that PTSD as well as panic disorder (PD, characterized by spontaneous recurrent panic episodes) is the result of inability to inhibit inappropriate learned fear responses caused by hyperactivity within the amygdala along with dysfunction in the medial OFC and rostral ACC. Although there is support for this model, there is also evidence that lesions and dysfunction of the OFC can alleviate anxiety. More research is needed to draw strong conclusions about the role of the PFC in disorders involving panic (Milad and Rauch 2007).

OCD is characterized by intrusive thoughts often accompanied by repetitive behaviors that are usually performed to alleviate the accompanying obsessive thoughts and anxieties (Milad and Rauch 2007; Chamberlain et al 2008). Milad and Rauch (2007) propose that this is the result of hyperactivity of the lateral OFC and while there is evidence to support this, OCD has also been linked to reduced activation of the lateral OFC.

Chamberlain and colleagues (2008) tested 14 OCD patients and 12 unaffected first order relatives on a reversal learning task and their performance was compared to 15 healthy controls with no family history of OCD. Both OCD patient and their relatives displayed reduced activation in the lateral OFC compared to controls.

Volumetric differences of the OFC have also been associated with OCD. Choi and colleagues (2004) measured gray matter volume of the OFC through MR images in 34 OCD patient and 34 age matched controls. Patients had reduced gray matter volume in the left anterior OFC compared to controls. Another group measured volume of both gray and white matter of 26 OCD patients and 26 controls and compared volumes for the superior frontal gyrus, ACC, OFC, hippocampus, and amygdala. Both the amygdala and OFC (although not the other regions examined) had significantly lower volumes in patients compared to controls, indicating a correlation between structural differences in these regions and OCD (Szezko et al 1999).

Two case studies of individuals who developed OCD symptoms late in life support the hypothesis that dysfunction of the OFC plays a role in OCD. One

patient suffered damage to the right OFC following a traffic accident at 42. Following this injury he displayed significant behavioral changes including obsessions, compulsions to organize things and repeat tasks until they were just right as well as a compulsion to borrow umbrellas. He claimed that performing these repetitive tasks alleviated anxiety. Prior to this injury he had displayed no OCD traits and had no history of psychiatric disorders (Ogai et al 2005).

A second case study of a 66 year old man revealed a change in behavior following a left medial OFC infarct. He began displaying stereotypical OCD traits and had obsessions about something bad happening. This led to repetitive ritualized behaviors to alleviate these fears. This patient had no previous history of psychiatric disorders (Kim and Lee 2002). These cases both suggest the importance of the OFC in the development of OCD traits.

Schizophrenia

Schizophrenia is a disabling disorder characterized by cognitive and emotional disturbances that has been associated with dysfunctions in the dorsolateral PFC. New research suggests a role for the orbital and medial PFC, including the ACC (Wilder et al 1998; Nakamura et al 2008). Benes and Bird (1987) examined Nissl stained cortical sections from the OFC (BA 10), ACC (BA 24) and primary motor cortex (BA 4). They found no difference in spacing between neurons in BA 10 or 4, but a significantly higher nearest neighbor distance (the distance between a cell and its nearest neighbor of the same type) in layer III of BA 24. Layers IV and V in BA 24 displayed the same

tendency, but did not reach statistical significance. Layer V also showed significantly lower cell density in schizophrenics compared to controls.

In addition to differences in nearest neighbor difference and density schizophrenics also displayed altered cell layout. Qualitative investigations revealed aggregations of neurons in layer II that were smaller than in controls with more neuron sparse space between aggregations in schizophrenics compared to controls (Benes and Bird 1987).

In a follow up study Benes and colleagues (1991) later examined whether the cell density decreases seen in schizophrenics was due to large projection cells (pyramidal neurons) or smaller, inhibitory interneurons. In layer II of both the PFC and ACC interneuron density was decreased significantly in schizophrenics. To address whether or not the decrease in interneuron density was due to general neurodegenerative processes glia numbers were also measured. They did not differ significantly between schizophrenics and controls, suggesting that interneurons are differentially reduced and are not lower as a result of more general processes (Benes et al 1991).

A comparison of pyramidal neuron numbers revealed a different pattern. The density of pyramidal cells was generally the same in schizophrenics and controls with the exception of layer V in the PFC. In this layer schizophrenic patients display a higher density of pyramidal neurons than controls. In a later study the same group found decreases in pyramidal neuron density in layer IV of the ACC. This was not seen in the previous study and could be due to the fact

that individuals in this later study were more severely affected than those in the 1991 study (Benes et al 2001).

Schizophrenic patients also display deficits on certain cognitive tasks. Waltz and Gold (2007) administered a reversal learning task to 34 patient and 24 healthy controls. Both the OFC and ACC have been implicated in reversal learning tasks. Patients and controls both learned the initial rule with ease, but when this initial contingency was reversed the performance of patients was significantly worse. No functional imaging was done in this study, however the behavior results strongly resembled the effects of OFC lesions (Waltz and Gold 2007; Fellows and Farah 2003).

Carter and colleagues (2001) tested 17 schizophrenic patient and 10 controls on a cognitive task where they were instructed to press a target button when a particular sequence of two letters was displayed on a computer screen and to press a non-target button in every other case. Activity was measured in the ACC during this task to analyze how patients processed and responded to errors. In normal controls ACC activity was associated with errors which were followed by greater reaction time on the next trial, that is, their performance slowed following an error. This was congruent with the current evidence of the role the ACC plays in error monitoring. Patients displayed much less ACC activity on error trial and significantly less slowing of reaction time following error trials. This does support the idea that ACC dysfunction may relate to the cognitive disturbances seen in schizophrenia. However, reduced ACC activity has also been associated with antipsychotic drugs. A follow up study of patients before

beginning antipsychotic drugs is needed to see if this factor confounded the results of this study (Carter et al 2001).

Down's Syndrome

Down's Syndrome (DS), or trisomy 21, is a relatively common disorder affecting approximately 1 of every 800 children born and one of the most common causes of mental retardation. Deficits in learning and memory processes are also common with DS. DS is caused by a complete (in 95% of cases) or partial (in the remaining 5% of cases) third copy of chromosome 21 (Pinter et al 2001). Due to the well-defined chromosomal aspects and cognitive deficits present in DS, it provides an excellent opportunity to examine the relationship of genetic and cognitive abnormalities, a relationship in which neuroanatomy may play a crucial role.

There are conflicting reports on the appearance of DS brains at birth, Schmidt-Sidor and colleagues (1990) claim that they are a similar size with similar gross morphology at birth while Kaufmann and Moser (2000) make the claim that DS brains are smaller than controls at birth and display an immature pattern of gyral development. It is clear that by 3-5 postnatal months differences in gross morphology as well as at the cellular level are apparent (Crome et al 1966).

In early childhood DS brains display a reduction in the rate of frontal lobe growth compared to controls as well as a reduction in total neuron numbers. Although these abnormalities were significant, there were relatively modest.

Volumes and neuron numbers in DS patients were within the low end of the values seen in controls (Crome et al 1966).

An MRI study conducted by Pinter and colleagues (2001) compared the total volume of 16 DS patients with a mean age of 11.3 years with 15 controls. They found an 18% reduction in total brain volume in the DS patients and a significant reduction in size in the cerebellum, frontal, and temporal lobes. When adjusted for total brain volume however the frontal lobe of the DS patients was no smaller than expected (Pinter et al 2001).

A study by Raz and colleagues (1995) provides evidence for a specific pattern to the volume reduction seen in the frontal lobes of DS patients. Raz et al (1995) compared MRIs of 13 adult DS patients and 12 controls. The anterior cingulate gyrus of DS patients was significantly smaller than that of the controls, while the size of the OFC was relatively preserved in the DS patients (Raz et al 1995). In a study of normal aging conducted by Raz and colleagues (1997) MRIs were obtained from 148 healthy individuals. Among these healthy controls there was a significant age related decline in gray matter, however this occurred in a slightly different pattern. There was a significant decline in OFC gray matter with increased age and the anterior cingulate gyrus was relatively preserved (Raz et al 1997).

In a study in aging in DS patients Taipel and colleagues (2004) examined MRIs of 27 DS adults with a mean age of 41 and a range of 25 to 62 years. Gray matter reduction occurred throughout the parietal, occipital, and frontal cortices.

Gray matter was notably preserved in the anterior cingulate and orbitofrontal cortices (Taipel et al 2004).

In addition to the gross anatomical and volumetric differences, there are also cellular differences in the brains of DS patients. Spine abnormalities are the most commonly reported difference, and both abnormally long and abnormally short spines have been observed as well as reductions in spine number and density. The spine reduction observed in DS does not appear to be a commonly found in the brains of patients with non-DS related mental retardation; it instead seems to be a specific trait of DS (Marin-Padilla 1976; Suetsugu and Mehraein 1980).

Although there are relatively few Golgi studies conducted in the PFC of DS patients a study conducted by Suetsugu and Mehraein (1980) revealed spine abnormalities within the cingulate gyrus. They examined pyramidal neurons in layer V of the cingulate gyrus of 7 post-mortem DS brains which ranged in from 3-23 years which were compared to 5 patients with mental retardation and 5 healthy controls. They measured the number of spines of the apical dendrites of these pyramidal neurons and discovered a significant reduction of spines in the DS brains compared to both control groups (Suetsugu and Mehraein 1980). This reduction of spines in the cells of the cingulate gyrus fits the pattern of spine reduction seen in DS patients in other regions of the brain such as the visual cortex and may be a general feature of DS brains (Becker et al 1986).

Autism Spectrum Disorder

Unlike Down's syndrome Autism Spectrum Disorder (ASD) does not have a well-defined genetic cause, but patients do have a distinct behavioral profile including social impairments and restricted, repetitive behaviors (Agam et al 2010). There are a number of disorders that often occur co-morbidly with autism, including epilepsy, which creates potential difficulties for neuroanatomical studies (Amaral et al 2008). Additionally, functional imaging studies are often limited to higher functioning ASD patients, excluding patients with the most severe cases of ASD (Agam et al 2010). Despite these limitations there are a number of interesting findings in both functional imaging and neuroanatomical studies of ASD patients.

One of the earliest common indicators of ASD is increased brain growth in the first year of life. Courchesne and colleagues (2003) measured the head circumference (an accurate proxy for brain size) of 48 patients diagnosed with ASD between the ages of 2 and 5 years, at various points in time from birth to 5 years. The mean head circumference of these patients was smaller than controls at birth, but by 6-14 months was significantly larger, falling in the 84th percentile of head circumference sizes. This indicates an early, rapid period of overgrowth in the first year of life (Courchesne et al 2003). This increased size persists until late childhood and has been observed in subjects as old as 8-12 years of age. However, by adolescence and adulthood there was no greater brain size observed in ASD patients (Courchesne and Pierce 2005). While no definitive reason for the overgrowth is known it may be due to an increase in the number

neurons and/or minicolumns in the cortex, both of which have been observed in ASD patients (Courchesne and Pierce 2005).

Courchesne and colleagues (2011) investigated the early overgrowth of the PFC is ASD patients. They compared neuron numbers in 7 young ASD patients, ages 2-16 years, to healthy controls and found significantly higher neuron counts within the ASD group. This overgrowth occurred primarily in the dlPFC, which had a 79% higher mean neuron number in patients. Smaller, but significant, overgrowth was observed in the medial PFC which had a 29% higher mean neurons count in ASD patients. This study suggest that the period of early overgrowth observed in the brains of ASD patients is due at least in part to increases in the number of neurons (Courchesne et al 2011).

Casanova and colleagues (2002) examined minicolumn structure in the dlPFC in 9 ASD patients. They observed minicolumns that were more numerous and narrower than those seen in controls. These findings were supported by a study conducted by Buxhoeveden and colleagues (2006). They examined two ASD cases, one of a two year old child, the other an adult and compared these to 5 controls which ranged in age from 2-75 years. They also found narrower minicolumns within the dlPFC as well as in the OFC (Buxhoeveden et al 2006). Together these studies suggest an increase in the number of minicolumns produced prenatally.

Due to the social impairments seen in autism the PFC is often the subject of investigation into abnormalities of ASD brains. Both Hardan and colleagues (2006) and Girgis and colleagues (2007) used MRIs to examine the volume of

the OFC in older children (from 8-12 years of age) and adults with ASD. Girgis et al (2007) found smaller gray matter volumes in the right lateral OFC of 11 young males with ASD compared to age matched controls. The total volume of the OFC did not vary significantly between patients of controls (Girgis et al 2007). These results were similar to a finding by Hardan et al (2006); this group also found volumetric differences within the right lateral OFC. Again, they found no significant difference in total OFC volume in patients and controls. In the children and adolescents in this study however, the right lateral OFC was significantly smaller than that of controls. This pattern was reversed in the adults of the study. The ASD adults possessed greater right lateral OFC volumes than controls (Hardan et al 2006).

Volumetric differences have also been found in the ACC which plays a role in affect recognition as well as monitoring of social behavior, skills which are often impaired in ASD patients. Haznedar and colleagues (1997) used MRI to compare ACC volume between seven ASD to that of age and sex matched controls. The ASD patients had overall lower ACC than volumes than controls, however this size disparity was not uniformly distributed throughout all areas of the ACC. The volume of BA 25 was in fact larger in the ASD patients, while BA 24' was smaller in the right hemisphere of ASD patients compared to controls (Haznedar et al 1997). A number of cellular abnormalities have also been observed in the ACC of ASD patients.

In an early study Kemper and Bauman (1998) investigated sections of the anterior cingulate gyrus in nine ASD patients, adults at the time of death. In eight

of these they found significantly smaller neurons which were more densely packed than the cells of controls. They also observed an indistinct laminar in portions of the gyrus (Kemper and Bauman 1998). A later investigation by Simms and colleagues (2009) revealed additional abnormalities in the ACC. They examined BA 24 in nine ASD patients and found decreased density in the infragranular layers of BA 24c along with decreased cell size, measured by soma area and volume, in both the infragranular and supragranular layers of BA 24b (Simms et al 2009). The also measured the density of VENs specifically throughout BA 24. As a whole the mean density of VENs was not significantly different in the ASD patients compared to controls. However, within the ASD patients two distinct groups were noticed. Three cases had a significantly higher density of VENs compared to controls, while the other six had a much lower density of VENs. In the patients with lower overall VEN density this was distributed across all areas of BA 24. In the three patients with higher overall density, this increase was localized to BA 24c, they in fact had has slightly lower density of VENs in BA 24a and BA 24b than controls. (Simms et al 2009). This is notable as in typically developing individuals the density of VENs is lowest in BA 24c (Vogt et al 1995).

Functional imaging studies of ASD patients have also revealed abnormalities within the ACC, OFC, and vmPFC. Agam and colleagues (2010) compared 11 adults with high functioning ASD to healthy controls on a saccade inhibition task. ASD patients appear to have difficulties inhibiting behavior that is contextually inappropriate which may be due to altered ACC activity. They

monitored eye movements and used fMRI to examine activity within the dorsal ACC, an area with a role in ocular motor control. The patients made more errors on trials involving saccade inhibition compared to controls as was expected. On correctly performed inhibition trials they exhibited lower levels of dorsal ACC activity compared to controls (Agam et al 2010). The poor performance and low activity within the dorsal ACC may be related to the structural abnormalities seen in this area.

The repetitive behaviors observed in autism are believed to be related to deficits with executive functioning. Schmitz and colleagues performed an fMRI study with 10 high functioning adult ASD patients and 12 healthy controls on a go/no-go task. Both groups performed equally well on this task, but activity patterns varied within the OFC and vmPFC between patients and controls. In control subjects the right OFC and vmPFC displayed high activity levels during this task while in ASD patients the left OFC and vmPFC had higher activity levels (Schmitz et al 2006). This may be related to the volumetric abnormalities observed in the right OFC of ASD patients (Girgis et al 2007; Hardan et al 2006).

ASD presents difficulties for researchers due to the high incidence of co-morbid disorders and the lack of a uniform neuroanatomical profile. Further studies with greater sample sizes could refine and add to the current knowledge and uncover traits that may be universal among or specific to particular subsets of ASD patients.

Conclusion

Structural and functional abnormalities within the OFC, vmPFC, and ACC are associated with a variety of affective and neurodevelopmental disorders. The exact neuroanatomical profiles of these disorders is still unknown, further studies would provide valuable information about how these conditions appear in the brain and how genetics may relate to cognition and behavior.

Chapter IV: Development

Development of the central nervous system (CNS) begins with the formation of the neural tube, from which the entire CNS will be formed. The interior of this tube forms a hollow cavity which will eventually become the ventricular system of the brain. After fusing the neural tube expands initially into three vesicles which later subdivide into five vesicles. Two of these, the telencephalon and diencephalon will become the forebrain, the mesencephalon becomes the midbrain, and the metencephalon and myelencephalon become the hindbrain (Stiles 2008).

Another major change to the gross anatomy of the brain that begins in the fetal period is gyrification. This process begins with the formation of the longitudinal fissure, which separates the two hemispheres of the brain, which begins in the rostral portion of the brain at eight weeks post conception and proceeds to develop caudally until it is complete. Following this event primary sulci begin to form, with the cingulate sulcus developing relatively early, followed a few weeks later by frontal sulci. Following the formation of the primary sulci, secondary and tertiary sulci form, a process which continues postnatally (Stiles and Jernigan 2010).

Gyrification of the developing brain occurs in an orderly manner and is constrained by the physical properties of the cortex and by the mechanical factors operating to fold it. Minimization of axonal tension across the cortex is one possible factor which may explain the increased thickness of the cortex in gyral compared to sulcal convolutions (Hilgetag and Barbas 2005).

Changes also take place on a cellular level prenatally. Lining the hollow cavity of the neural tube is a layer of neural progenitor cells in what is known as the ventricular zone. These neural progenitors divide to form most of the cortical projection neurons. These proliferating cells then migrate out to the cortex and form a laminar structure from the inside out, with the earliest born cells forming the innermost layers and later born cells migrating to more superficial layers (Stiles 2008).

The orderly migration of cells into their correct layer is regulated in part by reelin, a protein secreted by Cajal-Retzius cells. Reelin plays a role in cell interactions and signals cells to stop at the correct layer (Stiles 2008). Differentiation of cells is based in part on their birth date, with earlier born cells becoming neurons for deeper layers. Studies of transplanted neural progenitors in donor animals reveal that they undergo fate restriction. At first these progenitors are capable of producing many different types of cells, but with time are restricted to only producing the cells of more superficial layers (Stiles 2008).

These migrating neurons also begin to form connections, or synapses, prenatally, a process which continues postnatally. In line with the general pattern of brain development, the maturation of synapses proceeds in a caudal to rostral manner (Stiles 2008). Connections in primary motor and sensory areas mature earliest. This is followed by development in the temporal and parietal areas, and finally higher order association areas such as the PFC. In primary sensory areas, such as the primary visual and auditory cortices, synaptic density peaks relatively early, by around three months of age (Casey et al 2005). In contrast, synaptic

density in the PFC does not peak until three and half years of age and continues to decline for many years (Casey et al 2005). Neuronal density in the PFC is quite high at birth but decreases rapidly for the first year, and continues to decline slowly through adolescence (Huttenlocher 1979).

During the prenatal period most structures of the brain are developed and neurogenesis is largely complete however many changes continue postnatally. Myelination of axonal fibers begins prenatally but is largely a postnatal process (Stiles and Jernigan 2010). Rapid brain growth also occurs postnatally, with the brain reaching 90% of its adult volume by age 6 (Courchesne et al 2000).

Gray matter growth continues postnatally, the cortex as a whole reaches peak gray matter density by 6 to 9 years of age after which it begins to decline as a result of cell death and synaptic pruning. The PFC develops relatively late compared to other cortical regions. Gray matter in the PFC increases linearly prenatally and continues to increase postnatally for the first 11 to 12 years. Following this there is a substantial loss of gray matter density in the PFC during adolescence (Giedd et al 1997). Unlike the rest of the PFC, the cingulate gyrus displays a more gradual, linear loss of gray matter during late childhood and adolescence (Sowell et al 2012).

During this same period white matter is increasing in the brain with increased fiber tract growth and myelination. This growth continues linearly through childhood and adolescence. As with gray matter, white matter develops in a temporally and regionally specific course. In the frontal lobe white matter volume continues to increase well into early adulthood, much later than other

regions of the brain (Giedd et al 1997). Within the frontal lobe there is evidence of differences in regional growth of white matter. Reiss and colleagues (1996) examined the brains of 100 healthy individuals aged 5-17 through MR images. As expected, they found an increase in white matter in the PFC as a whole in the time period. However, they found a decrease in white matter in the OFC during the period, suggesting that perhaps this area matures earlier than more dorsal regions of the PFC (Reiss et al 1996).

These structural changes that occur during childhood relate to the significant cognitive development seen in childhood and adolescence. Although performance on cognitive tasks continues to improve through adolescence, cerebral volume does not increase significantly after age 6, and gray matter begins to decline in early adolescence. While gray matter begins to decline fiber tract myelination continues, suggesting that these gains in cognitive skills may be related regressive events such as loss of synaptic density as well as strengthening of the remaining connections and improved connectivity though myelination (Casey et al 2000).

Functional Development of the PFC

The PFC plays an important role in cognitive skills such as memory, inhibition, and attention. Performance on tasks involving these skills increases dramatically throughout childhood. Limited studies have been conducted on how children develop these skills, whether the amount or location of activity in the brain changes with age or some other developmental process takes place.

In a study of memory and inhibition 6 children between 9 and 11 were given a fMRI scan while completing a memory task previously studied in adults, In this memory task the children had to respond to a letter if and only if it matched the letter presented two letters back. A comparison task was also given where the children had to respond when the presented letter matched a pre-specified cue (Casey et al 2005). This task required children to keep a representation of the previous letters they had seen (or the letter specified at the beginning of the task) while inhibiting incorrect responses such as responding when two sequential letters matched. Although adults were able to perform this task much more successfully than the children examined, both age groups displayed similar activation in the ACC and dlPFC. However, given the relatively narrow age range and lack of young children in this study, this does not rule out the possibility of activation patterns changing with age, as is seen in other cognitive tasks (Casey et al 2000).

In another fMRI study comparing children and adults in a Go/No-go task, which involves attention and inhibition, activation did differ between children and adults. In this task nine older children (7 to 12 years) and nine young adults (21 to 24 years) were asked to respond to all letters presented to them except one pre-specified letter. As expected, the adult group was able to perform this task more successfully than the children. Both groups also showed activation in the ACC as well as the orbitofrontal, inferior, and middle frontal gyri. However, activation in these regions in was greater in children, who also showed activation of the dlPFC. Although adults showed some activity in the dlPFC, it was relatively

minor. As performance increased the amount of total activation decreased. This decrease is region specific. Decreased ACC activity is associated with better performance, perhaps due to few errors, and increased OFC activity is associated with better performance. Children appear to use more volume in their brain to complete this task and more readily recruit the dlPFC to solve tasks involving inhibition than adults (Casey et al 2000).

These results suggest that, at least in tasks of inhibition, children show different patterns of activation than adults. In tasks of memory children may recruit the same brain areas as adults, although a wider age range would provide more robust results. Both of these studies relied on relatively old children, with no individuals below school age which limits the scope of their results significantly. More studies with more individuals and wider age ranges are needed to fully understand how brain activation develops in children during cognitive tasks. Relatively little is known about developmental processes in young primates, in part due to the scarcity of tissue in this age range (Casey et al 2000). However, a greater understanding of development can provide a better base for understanding the adult state. Additionally, changes in developmental processes can have dramatic effects on a species (McNamara 2002). Minor changes to the timing of cell proliferation and migration can produce vast changes to total cortical size for example (Rakic 1995). More studies of development across a range of ages and species could provide valuable information for understanding the unique cognitive skills seen in humans.

Conclusion

The PFC develops quite late compared to other portions of the human brain. This allows it a great deal of plasticity which may relate to the high degree of cognitive change and development we observe that parallels the structural changes that occur in the PFC during childhood. This region of the brain is uniquely suited to allow humans to both learn rapidly and be able to flexibly adjust their behavior to suit the context and their current needs. Immaturity in this area may relate to the behavioral inflexibility often observed in young children. Normal development of the PFC allows children to learn about their environment and use that information to shape their behavior appropriately.

Chapter V: Evolution of the Prefrontal Cortex

There is some question as to when exactly the PFC first appeared and it seems as if the answer to this depends on how exactly the PFC is defined. There are some claims that all mammals possess a PFC and a significant amount of research has been done on the PFC of rats due to their ease of use for neuroscientific work (Passingham and Wise 2012). While it has been argued that rats have a PFC that is fully representative of all mammals, including primates, it seems clear that this is not the case. Rodents, along with other mammals, do possess a homologue of the agranular subdivision of the primate PFC. Although there are reports of the PFC in non-primate mammals containing a granular subdivision as well, these finding are questionable (Passingham and Wise 2012). Primates are the only animals that indisputably possess a granular division of the PFC and will be the focus of this discussion.

A comparison of the galago (a strepsirhine) and macaque (an anthropoid) by Preuss and Goldman-Rakic provide evidence of the early state of the primate PFC. While both species possessed agranular and granular areas of the PFC the granular region was much greater in the macaque. The galago has homologues of the caudal PFC and granular portions of the OFC, but lacks many of the granular areas found in anthropoid primates. In the macaque many more granular prefrontal areas were found, including the lateral, dorsomedial, ventral, and polar PFC (Preuss and Goldman-Rakic 1991).

It must be noted that both modern galagos and macaques have evolved separately for millions of years following their separation so the galago brain

must not be viewed as a primitive macaque brain. Loss of structures is possible during evolution and is a potential alternate explanation for the lack of many granular areas in galagos. However, fossil evidence suggests that modern galagos have frontal lobes as large as or larger than early primates, making loss of these areas in strepsirhines a less plausible explanation than the addition of these areas in haplorhines (Preuss and Goldman-Rakic 1991; Passingham and Wise 2012).

Passingham and Wise (2012) have proposed that as primates moved from a nocturnal to diurnal lifestyle they faced greater pressures from predation which led to larger and more sophisticated social groups. These new granular prefrontal areas support cognitive functions that make it possible to quickly learn and adapt to new situations. It would have allowed early anthropoids to develop more complex foraging strategies and live in more complex social groups (Passingham and Wise 2012).

It has long been argued that one of the major changes that took place during hominid evolution is the expansion of the frontal lobe beyond what would be expected for an ape brain of human size. Apes as a whole do display a hyperscaled frontal lobe compared to other anthropoids and it was believed that humans represented another such expansion when compared to other apes (Teffer and Semendeferi 2012). Given the role of the frontal cortex in higher order association function it was believed that this differential expansion of the frontal lobe played a large role in the vast behavioral and cognitive differences we see between humans and the rest of the great apes. However, more recent

work has suggested that this is not the case. The human frontal lobe, when compared to the other great apes is no larger than expected of an ape brain of its size (Semendeferi et al 1997).

An alternate hypothesis proposed was that although the frontal lobe as a whole may be the expected size, the PFC may have been differentially enlarged to occupy more of the frontal cortex. This does not appear to be the case. In regards to both total frontal lobe volume and volume of the frontal lobe occupied by the prefrontal cortex humans fit the general ape trends (Smaers et al 2011).

In terms of gross anatomy most regions of the human brain scale as would be expected for an ape brain of its size. There are some exceptions to this and the evidence supports the idea of mosaic brain evolution and reorganization of areas in the frontal lobe (Semendeferi et al 2010). Two sections of the prefrontal cortex that have been investigated by Semendeferi and colleagues are Brodmann's areas 10 and 13.

BA 10 is located in the frontal pole of the ape brain and is cytoarchitectonically similar across all of the great apes, including humans. There is also evidence of reorganization in this area. In the human BA 10 all six layers of the cortex are clearly visible. Layers I, II, and IV are thin, but easily distinguishable. Layer IV possess the granular cells characteristic of the prefrontal cortex (Semendeferi et al 2001). Layers III and V are wider with large pyramidal neurons. These are slightly larger in layer V than layer III. In layer III pyramidal neurons display a gradual increase in size, with those near layer IV being larger than those located more superficially (Semendeferi et al 2001).

In absolute terms human BA 10 is much larger than in other apes, which is unsurprising given humans' much larger brain, but BA 10 is larger in relative terms in humans compared to the rest of the great apes (Semendeferi et al 2001). The human area 10, also characterized by lower cell body density, demonstrated in this study through the grey-level index (GLI), a measure of the ratio of stained cell bodies to neuropil space. Lower GLI values indicate more space between cell bodies and potentially more room for connections between neurons. The human brains examined had the lowest GLI levels of all apes, which demonstrated greater neuropil space in the human area 10. This follows the general pattern of lower cell packing density with increased brain size seen in primates. Within the human brain the GLI is lower in the supragranular layers II and III, which are involved in cortico-cortical connections, than in infragranular layers V and VI which are involved in connections with subcortical structures of the brain (Semendeferi et al 2001).

BA 10 is thought to play an important role in higher cognitive abilities. Lesions of this area are associated with impaired cognitive abilities including thinking and planning future actions (Damasio and Anderson 1993). This area seems to have undergone a great increase in size during hominid evolution as well an increase in space that could allow for greater connectivity, particularly in short cortico-cortical connections with other higher order association areas (Semendeferi et al 2001). This may have played an important role in the development of humans' unique cognitive abilities.

Another sector of the PFC, BA 13, has been known to be part of the posterior OFC in macaques, and was demonstrated to be present in the great apes in an investigation by Semendeferi and colleagues (1999). It can be distinguished by the presence of an incipient layer IV, which is more fully developed in anterior section of the OFC, and cells that display a horizontal pattern of striation in layers V and VI (Semendeferi et al 1999).

In humans BA 13 is most strongly identified where the medial and posterior orbital gyri merge; this is true of most other apes as well. BA 13 in humans consists of a thin layer II, a thicker layer III with prominent pyramidal neurons, an incipient layer IV as mentioned previously, a very prominent layer V with large pyramidal neurons, and a layer VI which also contains pyramidal neurons and has a poor white matter boundary (Semendeferi et al 1999).

Unlike area 10, the volume of area 13 does not display much variability in absolute terms across humans and the rest of the great apes, with the exception of the bonobo, which has a smaller volume. Following this the human BA 13 is much smaller in relative volume compared to the rest of the brain in comparison to gorillas, chimpanzees, and orangutans which all have much smaller total brain volumes than humans. The volume of the bonobo BA 13 is similar in relation to their total brain volume to the relative volume of the human BA 13. In terms of anterior to posterior length humans have the shortest area 13, which is similar in length to that of the bonobo (Semendeferi et al 1999).

Similar to BA 10, in BA 13 the human brain has lower GLI levels than the other great apes, although the gibbon has an even lower GLI level. The

supragranular layers again display less cell packing density than infragranular layers. As with BA 10 this may indicate increased space for connections. In both the human and the bonobo brains BA 13 occupies a relatively small portion of the OFC which has more subdivisions and is less homogenous than the OFC of other apes. Orangutans present the greatest contrast to this, with a relatively small OFC which is occupied largely by BA 13 (Semendeferi et al 1999). Given the role of the OFC in social behaviors this could be seen as related to the relatively solitary lifestyle of orangutans compared to far more social bonobos and humans. However, it is important avoid jumping to conclusions prematurely.

As demonstrated in BA 10 and 13, humans have increased space between neuronal cell bodies relative to other great apes in certain areas of the brain. Another way to examine spacing differences and differential connectivity across species is to look at horizontal spacing between cell and minicolumns in the neocortex as well as white matter distribution.

Vertical arranged pyramidal neurons form minicolumns, a basic unit of organization of neurons in the cortex. Horizontal spacing distance (HSD) can be measured between neurons which could indicate the amount of space available for increased dendritic arborization. In a study by Semendeferi and colleagues HSD in layer III was measured in the frontal pole, primary motor, and primary somatosensory, and primary visual cortices, BA 10, 4, 3, and 17 respectively (Semendeferi et al 2011).

HSD did not vary greatly across the species examined except in BA 10. In this area humans had significantly greater HSD compared to BA 10 in the other

great apes as well as compared to other areas in the human cortex (Semendeferi et al 2011). This indicates that increased horizontal spacing did not occur on the cortex as a whole during hominid evolution, rather that certain areas of the brain underwent reorganization. Greater HSD in layer III most likely reflects greater dendritic numbers and complexity (Semendeferi et al 2011).

In addition to HSD, width of minicolumns themselves can be considered. Relative to brain size, humans have narrower minicolumns than other apes. However in absolute terms they are wider which allows more space for synapses. Due to their enlarged cortex humans also have more minicolumns than other apes, as well as more space between them, potentially providing them with a much greater capacity for information processing (Semendeferi et al 2011).

Another way to look at potential differences in connectivity between humans and nonhuman primates is to look at white matter. White matter can be divided into core and gyral white matter (GWM), which is the white matter immediately under the cortex. White matter tends to increase with increased brain size as well as axon width and myelination, the latter two of which increase conductance velocity, leading to increased speed of information transfer between cells.

In humans there is evidence for increased volume of gyral white matter in relation to core white matter. This increase in gyral white matter could be related to an increase in connectivity between nearby regions of the cortex (Schenker et al 2005). This supports the idea of increased short range cortico-cortical

communication suggested earlier when discussing lower cell packing density in the supragranular layers of the cortex.

Compared to more rostral areas of the PFC the ACC is relatively primitive, but changes have occurred in this area. Vogt and colleagues compared the ACC of macaques and humans and discovered a number of differences. Area 24' (the dorsal sector of BA 24) is relatively longer, measured anterior to posterior, in humans. BA 32 encompasses a much wider area in humans compared to nonhuman primates. In the macaque this area is located only rostral to BA 24, while in humans it extends around BA 24 both rostrally and dorsally (Vogt et al 1995).

In addition to changes in the ratio of anatomical areas, one class of cells found in the ACC, von Economo neurons (VENs), seem to have undergone evolutionary changes. VENs are present in humans and all the great apes, and have more recently been found in other primates (Evrard et al 2012). While they were once believed to be a primate specialization they have since been found in other large brained social mammals such as cetaceans and elephants. There are more VENs present in the human brain in comparison to other apes, but the density of VENs to other cell types is lower in humans than other apes. This is possibly due to an increase in other classes of neurons rather than a decrease of VENs (Allman et al 2010). These cells may allow the fast paced communication between cells required for animals that live in complex social groups.

Conclusion

Research on evolution of the human brain is largely done through comparative studies of primates. Comparisons across a range of species can allow us to see how hominid brains may have changed through time. However, it is important to keep in mind that no modern animal can be viewed as the primitive version of another modern animal. That is, apes brains are not scaled up monkey brains just as human brains are not scaled up ape brains (Semendeferi 1998). For this reason it is important to avoid coming to premature conclusions about ancestral states of the brain or how differences in neural structure may be related to cognitive and behavioral changes.

Chapter VI: Conclusions

The OFC, vmPFC, and ACC make up the agranular and dysgranular

region of the PFC. The OFC, which also includes a granular subdivision, is a

sensory integration site and can represent the reward value of reinforcers. It also

has strong reciprocal connections with the amygdala. Taken together this pattern

of connections suggests roles in emotional processing as well as reversal

learning which is supported by studies of lesioned subjects as well as functional

imaging studies (Kringelbach and Rolls 2004).

The vmPFC, through connections with the hypothalamus, periaqueductal

gray, and regions in the PFC appears to play a role in emotional regulation and

well as decision making which is supported by results from the Iowa Gambling

task and the Ultimate Game. Individuals with vmPFC lesions display poor

emotional regulation along with irrational decision making skills (Bechara et al

2000; Koenigs and Tranel 2007).

Similar to both the OFC and vmPFC, the ACC has connections with other

PFC areas as well as with subcortical structures including the amygdala. It also

plays a role in emotional regulation and executive functions including error

detection and attention (Devinsky et al 1995).

As a whole these regions contribute to emotional regulation and reward

learning, which are both critical to decision making processes. Additionally the

role these regions play in emotional and social regulation is vital in a species as

highly social as humans. Deficits in these regions, particularly the right vmPFC,

can produce profound disturbances in emotion and personality (Tranel et al 2002).

Although relatively little is known about the development of these regions specifically, structural changes during development of the PFC parallel important behavioral and cognitive changes that occur in children and adolescents, such as increasing performance on the IGT from childhood through adolescence into adulthood (Hooper et al 2004).

There are few comparative studies of these regions in primates, especially apes. However, there is evidence of reorganization within the PFC as well as increased cell spacing and altered ratios of certain cell types such as VENs in the ACC (Allman et al 2010). These results suggest a general trend toward greater connectivity and more efficient communication within the human brain as compared to nonhuman primates (Teffer and Semendeferi 2012).

Even fewer developmental comparative studies have been conducted in humans or apes, in large part due to the scarcity of juvenile tissue. More investigations into the development of the PFC across a range of nonhuman primates could further illustrate possible changes that have occurred in developmental processes through hominid evolution. Developmental studies in non-human primates are exceedingly rare and often confounded by the use of human reared animals. However, these studies would reveal important information about the behavioral development of non-human primates to relate to neuroanatomical findings.

The OFC, vmPFC, and ACC play an important role in allowing humans learn about their environment and appropriately use that information to shape and adjust their behavior. Abnormalities in these regions may lead to impairments in these abilities, as observed in ASD, and immaturity in these regions may relate to the behavioral inflexibility often observed in young children. More developmental studies including behavioral, imagining, and histological work on a wide range of primate species would provide information about the structural development of these regions and the connections between them as well as the behavior and cognitive developments that occur with these anatomical changes.
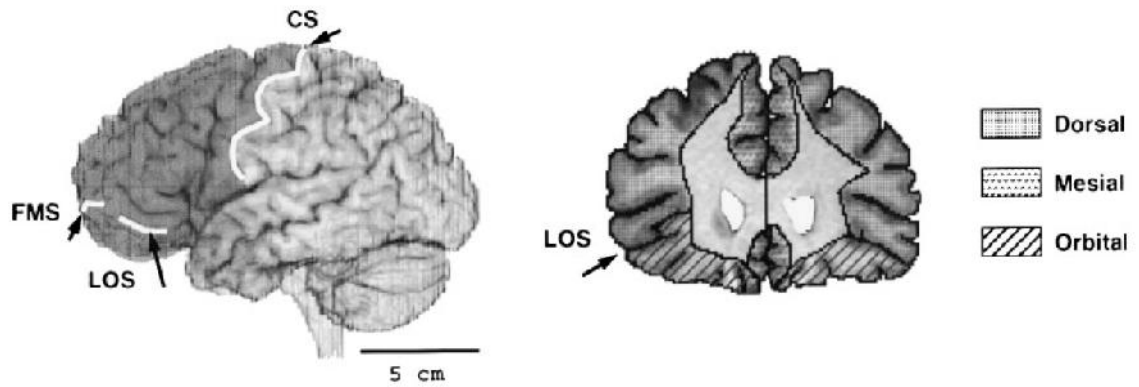
Figure 1. Lateral view (left) and coronal section (right) of the human brain depicting major landmarks, the central sulcus (CS), frontomarginal sulcus (FMS), and lateral orbital sulcus (LOS), and showing the dorsal, mesial, and orbital subdivisions. Adapted from Semendeferi et al 1997.
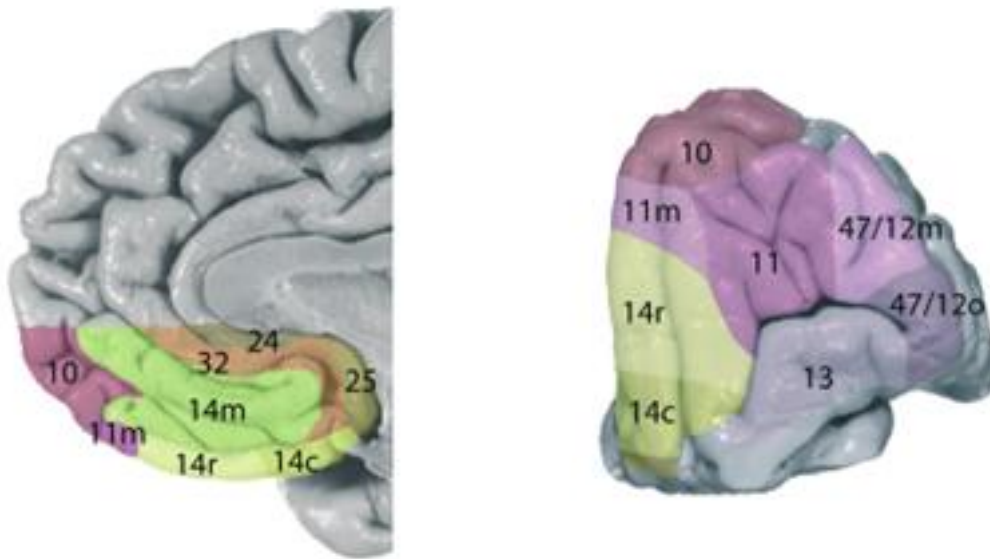
Figure 2. Parcellation of the human orbitofrontal and ventromedial prefrontal cortices. The OFC is comprised of BA 10, 11, 11m, 14r, 14c, 13, 47/12m, and 47/12o. The vmPFC is comprised of Ba 14m, 25, and 32. Adapted from Mackey and Petrides (2010).
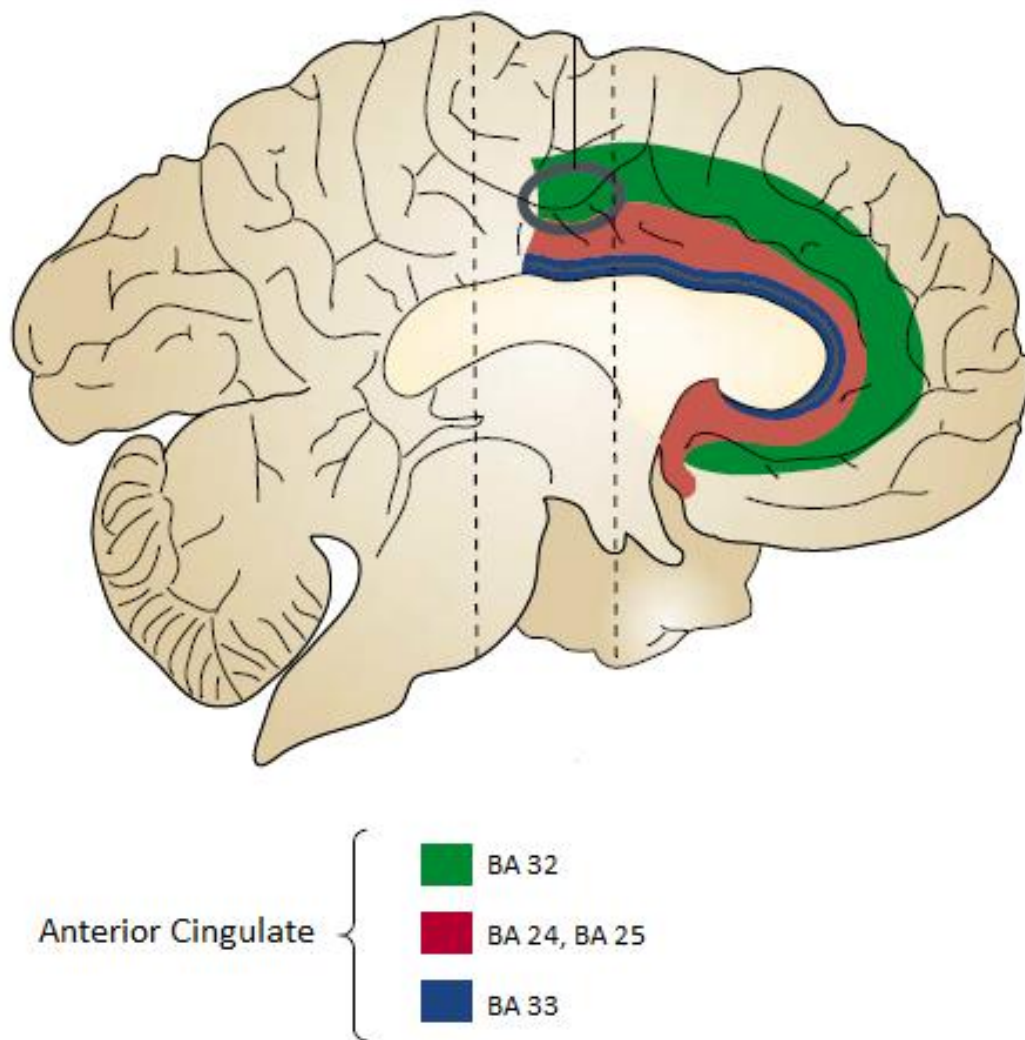
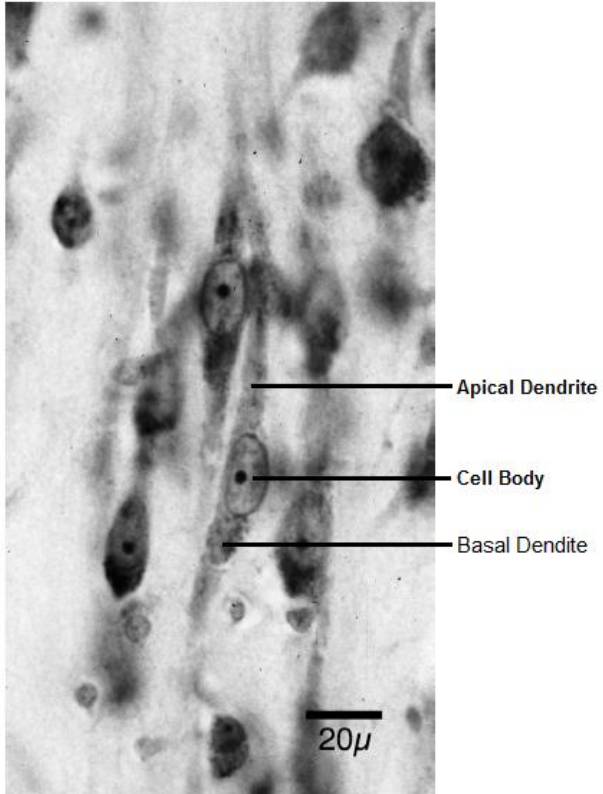Figure 3. Anterior cingulate cortex. Adapted from Paus (2001).

Figure 4. Pair of VENs located in the human ACC. Adapted from Allman et al (2001).

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