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Size always matters: An investigation of the influence of connection length on the organization of white-matter in typical development and in autism.

A dissertation submitted in partial satisfaction of the requirements
for the degree of Doctor of Philosophy

in

Cognitive Science

by

John D. Lewis

Committee in charge:

Professor Jeffery L. Elman, Chair
Professor Marta Kutas
Professor Terrence J. Sejnowski
Professor Martin I. Sereno
Professor Jeanne Townsend

2008

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The dissertation of John D. Lewis is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

2008

To

My mother

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Acknowledgements

I came to San Diego on a mission: to transform myself from a computer scientist / linguist to a developmental neuroscientist. I believe I have made inroads in that direction. For the freedom to do that, I owe a huge debt of gratitude to Jeff Elman, as well as the rest of my committee. Jeff listened to my vague, not-yet-thought-through proposal, and saw that it could be worth pursuing. And despite that it was somewhat far removed from his area of interest, he supported me in my attempt to turn those ideas into a dissertation.

The pursuit of data with which to explore those ideas led me to Eric Couchesne's Laboratory for Research on the Neuroscience of Autism in 2003, where I first tested my hypothesis. That research eventually led to publications on which I was not even included as a coauthor — which led to my departure from that lab. Thank you very much, Eric Courchesne.

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All chapters of this dissertation, with the exception of the first and last, have either been published in, or are submitted to, scientific Journals. Chapter II has been published, and appears as *Lewis, J.D., Theilmann, R.J., Sereno, M.I., and Townsend, J. (2008) The relation between connection length and degree of connectivity in young adults: A DTI analysis, Cerebral Cortex, doi:10.1093/cercor/bhn105.* Chapter III has been submitted for publication as *Lewis, J.D., Theilmann, R.J., Travis, K., Onishi, M., and Townsend, J. The relation between connection length and degree of connectivity*

in children and adults: A DTI analysis. Chapter IV has been published, and appears as *Lewis, J.D. and Elman, J.L. (2008) Growth-related neural reorganization and the autism phenotype: a test of the hypothesis that altered brain growth leads to altered connectivity, Developmental Science, 11(1), 135-155.* Chapter V has been submitted for publication as *Lewis, J.D., Theilmann, R.J., Lincoln, A., and Townsend, J. The relation between connection length and degree of connectivity in autism: A DTI analysis of the impact of brain overgrowth on connectivity.*

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Abstract Of The Dissertation

Size always matters: An investigation of the influence of connection length on the organization of white-matter in typical development and in autism.

by

John D. Lewis

Doctor of Philosophy in Cognitive Science

University of California, San Diego, 2008

Professor Jeffrey L. Elman, Chair

Across species, increases in white matter volume outpace increases in gray-matter volume, but increases in gray-matter volume outpace increases in the size of the corpus callosum. This dissertation explores the hypothesis that this hyposcaling of the callosum stems from the impact of the conduction delays and cellular costs of the long-distance connections on normal developmental mechanisms.

Neuroanatomy research to date has only indirectly examined this relation, using measures such as brain volume. The research in this dissertation uses diffusion tensor imaging to more directly measure the relation between the length of the interhemispheric connections and the degree of connectivity — the ratio of between-area connections to total projection neurons in the areas connected. Using tractography to detail the patterns of interhemispheric connectivity and to determine

the length of the connections, and formulae based on histological results to estimate degree of connectivity, we show that, across normal young adult males, connection length is significantly negatively correlated with degree of connectivity in the anterior, posterior, and body of the callosum. Using the same methodology, in typically developing boys a significant relation between connection length and degree of connectivity was found only in the posterior of the callosum. The combined results indicate that the relation between connection length and degree of connectivity develops during childhood and adolescence.

Children with autism are known to have enlarged brains during the first years of life. This is predicted to lead to decreased long-distance connectivity. To explore this prediction, neural networks which modeled inter-hemispheric interaction were grown at the rate of either typically developing children or children with autism. By 2 years of simulated age, the networks that modeled autistic growth showed a reduced reliance on long-distance connections, performance reductions, and reductions in structural connectivity.

Using the same methodology as with the adults and children, the relation between connection length and degree of connectivity in adults with autism was examined. Connection length and degree of connectivity showed the typical negative relation, but with a reduced degree of connectivity in anterior regions — the locus of development during the period of maximal brain overgrowth, and where axon diameters are smallest.

Chapter I
General Introduction

Ramón y Cajal (1853–1934) postulated that neural circuit design is under pressure to minimize cellular costs and conduction delays (1995). Recent work has related these design principles to a variety of cross-species scaling facts (Changizi, 2001, 2005; Changizi & Shimojo, 2005; Chklovskii, Schikorski, & Stevens, 2002; Chklovskii & Stevens, 2000; Kaas, 2000; Karbowski, 2001, 2003, 2007; Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994; Zhang & Sejnowski, 2000). The current work extends these ideas to individual variation in brain size within humans, and investigates these scaling relations during development, and the impact of deviant growth on brain organization. Central to this research is the hypothesis that cellular costs and conduction delays influence brain organization via normal developmental mechanisms, and thus differences in brain size during development will result in differences in structural and functional organization.

I.A Scaling the Brain

Large brains are not big small brains. Differences in brain size, across species, are associated with a variety of differences in brain structure. As brain volume increases, the organization of both gray- and white-matter changes, and also the relation between gray- and white-matter. Increases in the number of cortical neurons are accommodated by increasing cortical surface area. Cortical thickness increases only slightly (Hofman, 1985, 1989; Jerison, 1982; Prothero, 1997a; Prothero & Sundsten, 1984), and is balanced by a decrease in neuron density (Jerison, 1973;

Prothero, 1997b; Tower, 1954); so, ignoring some architectonic variation, and some perhaps ecology-driven variation, each unit area of cortex contains approximately the same number of neurons, regardless of brain size (Braitenberg & Schüz, 1998; Powell, 1981; Rockel, Hiorns, & Powell, 1980). The density of synapses in a unit area of cortex is also approximately constant across cortical layers, regions, and species of different brain sizes (Braitenberg & Schüz, 1998). And thus, the number of axons entering or exiting the white-matter per unit cortical area is also approximately constant across differences in brain size; and axon diameter increases slightly (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Olivares, Montiel, & Aboitiz, 2001), so white-matter expands rapidly (Changizi, 2005; Danilewsky, 1880; Zhang & Sejnowski, 2000). The distribution of long- and short-distance connections, however, does not remain constant; as cortical volume increases, relative long-distance connectivity decreases (Hopkins & Rilling, 2000; Rilling & Insel, 1999a; Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994). And with increasing brain size, there is a substantial increase in cortical folding (Hofman, 1985, 1988; Jerison, 1982; Prothero & Sundsten, 1984).

I.B Optimal Wiring

I.B.1 Conduction Delay

The conduction delay associated with either a myelinated or an unmyelinated axon is primarily a function of its diameter and length (Waxman, 1977). For myelinated fibers, conduction velocity is approximately linearly proportional to axon diameter (Hursh, 1939; Waxman, 1977). For unmyelinated fibers, conduction

velocity is approximately proportional to the square root of axon diameter (Hoffmeister, Janig, & Lisney, 1991; Waxman, 1977). Across a variety of species, from least shrew to man, most long-distance fibers — at least in the corpus callosum — are under 1 μm in diameter, and there is little scaling with brain size (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Jerison, 1991; Olivares, Montiel, & Aboitiz, 2001; Wang et al., 2008); but the length of these fibers does vary with brain size. Thus, for both myelinated and the majority of unmyelinated fibers, conduction delay will increase with brain size; a small percentage of myelinated fibers scale with brain size such that the shortest cross-hemisphere conduction times increase little with increases in brain size (Wang et al., 2008). Interhemispheric conduction delay for the average myelinated fiber has been estimated to range from approximately 1 msec in the least shrew to approximately 20 msec in humans. And for species with larger brains, interhemispheric conduction delays will presumably be even greater.

Ringo *et al* (1994) hypothesized that the conduction delays in large brains are too long to support complex, time-critical computations, and that such functions would be lateralized in large brains. They investigated the implications of this inference with connectionist models. Networks with two fully recurrent 'hemispheres', inter-connected with either short or long conduction delays, were trained on association pairs, and then the interhemispheric connections were lesioned. The models with the longer interhemispheric conduction delays showed less impact of lesioning, implying that the longer delays forced greater hemispheric independence. Based on these results they predicted that species with large brains would be found to

have a high degree of functional lateralization, and that this would be reflected in callosum size relative to brain size.

Comparative neuroanatomy research to date is consistent with the Ringo *et al.* (1994) prediction. Across a wide variety of species, though increases in cerebral white matter volume outpace increases in neocortical gray matter volume (Rilling & Insel, 1999b; Zhang & Sejnowski, 2000), increases in cortical gray-matter volume outpace increases in the size of the corpus callosum (Hopkins & Rilling, 2000; Rilling & Insel, 1999a) and presumably other long-distance connections, as well.

Within species, and within individual brains, fiber diameter also varies considerably. Myelinated fiber sizes range from 0.2 to more than 10 μm in diameter in the human corpus callosum (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). Fiber length also varies considerably; the homotopic connections that traverse the human callosum are estimated to be between 80 and 180 mm in length (Ringo, Doty, Demeter, & Simard, 1994). Thus conduction delays will vary from a few hundred msec for small unmyelinated axons, which have conduction velocities of 1 m/sec or less, to about 1.5 msec for the largest myelinated fibers. For the majority of myelinated fibers, the interhemispheric conduction delay will be between about 10 msec and 25 msec, varying with connection length and fiber diameter. The median axon diameter increases from anterior to posterior, from 0.6 μm in the genu to 1 μm in the splenium (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). Thus, for an average diameter fiber 180 mm long in the genu, the conduction delay would be approximately 34.5 msec, and for a fiber 80 mm long the conduction delay would be approximately 15.4 msec.

The increased conduction delays associated with increased connection length can be mitigated by either increases in axon diameter or the addition of a myelin sheath (Ritchie, 1995). Both of these adjustments, however, add significantly to volume, and thus exacerbate the problem by increasing the distance across the brain (Chklovskii & Stevens, 2000). For both myelinated and unmyelinated axons, volume is proportional to the square of the external diameter of the fiber; whereas conduction velocity is proportional to axon diameter and the square root of axon diameter, for myelinated and unmyelinated axons, respectively. Across species, there is some increase in the percentage of myelinated callosal fibers (Wang et al., 2008), and some increase in diameter for a small percentage of myelinated fibers (Ringo, Doty, Demeter, & Simard, 1994; Wang et al., 2008), but not changes sufficient to generally compensate for the increased length of the fibers (Olivares, Montiel, & Aboitiz, 2001; Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994; Wang et al., 2008). Such adjustments would lead to an unwieldy and expensive brain (Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994).

I.B.2 Cellular Costs

Neural material is expensive to construct, to maintain, and to operate. The larger the brain, the greater the cost (Aiello, 1997; Aiello, Bates, & Joffe, 2001; Isler & van Schaik, 2006; Karbowski, 2007; Sherwood et al., 2006). Larger brains have a greater number of neurons (Pakkenberg & Gundersen, 1997), and a greater number of glia per neuron (Herculano-Houzel, Mota, & Lent, 2006; Sherwood et al., 2006). A fraction of the neurons also show increases in axon diameter and length (Ringo, 1991;

Wang et al., 2008); surface area increases with the square of axon diameter and with length, and membrane thickness increases with axon diameter, as well. These neurons also have larger dendritic arbors, and cell bodies (Changizi, 2005). Further, an increased percentage of the fibers are myelinated in larger brains (Wang et al., 2008), and axon diameter and myelin sheath thickness are positively correlated (Fraher & Dockery, 1998; Fraher et al., 1990; Friede & Samorajski, 1967). Myelination requires protein and lipid synthesis (Kandel, Schwartz, & Jessell, 2000).

Neurons also consume considerable energy. Neural tissue has a much higher metabolic rate than most other tissues (Aiello, 1997). The adult human brain consumes approximately 20% of the total energy used (Hofman, 1983). The contribution to this by a single unmyelinated neuron is proportional to the total surface area of the neuron. This is primarily due to Na^+/K^+ pumps (Kandel, Schwartz, & Jessell, 2000); and Na^+/K^+ pumps continually operates, even when the cell is not firing, in order to maintain the neuron at the resting potential. But the metabolic costs associated with neural firing are far greater (Attwell & Laughlin, 2001). Myelinated neurons incur considerably lower Na^+/K^+ pump-related costs, but those costs increase with increasing cell size. The synaptic contribution to energy consumption per neuron is proportional to the number of synapses per neuron (Karbowski, 2007); this also scales with brain size (Changizi, 2005). Thus, the metabolic cost per neuron increases with brain size, and so too the total metabolic cost of the brain (Karbowski, 2007). The metabolic cost of cortex scales with cortical volume with the exponent ~0.85; the metabolic cost of white-matter scales with the exponent ~0.75 (Karbowski, 2007).

The latter exponent agrees with supply-limited models of brain scaling (Banavar, Damuth, Maritan, & Rinaldo, 2002; West, Brown, & Enquist, 1997).

I.B.3 Minimal Wiring Length

Consideration of these aspects of neural architecture has led to the idea that these are forces which have, through evolution, resulted in a design in which the total length of cortical connections is minimized, while inter-area connectivity is preserved (Cherniak, 1995; Chklovskii, Schikorski, & Stevens, 2002; Chklovskii & Stevens, 2000; Kaas, 2000; Karbowski, 2004; Mitchison, 1992; Van Essen, 1997; Zhang & Sejnowski, 2000). Minimal total axon length ensures reasonably short conduction delays, and metabolic costs that are near-optimal. This idea has been used to explain a variety of aspects of scaling — *e.g.*, the rate at which white-matter scales with gray-matter across species spanning several orders of magnitude (Zhang & Sejnowski, 2000); the increase in modularity with increases in brain size (Kaas, 2000); the placement of cortical areas (Cherniak, 1994, 1995); and the increase in gyrification with increasing brain size (Van Essen, 1997) — as well as various scale-free characteristics of brain structure — *e.g.*, why retinotopic maps, ocular dominance columns, and orientation preference patterns exist (Allman & Kaas, 1974; Chklovskii, 2000a; Chklovskii & Koulakov, 2000; Cowey, 1979; Durbin & Mitchison, 1990; Koulakov & Chklovskii, 2001; Mitchison, 1991); why cortical regions are separated (Mitchison, 1992); why gray- and white-matter are partitioned (Ruppin, Schwartz, & Yeshurun, 1993); and why axonal and dendritic arbors have the particular size and branching angles that they do (Cherniak, 1992; Chklovskii, 2000b).

I.C Optimal Wiring via Development

There are reasonable candidate mechanisms by which these forces could impact the growth and retention of connections during development. Adult patterns of connectivity are arrived at via processes of overproduction and elimination. Naturally occuring cell death eliminates 20 to 80 percent of neurons, depending on species and cortical region (Oppenheim, 1985, 1991). Across a variety of mammals, on average, approximately 50 percent more connections are generated than are retained in the mature animal (Janowsky, 1993). Humans show similar levels of neural loss (Huttenlocher, 1994, 2002; Huttenlocher & Dabholkar, 1997). Synaptic density increases until about age 2 years, at which time it is approximately at double the adult level (Huttenlocher, 1979). Synaptic and neuronal density then steadily decline to adult levels over the next 1 to 2 decades (Huttenlocher, 1979). This naturally occuring cell death is activity- and competition-based, and so can be considered selective pruning. Post-synaptic neurons release neurotrophic factors, which are taken up by the pre-synaptic neurons through specific receptors in their terminal boutons. These neurotrophic factors are delivered according to the pre-synaptic neuron's role in generating activity in the post-synaptic neuron, and are a limited resource. The competition for these neurotrophic factors favors more active neurons with low metabolic demands. Firing rate appears to either be invariant with connection length, or to decrease, and the metabolic cost of spike transmission scales up linearly with connection length (Wang et al., 2008). Thus, long-distance connections will generally be disfavored, and more so as their length increases.

Moreover, the differences in conduction delays and cellular costs associated with differences in connection length are substantially greater in the developing brain than in the mature brain. Axon diameters and levels of myelination do not reach adult levels until at least late adolesence (Benes, Turtle, Khan, & Farol, 1994; Brody, Kinney, Kloman, & Gilles, 1987; Pujol, Vendrell, Junqué, Martí-Vilalta, & Capdevila, 1993). Conduction velocity increases with axon diameter, and unmyelinated axons are considerably slower and more metabolically expensive than myelinated axons. And in keeping with this, children have longer interhemispheric conduction delays (Brizzolara, Ferretti, Brovedani, Casalini, & Sbrana, 1994; Fagard, Hardy-Léger, Kervella, & Marks, 2001; c.f. Ratinckx, Brysbaert, & d'Ydewalle, 1997), and the glucose metabolic rate is approximately double that of adults at 9 years of age (Chugani, 1998). Data relating differences in brain size during development to conduction delay or metabolic costs are not available. But brain size does not increase greatly after 5 years of age, so assuming that connection length varies as much in children as in adults — *i.e.*, by approximately 30 mm — conduction delay for a myelinated axon with a diameter of 0.5 μm will differ by ~7 msec; and metabolic costs scale linearly. Thus, given that neurotrophic factors are limited, brain size differences during development should be expected to have a considerable impact on the growth and retention of long-distance connections.

I.D Early Brain Overgrowth in Autism

Autism is a developmental disorder defined by impairments in reciprocal social interactions, impairments in verbal and nonverbal communication, and a

restricted repertoire of activities and interests [American Psychiatric Association, 1994]. There are four aspects of each of these three areas of impairment, and only six of the twelve aspects are required for a diagnosis of autism. So the behavioral phenotype is variable. The onset of the disorder also varies: some children exhibit a failure to progress appropriately and show gradual development of any aberrant behaviors, others appear to develop normally for one or two years and then show sudden losses in acquired behaviors and the appearance of aberrant behaviors (Bailey, Phillips, & Rutter, 1996; Filipek et al., 1999; Kolvin, 1971; Janet E. Lainhart et al., 2002; Luyster et al., 2005; Short & Schopler, 1988; Siperstein & Volkmar, 2004).

Children with autism spectrum disorder also have abnormally large brains after about the second year of life (Aylward, Minshew, Field, Sparks, & Singh, 2002; Bailey et al., 1993; Bailey et al., 1998; Bauman & Kemper, 1985; Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Davidovitch, Patterson, & Gartside, 1996; Dementieva et al., 2005; Fombonne, Roge, Claverie, County, & Fremolle, 1999; Hazlett et al., 2005; Kemper & Bauman, 1998; J.E. Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000; Piven et al., 1995; Sparks et al., 2002; Woodhouse et al., 1996). Brain size can be multiple standard deviations above the norm for several years thereafter (Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Dementieva et al., 2005; Hazlett et al., 2005; Redcay & Courchesne, 2005; Sparks et al., 2002). This provides a natural test case for the hypothesized impact of differences in the length of long-distance connections on the organization of connectivity. The increased conduction delays and cellular costs

associated with the longer long-distance connections of these larger brains should lead to reduced long-distance connectivity during development.

Indeed, large-scale functional and anatomical under-connectivity has been reported in autism (Alexander et al., 2007; Boger-Megiddo et al., 2006; Castelli, Frith, Happe, & Frith, 2002; Egaas, Courchesne, & Saitoh, 1995; Hardan, Minshew, & Keshavan, 2000; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; Kilian et al., 2008; H. Koshino et al., 2005; Manes et al., 1999; Murias, Webb, Greenson, & Dawson, 2007; Piven, Bailey, Ranson, & Arndt, 1997; Ring et al., 1999; Vidal et al., 2006; Waiter et al., 2005). Structural reductions have been reported in the anterior of the callosum (Hardan, Minshew, & Keshavan, 2000; Manes et al., 1999; Vidal et al., 2006), the posterior of the callosum (Egaas, Courchesne, & Saitoh, 1995; Piven, Bailey, Ranson, & Arndt, 1997; Waiter et al., 2005), and more broadly in the callosum (Alexander *et al.*, 2007; Boger-Megiddo *et al.*, 2006; Vidal *et al.*, 2006). Individuals with autism show significantly fewer large positive correlations in regional cerebral metabolic rates for glucose between frontal and parietal regions (Horwitz, Rumsey, Grady, & Rapoport, 1988). Functional connectivity — *i.e.*, the degree of synchronization — between the frontal and parietal areas of activation is lower for autistic than for control participants, during an executive function task (Just, Cherkassky, Keller, Kana, & Minshew, 2007); and between Broca's area in the frontal lobe and Wernicke's area in the superior temporal gyrus, during sentence comprehension (Just, Cherkassky, Keller, & Minshew, 2004). Also, there is evidence that the mirror-neuron system (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, &

Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996) — which spans from visual cortex to the inferior frontal gyrus — is dysfunctional in autism (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006; Oberman et al., in press).

Under-connectivity has thus been associated with many aspects of the behavioral phenotype — *e.g.*, deficits in language (Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006), executive function (Just, Cherkassky, Keller, Kana, & Minshew, 2007), face processing (Hideya Koshino et al., 2008), Theory of Mind (Mason, Williams, Kana, Minshew, & Just, 2008), and imitation (Rizzolatti & Craighero, 2004; Williams, Whiten, & Singh, 2004). Further, assuming that the abnormal early brain overgrowth in autism leads to this later-observed under-connectivity (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008; Lewis, Elman, & Courchesne, 2005), there will be an abnormally rapid loss of long-distance connections during early childhood. This will plausibly be extremely functionally disruptive, and may explain the timing of the onset of the behavioral symptoms, and the frequent occurrence of developmental regression.

The hypothesis that normal developmental mechanisms, influenced by the early brain overgrowth in autism, cause the loss of a greater number of long-distance connections (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008; Lewis, Elman, & Courchesne, 2005) thus potentially provides a parsimonious explanation for the etiology of under-connectivity, and for many aspects of the behavioral phenotype. But, it is not known to what extent individual differences in brain size during development underlie these

group findings of under-connectivity, or, in fact, how individual differences in brain size correlate with connectivity.

I.E Overview of the Dissertation

The following four chapters present the studies which make up the body of this dissertation. Chapter II presents a structural imaging study of the relation between connection length and degree of connectivity in young adults. The study uses diffusion tensor imaging and tractography to overcome some of the limitations of previous studies (Jäncke, Preis, & Steinmetz, 1999; Jäncke, Staiger, Schlaug, Huang, & Steinmetz, 1997). Tractography allows the patterns of interhemispheric connectivity and the length of the connections to be determined. Formulae based on histological results utilize volumetric measures from magnetic resonance imaging to provide reasonable estimates of degree of connectivity. This study establishes that the hyposcaling of the corpus callosum reported in cross-species studies (Rilling & Insel, 1999a) is also seen with individual variation in human adults: connection length is negatively correlated with degree of connectivity in the normal adult brain.

Chapter III presents a study comparing the relation between connection length and degree of connectivity in children to the relation found in young adults. The study utilizes the same methodology as that used in adults to investigate this relation in children. The study shows that the relation observed in the adults is established over development. The children showed a significant relation between connection length and degree of connectivity only in the posterior of the callosum; the adults showed a significant relation in the anterior, the body, and the posterior of the callosum.

Chapter IV presents a computational modeling study of the impact of the abnormal early brain overgrowth in autism on connectivity. The prediction that this early brain overgrowth will lead to decreased long-distance connectivity was tested using neural networks which modeled interhemispheric interaction — similar to those used by Ringo *et al* (1994). These networks were grown at the rate of either typically developing children or children with autism. By 2 years of simulated age, the networks that modeled autistic growth showed a reduced reliance on long-distance connections, performance reductions, and reductions in structural connectivity. This study thus provides a proof of concept.

Chapter V presents a structural imaging study of the relation between connection length and degree of connectivity in young adult males with autism, using the same methodology as used to examine this relation in typical adults and children. The results confirm the prediction: connection length and degree of connectivity showed the typical negative relation, but with a reduced degree of connectivity in anterior regions. That connection length and degree of connectivity show the typical negative relation is consistent with the hypothesized influence of individual differences in connection length. And, that it is the anterior of the callosum that shows a significantly reduced degree of connectivity fits with evidence that developmental changes are most rapid in the anterior of the callosum during early childhood (Thompson *et al.*, 2000), and that the smallest diameter fibers, and thus the fibers most effected by differences in connection length, are in the anterior of the callosum (Aboitiz, Scheibel, Fisher, & Zaidel, 1992).

Chapter VI is a brief summary and discussion of the findings of the dissertation.

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Chapter II
The Relation Between Connection Length and Degree of Connectivity in Young Adults: A DTI Analysis

II.A Abstract

Using diffusion tensor imaging and tractography to detail the patterns of inter-hemispheric connectivity and to determine the length of the connections, and formulae based on histological results to estimate degree of connectivity, we show that connection length is negatively correlated with degree of connectivity in the normal adult brain. The degree of interhemispheric connectivity — the ratio of interhemispheric connections to total cortico-cortical projection neurons — was estimated for each of five sub-regions of the corpus callosum in 22 normal males between 20 and 45 years of age (mean 31.68; stddev 8.75), and the average length of the longest tracts passing through each point of each sub-region was calculated. Regression analyses were used to assess the relation between connection length and the degree of connectivity. Connection length was negatively correlated with degree of connectivity in all five sub-regions, and the regression was significant in four of the five, with an average r^2 of 0.255. This is contrasted with previous analyses of the relation between brain size and connectivity, and connection length is shown to be a superior predictor. The results support the hypothesis that cortical networks are optimized to reduce conduction delays and cellular costs.

II.B Introduction

Variation in brain size, both across species and across individuals within a species, is associated with variation in the organization of both gray- and white-matter. Increases in white matter volume outpace increases in gray-matter volume (Frahm, Stephan, & Stephan, 1982; Rilling & Insel, 1999b; Schlenska, 1974; Zhang & Sejnowski, 2000); but increases in gray-matter volume outpace increases in the size of the major white-matter bundles that interconnect the cerebral hemispheres (Jäncke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Rilling & Insel, 1999a). The disproportionate increase in white-matter volume has been interpreted as a consequence of the high-degree of connectivity within the cortex (Allman, 2000; Frahm, Stephan, & Stephan, 1982; Zhang & Sejnowski, 2000). The hyposcaling of the commissural white-matter bundles likely reflects decreases in the degree of inter-hemispheric connectivity — the ratio of interhemispheric connections to total cortico-cortical projection neurons — with increases in brain size, and has been hypothesized to be due to the increased conduction delays and cellular costs associated with these fibers (Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994), which tend to be longer in larger brains (Braitenberg, 2001). The conduction delay associated with either a myelinated or an unmyelinated axon is primarily a function of its diameter and length (Waxman, 1977). The conduction delay for long-distance connections must therefore increase with increases in brain size, unless there is a proportional increase in axon diameter — which appears not to be the case (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Jerison, 1991; Olivares, Montiel, & Aboitiz, 2001; Schüz & Preissl, 1996) — and the cellular costs for such connections will increase regardless (Karbowski, 2007).

This hypothesis thus predicts a negative correlation between connection length and degree of connectivity.

Neuroanatomy research to date has only indirectly tested this prediction. The use of magnetic resonance morphometry has limited these studies to measures such as brain volume and cortical surface area; and differences in brain shape would suggest that these measures are not particularly good indices of the length of the long-distance connections. This paper reports on a study which uses diffusion tensor imaging (DTI) to more directly measure the predicted relation between the length of the long-distance connections that traverse the corpus callosum and the degree of interhemispheric connectivity.

II.C Methods

II.C.1 Subjects

A total of 22 normal healthy males ranging between 20 and 45 years of age (mean 31.68; stddev 8.75) participated in the study. All subjects gave informed consent, and the study was approved by the ethics committee at the University of California, San Diego.

II.C.2 Imaging and Image Processing

All subjects were scanned at the UCSD Center for fMRI on a GE Signa EXCITE 3.0T short bore scanner with an eight-channel array head coil. Four types of images were acquired from each subject: (i) one set of 3D T_1-weighted images (Fast Gradient Echo, Spoiled Gradient Recalled; Echo Time [TE] = 3.1ms; flip angle = 12°;

Number of EXcitations [NEX] = 1; Field Of View [FOV] = 25cm; matrix=256x256); (ii) two sets of T_2-weighted images (dual spin-echo, Echo Planar Imaging [EPI]; Time to Repetition [TR] = 15s; TE = 89ms; 45 axial slices; NEX = 2; FOV = 24cm; matrix = 128x128; resolution = 1.875x1.875x3 mm; 3mm interleaved contiguous slices); (iii) two sets of diffusion weighted images isotropically distributed along 15 directions (dual spin-echo, EPI; TR = 15s; TE = 89ms; 45 axial slices; NEX = 2; FOV = 24cm; matrix = 128x128; resolution = 1.875x1.875x3 mm; 3mm interleaved contiguous slices; b value = 1,400 s/mm^2); and (iv) fieldmaps matched to the diffusion-weighted images.

Note that two sets of diffusion weighted images were acquired, each with a NEX of 2; thus each image was acquired four times. Likewise for the T_2-weighted images, which were acquired together with the diffusion weighted images.

Fieldmaps were acquired before the first diffusion-weighted images were acquired, and, in cases where there was between scan motion, an additional set of fieldmaps was acquired after the second.

The T_1-weighted images were converted to AFNI (Cox, 1996) — an open source environment for processing and displaying MRI data — and the resulting volume was anterior-commissure (AC) - posterior-commissure (PC) aligned. The boundary and divisions of the corpus callosum were then identified on the midsagittal slice of the AC-PC aligned T_1-weighted images using a semi-automated procedure created for this project. The boundary and divisions of the corpus callosum were determined as follows. A point manually inserted at the boundary of the callosum was used to seed an intensity-based floodfill of the callosum; additional points were used,

in cases where the division between the callosum and fornix was unclear, to identify the boundary of the callosum in that region. The outline of the resulting area was then used as a starting point for an implementation of the active contour algorithm which smoothed the boundary, and moved it to the center of the gradient at the edge of the callosum. The resulting boundary was then divided into five regions via Clarke's method (Clarke, Kraftsik, van der Loos, & Innocenti, 1989) —*i.e.*, the midline of the callosum was computed and divided into five equal length segments, and the shortest length lines that cut the callosum at the points defined by these segments were the regional boundaries. Figure II-1 illustrates the sub-regions arrived at via this procedure.

Four-dimensional volumes were created from both sets of diffusion-weighted images; software developed by the UCSD Center for fMRI was used to correct the

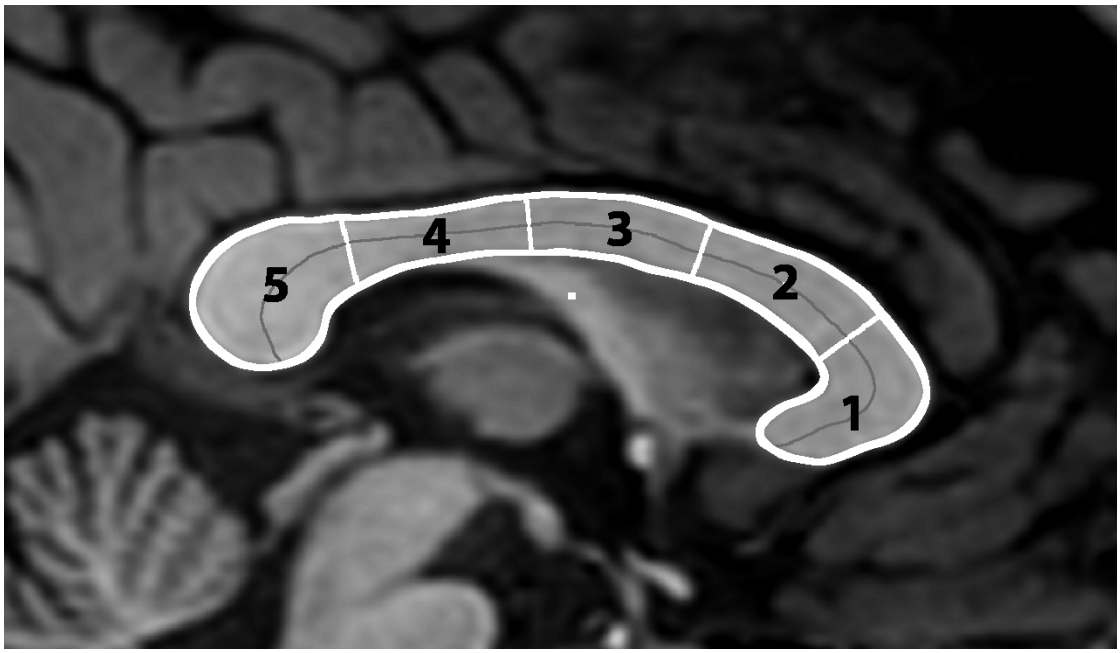

Figure II-1. The divisions of the corpus callosum.

inhomogeneities in the magnetic field, and to correct for within-scan motion. Using the 3D Slicer DTMRI module (an Open Source development project begun at the Massachusetts Institute of Technology [MIT] Artificial Intelligence Laboratory and the Surgical Planning Laboratory at Brigham and Women's Hospital), the two 4D diffusion-weighted volumes were then converted to diffusion-tensor volumes, coregistered using non-linear tensor-to-tensor registration (Park et al., 2003), and the resulting tensors averaged across volumes. The average diffusion-tensor volume was then coregistered with the T_1-weighted volume by generating a fractional anisotropy volume from the tensors, coregistering the fractional anisotropy volume to the T_1-weighted volume, and applying that transform to the tensor volume.

The non-linear transformation used to register the two tensor volumes was also used to register the corresponding T_2-weighted volumes. These two T_2-weighted volumes were then averaged, and together with the T_1-weighted volume were processed with *freesurfer* (BioMedical Imaging, Charleston, Mass., and Cortech Labs, La Jolla, Calif.) to obtain a segmentation. This segmentation provided the cortical gray-matter measures used in the analyses, and allowed for the creation of a seed region for fiber-tract generation.

Tracts were seeded along the edge of the white-matter where the white matter was bounded by cortical gray-matter. This was achieved by dilating a mask of the cortical gray-matter, and retaining the areas that overlapped with the white-matter. Tracts were then generated from all voxels within this seed region. Tracts were generated using a modified version of *3D Slicer*, which allowed tracts to be terminated at the mid-sagittal point of the corpus callosum, and to be filtered out if they

terminated elsewhere. Tracts were further constrained by a radius of curvature limit of 1mm, and a fractional anisotropy threshold of 0.15. The volume in which the sub-regions of the callosum had been labeled was then used to identify the set of fiber tracts that passed through each sub-region of the callosum. Figure II-2 shows the set of fiber tracts produced by this method.

Note that sub-region 5 of the callosum consists of both tracts that originate in occipital and parietal cortices, and also a smaller number of tracts that originate in temporal cortex. Temporal cortex poses particular difficulties for tractography.

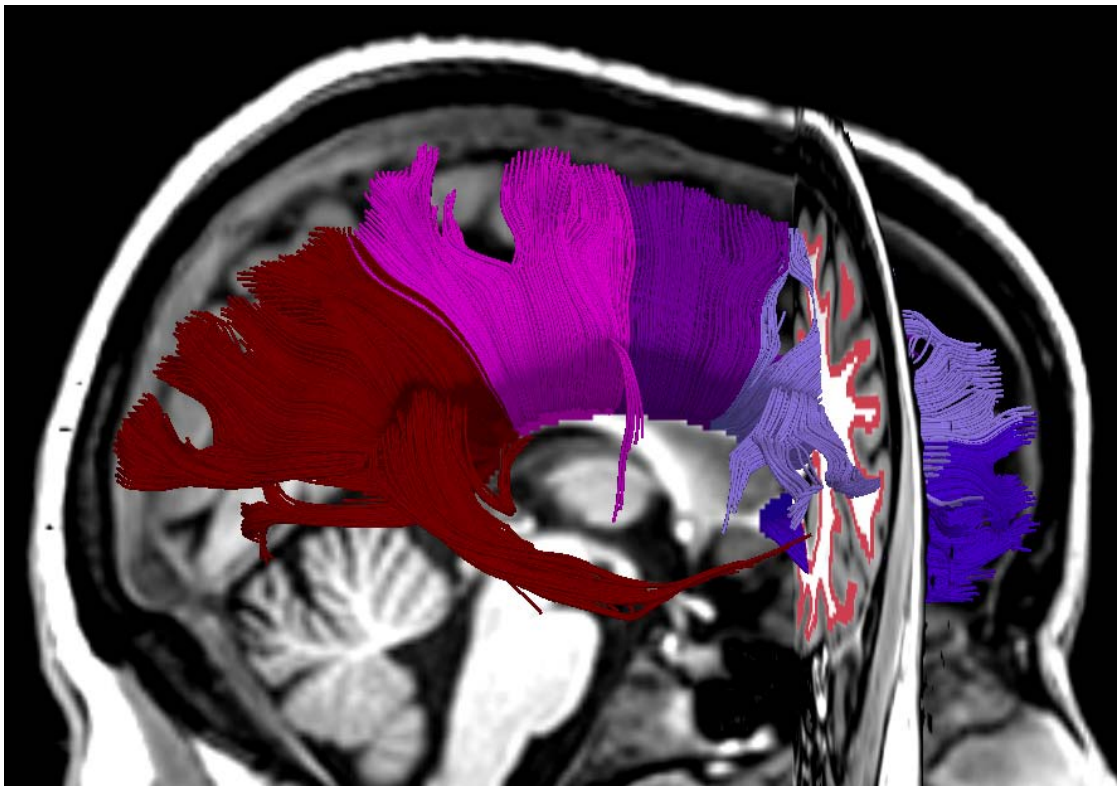

Figure II-2. The set of tracts that pass through the five subregions of the corpus callosum. The seed region for the tracts is visible in the coronal plane.

Fibers descending from the splenium cross through thalamo-cortical connections, and intermingle with non-callosal fibers in the inferior longitudinal fasciculus. Crossing fibers result in a reduced fractional anisotropy value, which if severe will result in the early termination of any tracts in that area. Fibers that run parallel to one another, in close proximity — kissing fibers — cannot be discerned, and may result in false tracts. In some subjects, low fractional anisotropy values due to crossing-fibers resulted in very few tracts descending from the splenium into the temporal lobe; in others, kissing fibers resulted in a large number of apparently false tracts that originated in anterior regions of temporal cortex. Tractography was thus unreliable, and temporal cortex was excluded from the analysis. The estimate of the number of fibers passing through sub-region 5 of the callosum was based on the percentage of sub-region 5 that contained fibers that originated from other areas of cortex.

The automatic parcellation of the cortex provided by *freesurfer* was used to divide the cortex into areas corresponding to the callosal sub-regions. A weighted assignment of cortical labels to callosal sub-regions was made. Cortical labels were assigned to callosal sub-regions with weights that reflected their contribution. Their contribution to a given sub-region was defined in terms of the fraction of interhemispheric connections that originate in the area, and the fraction of such connections that pass through the subregion. Since the vast majority of the fibers that traverse the callosum connect close to the midline, weighted assignments of medial cortical areas to callosal sub-regions summed to 1.0; lateral areas were assumed to produce, at most, one quarter as many inter-hemispheric connections, and thus weighted assignments of these areas to callosal sub-regions summed to 0.25; weighted

assignments to callosal sub-regions of areas between summed to 0.5. Cortical labels for which, consistently across subjects, all tracts that originated in that cortical area terminated in the same sub-region of the callosum contributed their full weight to that callosal sub-region. Cortical labels for which some tracts that originated in that cortical area terminated in one callosal sub-region, and some in another, contributed the fraction of their weight to each of the associated sub-regions that reflected the division of their contribution of connections. These cortical divisions are depicted in Figure II-3, and detailed in Table II-1.

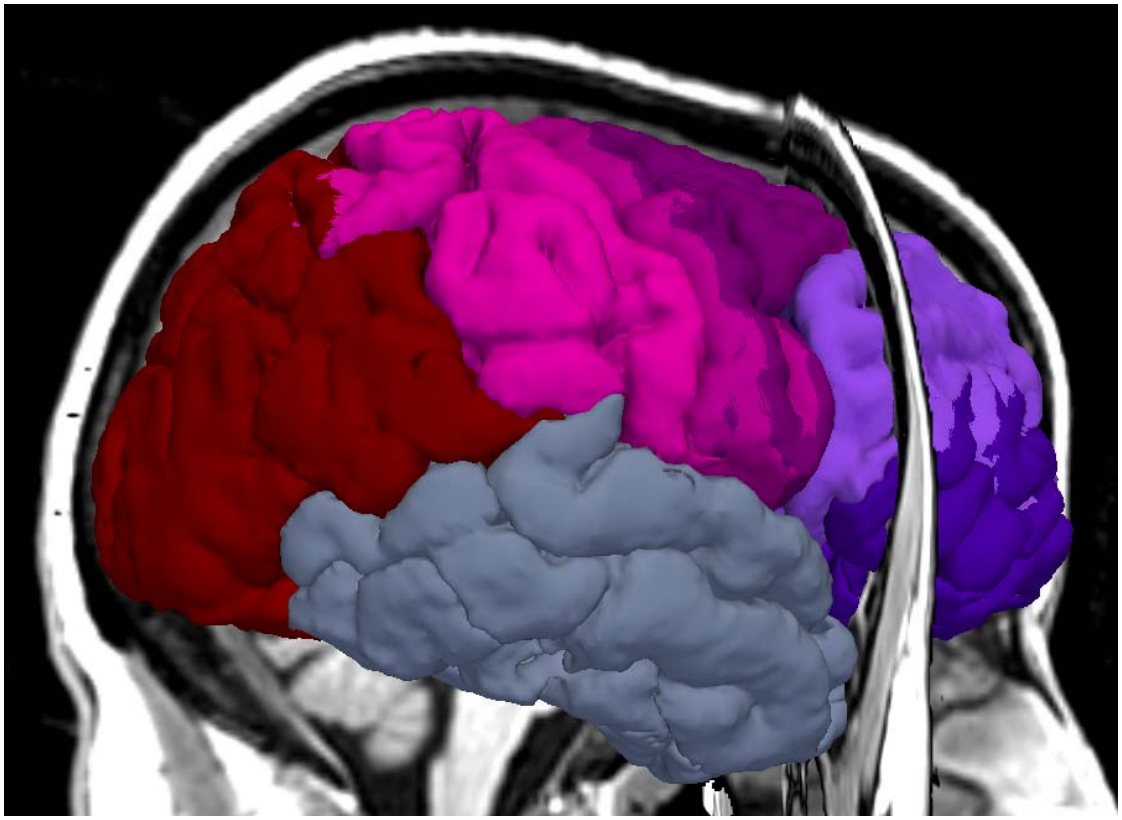

Figure II-3. The cortical divisions corresponding to the five subregions of the corpus callosum.

Table II-1. The cortical divisions. Cortical labels that were assigned to more than one callosal region are shown centered between those regions; the surface area and volume associated with the cortical label were divided equally between the associated callosal regions. A fraction prefixed to a cortical label indicates that only that much of the surface area and volume will be used.

CC1	CC2	CC3	CC4	CC5
frontal pole			¾ postcentral	cuneus
½ lat. orbitofrontal		paracentral		lingual
¼ parstriangularis	caudal middle frontal		precuneus	
¼ parsorbitalis	¾ precentral		superior parietal	
¼ parsopercularis			½ inf. parietal	
rostral middle frontal			¼ supramarginal	½ lat. occipital
superior frontal				¼ bankssts
				pericalcarine

II.C.3 Data Analysis

The hypothesized relationship is a negative correlation between connection length and degree of connectivity. This prediction was tested with regression analyses for each sub-region of the callosum. The degree of connectivity was calculated as the ratio of an estimate of the number of interhemispheric connections in each sub-region of the callosum to an estimate of total cortico-cortical projection neurons in the cortical areas connected by the sub-region; connection length was estimated as the average length of the longest 10% of the fibers passing through each sub-region. Note

that this definition of degree of connectivity should not be confused with probabilistic definitions of connectivity, *e.g.,* the probability of a direct connection between two neurons (Karbowski, 2001, 2003), or the probability of a direct connection between two areas (Changizi & Shimojo, 2005; Karbowski, 2003).

The midsagittal area of the corpus callosum has been shown to be a reasonable index of the number of interhemispheric connections (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Aboitiz, Scheibel, & Zaidel, 1992). Studies of axon diameter in the corpus callosum have found that the diameter of the largest approximately 0.1% of the fibers increases with brain size, but that other populations of fibers do not vary (Aboitiz, Scheibel, & Zaidel, 1992; Jerison, 1991; Olivares, Montiel, & Aboitiz, 2001; Schüz & Preissl, 1996). The callosum consists of approximately 190 million fibers (Tomasch, 1954). Thus, the number of interhemispheric connections in each region can be estimated to be approximately 190 million times the ratio of the area of that region to the across-subject average total area of the callosum. This estimate, however, must be corrected for the effects of age; the callosum continues to grow, at least in posterior regions, throughout the third decade of life (Pujol, Vendrell, Junqué, Martí-Vilalta, & Capdevila, 1993), but this growth represents primarily an increase in myelination, rather than an increase in the number of axons which comprise it. The area measures of each sub-region are thus adjusted for age effects, and the adjusted measures are used in the estimate of the number of axons that pass through that sub-region.

The number of cortico-cortical projection neurons can also be estimated with reasonable accuracy from gender, age, cortical volume, and cortical surface area.

Across mammals, cortical thickness increases as the 1/9 power of gray matter volume (Hofman, 1985, 1988, 1989), but neuron density decreases as the -1/3 power of gray matter (Prothero, 1997; Rockel, Hiorns, & Powell, 1980; Tower, 1954). Individual variation in humans does not differ greatly from this pattern, but gender and age effects must be taken into account. Neocortical neuron number can be predicted with a 95% tolerance limit of ±24% based on gender, age, gray matter volume, and cortical surface area (Pakkenberg & Gundersen, 1997). The formula is as follows:

$$N_{neurons} = 10^9 * \exp[-3.406 (+ 0.031 \text{ if male}) + (0.00018 * \text{age}) + (0.579 * \ln[Vol_{cortex}]) + (0.379 * \ln[Surf_{cortex}])].$$

This formula was used to estimate the number of projection neurons associated with each of the divisions of cortex, as defined above, assuming that projection neurons scale with the total number of neurons. The measures of cortical gray-matter volume and cortical surface area for each cortical area were provided by *freesurfer*.

The length of the interhemispheric connections was estimated from the tracts emanating from the gray-matter and terminating at the mid-sagittal point of the callosum. The measure of length for each region of the callosum was an average of the lengths associated with each voxel of that region on the midsagittal slice; the length associated with each voxel was calculated as the average of the longest 10% of the fibers terminating at that voxel.

II.C.4 Results

Regressing the cross-sectional area of each sub-region of the callosum against the average length of the connections in that sub-region yielded no significant relationships, but showed a tendency for increased connection length to be associated with decreasing callosal area. This is shown in Figure II-4. Note that all sub-regions show a negative correlation between connection length and callosal area. The significance and r^2 values are given in Table II-2.

Regressing the degree of connectivity for sub-region *i* of the callosum against the average length of the connections passing through sub-region *i* yielded significant relationships for four of the five sub-regions — all but area 4, roughly the isthmus — with an average r^2 value of 0.255. The results are shown in Figure II-5, with the significance and r^2 values, as well as the equations for the regression lines. The significance and r^2 values are also given in Table II-2.

Table II-2. The significance and r^2 values for the regression analyses, for each of the five sub-regions of the callosum. The top row provides the results for regressions of the cross-sectional area of sub-region *i* of the callosum on the average length of the connections passing through sub-region *i*. These values correspond to the regression plots in Figure II-4. The bottom row provides the results for regressions of the degree of connectivity — abbreviated here as *connect°* — for sub-region *i* against the average length of the connections in sub-region *i*. These values correspond to the regression plots in Figure II-5.

	CC_1		CC_2		CC_3		CC_4		CC_5	
	Sig.	**r^2**	**Sig.**	**r^2**	**Sig.**	**r^2**	**Sig.**	**r^2**	**Sig.**	**r^2**
CC vs length	.194	.083	.440	.030	.903	.001	.982	.000	.640	.011
connect° vs length	**.008**	**.304**	**.002**	**.390**	**.015**	**.263**	.125	.114	**.036**	**.203**

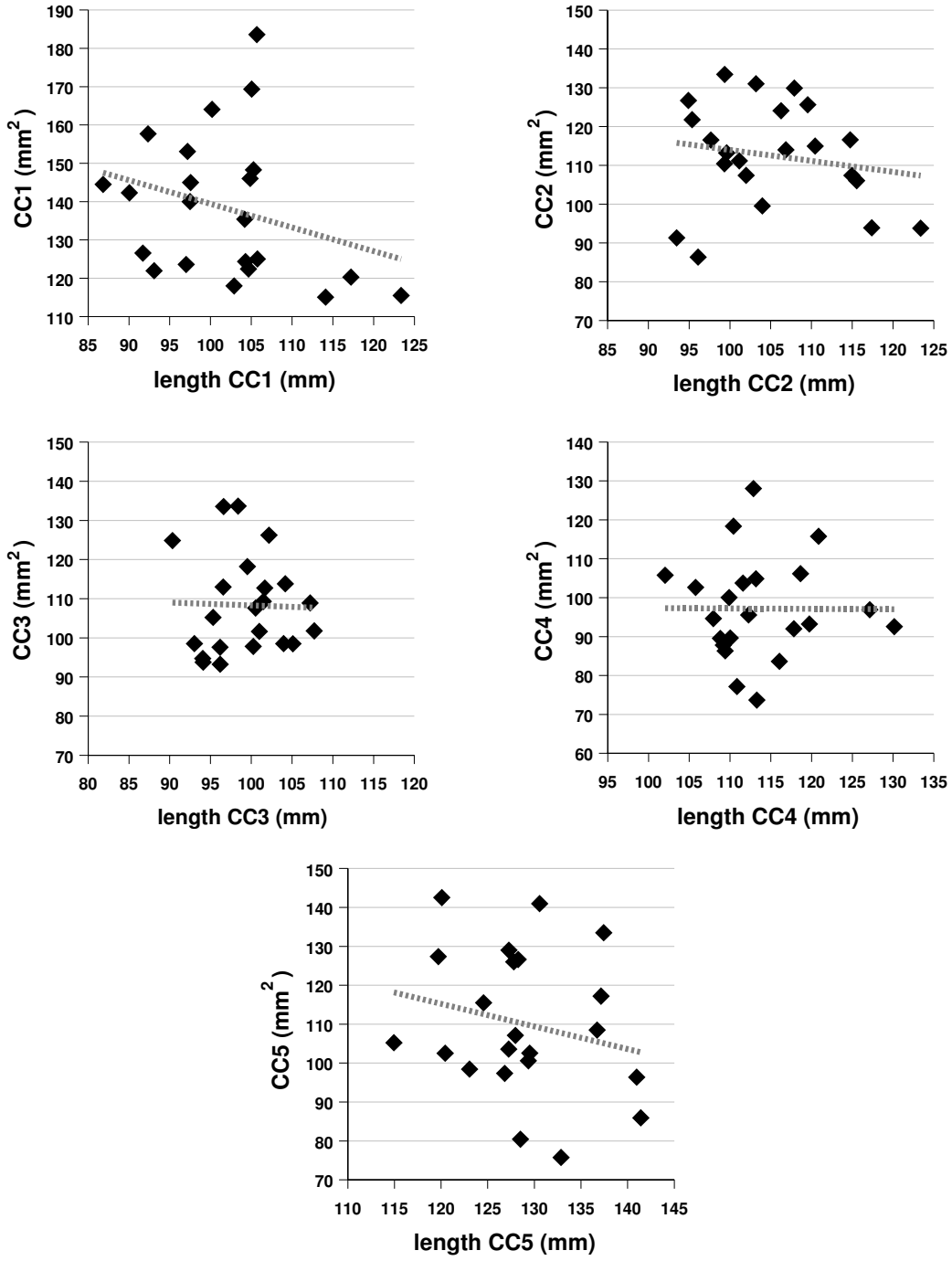

Figure II-4. The relation between the cross-sectional area for a given sub-region of the callosum and the average length of the connections passing through that sub-region. The dashed lines show that the correlation is negative — callosum size decreases as connection length increases — in all sub-regions, though none of the relationships are significant at $P \leq 0.05$. The significance and r^2 values are given in Table II-2**.**

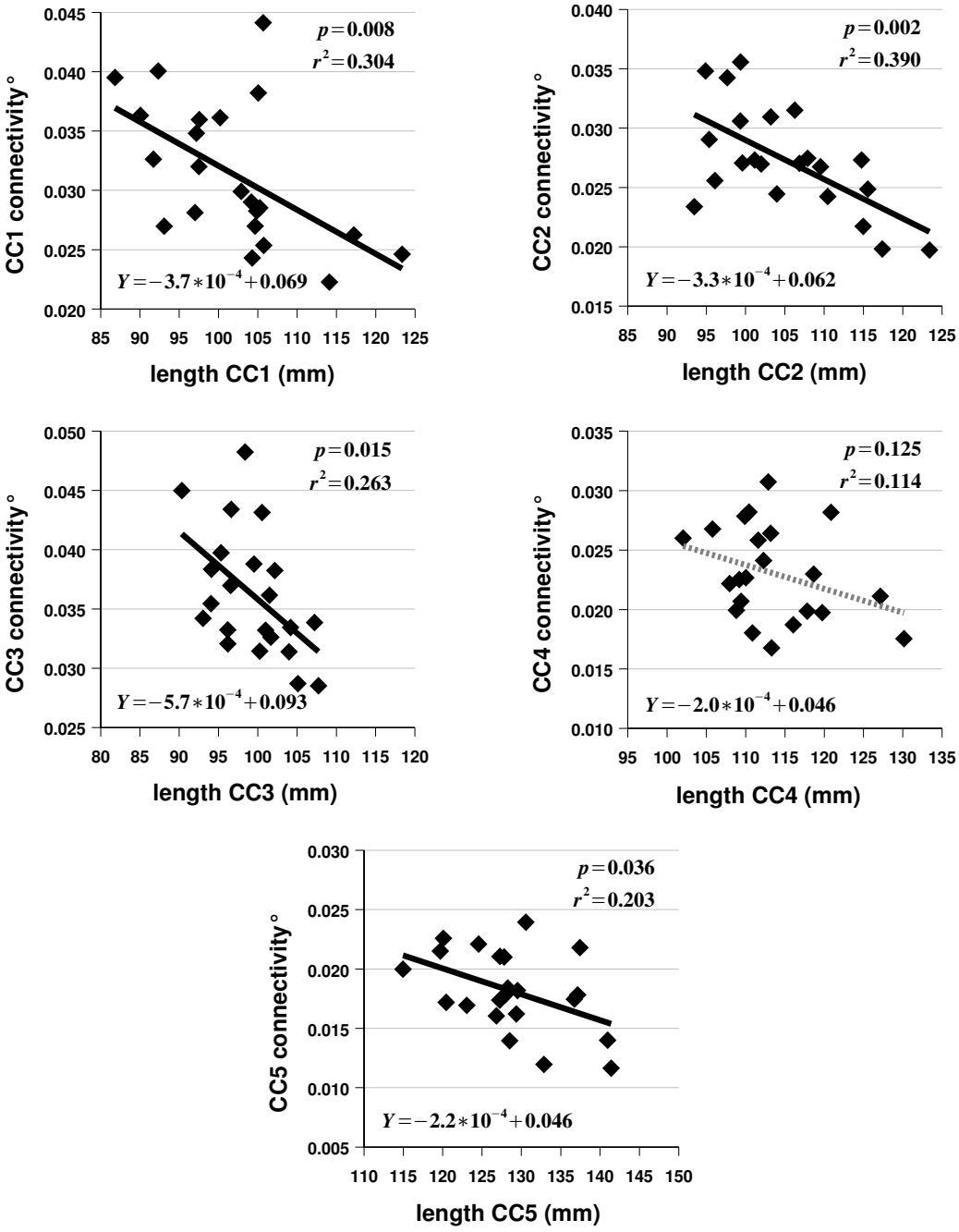

Figure II-5. The relation between degree of connectivity for sub-region *i* of the callosum — indicated as CC_i *connectivity*° — and the average length of the connections passing through region *i*. The black regression lines in sub-regions 1,2,3 and 5 indicate that the relationship is significant at $P \leq 0.05$. The equation for each regression line is given in the lower left corner of each plot, and the significance and r^2 values are presented in the upper right corner.

It should be remembered that the values shown in Figure II-5, though plausible — a few percent — are crude estimates based on the assumption that the number of projection neurons scale with the total number of neurons, and that there is less interhemispheric connectivity in lateral regions of cortex. But it is the relative values that are of real interest, and the relative values should be roughly correct.

II.C.5 Discussion

Using diffusion tensor imaging and tractography to detail the patterns of inter-hemispheric connectivity and to determine the length of the connections, and formulae based on histological results to estimate degree of connectivity, we have shown that, for inter-hemispheric connectivity, connection length is negatively correlated with degree of connectivity in the normal adult male brain. Significant relationships were found in four of five sub-regions of the callosum — the exception being the isthmus — with an average r^2-value of 0.255 over the five regions; thus, on average, connection length accounted for about 25.5 percent of the variance in degree of connectivity. The results concur with the hypothesis that, due to the increased conduction delays and cellular costs associated with the long-distance connections, larger brains should have relatively less long-distance connectivity (Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994). The impact of connection length on intra-hemispheric connectivity, and on area-to-area connectivity, remains to be tested.

Comparison with previous research relating measures of brain size to inter-hemispheric connectivity (Jäncke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Rauch

& Jinkins, 1994) shows that connection length is a considerably better predictor. Rauch & Jinkins (1994) studied a group of adults between 20 and 87 years of age (mean 36 years, stddev not reported). T_1-weighted images were used to measure the callosum, and to estimate brain size. The callosum was traced on the midsagittal slice; the cerebral outline was traced on the axial and sagittal slices for which cerebral area was greatest, and the average of these two areas was taken as the measure of brain size. A statistically significant positive correlation was found between callosal size and brain size, with an r^2 of 0.211. But the values for callosal size and brain size were not adjusted for age, though a positive correlation with age was shown in both cases. Also, though it is primarily the posterior of the callosum that continues to grow until the fourth decade of life (Pujol, Vendrell, Junqué, Martí-Vilalta, & Capdevila, 1993), since the callosum was not sub-divided, the overall correlation is confounded by the age effect. It is nonetheless noteworthy that the reported correlation was positive. Our data show a negative, though non-significant, correlation between the cross-sectional area of each of the regions of the callosum and the length of the tracts that pass through those regions. The measure of brain size used by Rauch & Jinkins (1994), however, is known to correlate poorly with brain volume (de Lacoste, Adesanya, & Woodward, 1990), and presumably also correlates poorly with the average length of the inter-hemispheric connections.

Jäncke *et al.* (1997) studied a similar age group (range 18 to 45; mean 25.7; stddev 4.7) to the group reported on here, but with both males and females. Using T_1-weighted images, they divided the callosum into four regions — the anterior third, the middle third, the posterior fifth, and the remainder — and regressed the cross-

sectional area of each sub-region against forebrain volume. They report a significant positive correlation in all four regions, with an r^2 reported separately for men in the middle third and splenium — 0.07 and 0.08, respectively — and an r^2 for men and women together in the anterior third and the isthmus — 0.23 and 0.15, respectively. Again, however, there was no control for age effects. The same analysis with our data, but with age-adjusted measures of corpus callosum sub-region area and forebrain volume, and with the callosum divided into five sub-regions, rather than four, yielded a significant relationship only in sub-region 3 — and no marginal relationships — and r^2 values of 0.002, 0.055, 0.161, 0.000 and 0.078 in sub-regions 1 through 5, respectively. That it is sub-region 3 that shows a relation with forebrain volume is interesting; across subjects, sub-region 3 has the shortest tracts, and shows the least variation in connection length. But forebrain volume only accounts for 16.1 percent of the variation in cross-sectional area in sub-region 3, and an average of 3.4 percent of the variation in the other four sub-regions.

In contrast, as shown in Table II-2, regressing the estimate of the degree of inter-hemispheric connectivity associated with sub-region *i* of the callosum against the length of the inter-hemispheric connections passing through sub-region *i* yields significant results in sub-regions 1,2,3 and 5, with r^2 values of 0.304, 0.390, 0.263 and 0.203, respectively. The lack of significance in sub-region 4 might be due to measurement problems associated with the fornix. The fibers of the fornix leave the hippocampus at the level of the splenium and run in a rostro-medial direction until they reach the midline under sub-region 4 and curve downward to the mamillary bodies. Under sub-region 4 the fornix can distort the tensors that determine the path

of the tracts that enter the callosum, and so introduce inaccuracies in the estimate of the length of the tracts passing through sub-region 4. The fornix also confuses the task of identifying the ventral boundary of sub-region 4; and any measurement errors are likely amplified due to the relative narrowness of the callosum at that point. The lack of significance in sub-region 4 might also be due to an increase in the proportion of very large diameter fibers interconnecting the primary sensory areas of the two hemispheres. In cross-species analyses, such an association with brain size has been reported (Olivares, Montiel, & Aboitiz, 2001; Schüz & Preissl, 1996). The connections between sensory areas pass through sub-region 4 (Hofer & Frahm, 2006). In any case, including sub-region 4, an average of 25.5 percent of the variability in degree of inter-hemispheric connectivity associated with each sub-region is accounted for by the length of the inter-hemispheric connections.

Moreover, and most relevant to the hypothesis being tested here, as shown in Figure II-5, degree of inter-hemispheric connectivity is negatively correlated with the length of the inter-hemispheric connections. The strength of this relationship is even apparent in Figure II-4, which shows the regressions of the cross-sectional area of sub-region *i* on the length of the connections that pass through sub-region *i*. Ringo *et al.*'s (1994) hypothesis predicts that longer connections should be associated with a lesser degree of connectivity, but not necessarily with absolutely smaller callosa. The importance of utilizing meaningful relative measures has been demonstrated elsewhere (Jungers, Falsetti, & Wall, 1995; Smith, 2005). Nonetheless, Figure II-4 shows a tendency for longer connections to be associated with absolutely smaller callosa. Taking into account which portion of cortex is connected via each sub-region

of the callosum, and estimating the degree of connectivity from this and the histological results of Pakkenberg and Gundersen (1997), substantially reduces the variability seen in Figure II-4, and strengthens the relationship.

Still more of the variation in the degree of connectivity might be accounted for if developmental data were available. The shape of the growth trajectory during early development may have a substantial impact on connectivity (Lewis & Elman, 2008), and brain growth rates can vary considerably during development.

The impact of connection length on the degree of connectivity throughout development may, in fact, be an important part of an account of structural and functional abnormalities in developmental disorders, and possibly of an account of the behavioral phenotypes. Children with autism spectrum disorder, for example, undergo a period of brain overgrowth during the first years of life (Aylward, Minshew, Field, Sparks, & Singh, 2002; Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Fombonne, Roge, Claverie, County, & Fremolle, 1999; Hazlett et al., 2005; Lainhart et al., 1997; Sparks et al., 2002), and subsequently show structural and functional under-connectivity (Belmonte et al., 2004; Egaas, Courchesne, & Saitoh, 1995; Herbert, 2005; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Just, Cherkassky, Keller, & Minshew, 2004; Murias, Webb, Greenson, & Dawson, 2007). Computational modeling has shown that the increased conduction delays presumably accompanying the early brain overgrowth may account for these findings, with increased conduction delays leading to decreased functional connectivity, and decreased functional connectivity subsequently leading to decreased structural connectivity (Lewis & Elman, 2008); and *in vivo* magnetic resonance imaging studies

of children with autism have related brain size to the relative size of the corpus callosum (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004), and to changes in the relative size of the callosum (Lewis, Elman, & Courchesne, 2005). Abnormalities in brain size are pervasive in developmental disorders, and thus the hypothesized effect of connection length on brain organization might have considerable explanatory value.

Additionally, white-matter continues to change throughout life (Courchesne et al., 2000; Ge et al., 2002), and so during aging in such developmental disorders, in which macrocephaly may persist into adulthood (Lainhart *et al.*, 1997), as well as in normal aging, connection length is expected to show a negative correlation with changes in the degree of connectivity.

Brain size also appears to explain differences in inter-hemispheric connectivity between genders (Jäncke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Jäncke & Steinmetz, 1998; Luders, Narr, Zaidel, Thompson, & Toga, 2006), as well as across species (Rilling & Insel, 1999a). On average, males have larger brains than females (Pakkenberg & Gundersen, 1997), and thus longer inter-hemispheric connections. The results here suggest that connection length is the relevant aspect of brain size that lies behind the differences in inter-hemispheric connectivity. Further research is needed, however, to confirm this; in order to eliminate this potential confound, our subject population was limited to males.

Brain size is also positively correlated with the degree of sulcal convolution (Im et al., 2008), and sulcal folding has been hypothesized to result from the mechanical forces associated with connectivity, with greater local connectivity driving

a greater degree of sulcul convolution (Van Essen, 1997). Retrograde tract-tracing experiments in adult rhesus monkeys has supported this link between connectivity and cortical folding (Hilgetag & Barbas, 2006). Thus, the relation between connection length and degree of connectivity may also explain patterns of sulcal folding — in humans, and in general.

Connection length is, of course, not the only factor that might determine the degree of long-distance connectivity. There is evidence that experience, environment, and genetics play a substantial role (Lee, Chen, & Schlaug, 2003; Öztürk, Tasçioglu, Aktekin, Kurtoglu, & Erdin, 2002; Pfefferbaum, Sullivan, Swan, & Carmelli, 2000; Scamvougeras, Kigar, Jones, Weinberger, & Witelson, 2003). But connection length appears to be a more important factor than previously suggested. Even with the limited amount of variation in brain size and connection length in our sample, connection length accounted for about 25 percent of the variance in degree of connectivity. A sample with substantially more variation in brain size — *e.g.*, a cross-species sample — would, we predict, show a considerably stronger relationship.

Several caveats, however, must be considered. The results reported here rely on the assumption that the number of cortico-cortical projection neurons scales with the total number of neurons in cortex — similar to the assumption of Zhang and Sejnowski (2000) that the number of projection neurons scales with surface area. Additional histological studies will be required to determine if this is correct. An apparent decrease in the degree of interhemispheric connectivity would also be seen if the number of cortico-cortical projection neurons did not scale with the total number of neurons. But the fact that increases in white matter volume outpace increases in

gray-matter volume (Frahm, Stephan, & Stephan, 1982; Rilling & Insel, 1999b; Schlenska, 1974; Zhang & Sejnowski, 2000) suggests that this is not the case. The impact of the increase in diameter of the largest fibers of the callosum is also unclear. If these large diameter fibers connect to a large number of neurons, considerable compensation might be achieved through these increases; and if the branching patterns of callosal neurons depend on brain size, degree of connectivity estimates must be adjusted in accord. Also, crossing fibers interfere with tractography, and so with measures of the length of the inter-hemispheric connections. As mentioned, this is particularly a problem in the temporal lobe, where fibers descending from the splenium travel parallel to non-callosal fibers in the inferior longitudinal fasciculus; thus the temporal lobe was eliminated from consideration. But there are also problems with tractography elsewhere. Callosal fibers projecting to, or coming from, lateral cortical areas cross with thalamo-cortical connections. This will produce low fractional anisotropy values, and so callosal tracts from lateral cortex may be truncated and discarded. To the extent that such tracts are among the longest that comprise a sub-region of the callosum, and are substantially different in length from tracts for which tractography succeeds, this will introduce inaccuracies in the length measurements. Callosal fibers projecting to more medial areas of cortex in frontal, parietal and occipital lobes may become confused with thalamo-cortical connections, as well. But the longest callosal fibers and the longest thalamo-cortical fibers will both originate or terminate at the outermost point of a gyrus. And finally, in contrast to the hypothesis explored here, decreases in interhemispheric connectivity — and long-distance connectivity, generally — might force a compensatory increase in more

local connectivity, and this may give rise to the increased brain size. Longitudinal studies will be critical to determining the direction of causation.

But the estimates of degree of connectivity are presumably a considerable improvement over approaches which ignored the histological results; and the tractography-based estimates of length an improvement over volumetric measures. Further, the results here concur with a growing body of evidence that metabolic costs and processing efficiency constrain the way the cortex is organized (Achard & Bullmore, 2007; Bassett & Bullmore, 2006; Changizi, 2001, 2005; Changizi & Shimojo, 2005; Chklovskii & Koulakov, 2000; Chklovskii, Schikorski, & Stevens, 2002; Harrison, Hof, & Wang, 2002; He, Chen, & Evans, 2007; Kaiser & Hilgetag, 2004; Karbowski, 2001, 2003; Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994; Schüz & Miller, 2002; Sporns & Honey, 2006; Sporns & Zwi, 2004; Watts & Strogatz, 1998), and support theoretical notions of how cortical organization should scale (Changizi, 2001, 2005; Changizi & Shimojo, 2005; Kaas, 2000; Karbowski, 2001, 2003; Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994).

II.C.6 Acknowledgements

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Chapter III
The Relation Between Connection Length and Degree of Connectivity in Children and Adults: A DTI Analysis

III.A Abstract

Adults show a negative relation between the length of interhemispheric connections and the degree of connectivity — the ratio of between-area connections to total projection neurons in the areas connected. We show that this relation has not yet developed by late childhood. Using MRI and DTI, in 19 typically developing boys between 7 and 11 years of age, we estimated the average length of the longest connections in five divisions of the corpus callosum, and the degree of connectivity. A significant relation between connection length and degree of connectivity was found only in the posterior-most subregion. In contrast, young adult males show a significant relation between connection length and degree of connectivity in the three anterior-most subregions, as well as the posterior-most. Moreover, in the children, averaging over the anterior 4 subregions, connection length accounted for less than 7 percent of the variance in degree of connectivity — one subregion contributing a positive rather than negative relation — whereas in the adults, connection length accounted for almost 27 percent of the variance in these subregions. The combined results indicate that the relation between connection length and degree of connectivity develops during late childhood and adolescence.

III.B Introduction

Across species, increases in white-matter volume outpace increases in gray-matter volume (Frahm, Stephan, & Stephan, 1982; Rilling & Insel, 1999b; Schlenska, 1974; Zhang & Sejnowski, 2000), but increases in gray-matter outpace increases in the size of the corpus callosum (Rilling & Insel, 1999a). The high-degree of connectivity within the cortex explains the greater increase in white-matter volume as gray-matter volume, and thus neuron number, increases (Allman, 2000; Frahm, Stephan, & Stephan, 1982; Zhang & Sejnowski, 2000). The hyposcaling of the corpus callosum reflects reduced relative interhemispheric connectivity with increases in the length of the interhemispheric connections, which tend to be longer in larger brains (Braitenberg, 2001). This phenomenon has been hypothesized to be due to the increased conduction delays and cellular costs associated with the longer fibers of larger brains (Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994). The conduction delay associated with either a myelinated or an unmyelinated axon is primarily a function of its diameter and length (Waxman, 1977). The greater the diameter of an axon, the greater the conduction speed; and the longer the axon, the larger the conduction delay. For the vast majority of the interhemispheric connections, axon diameter does not scale sufficiently with brain size to compensate for the increased length (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Jerison, 1991; Olivares, Montiel, & Aboitiz, 2001; Schüz & Preissl, 1996). Larger brains also incur greater metabolic costs (Aiello, 1997; Aiello, Bates, & Joffe, 2001; Isler & van Schaik, 2006; Karbowski, 2007; Sherwood et al., 2006). In primates, for instance, controlling for body size, brain mass is positively correlated with basal metabolic rate (Isler & van

Schaik, 2006). And the metabolic costs are substantial: during rest, brain tissue uses almost an order of magnitude more energy per unit weight than the next most expensive tissue (Mink, Blumenschine, & Adams, 1981).

Within species, at least for human adult males, there is also hyposcaling of the corpus callosum (Jäncke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Lewis, Theilmann, Sereno, & Townsend, 2008b). In this case, diffusion tensor imaging data has been used to look at this hyposcaling more directly in terms of connection length; the results showed a negative relation between connection length and degree of connectivity — the number of axons that interconnect areas in either hemisphere relative to the number of projection neurons in the areas connected (Lewis, Theilmann, Sereno, & Townsend, 2008b).

This negative relation between connection length and relative interhemispheric connectivity might stem from a variety of processes, *e.g.*, relatively fewer long-distance connections might be generated in brains destined to become larger, or due to the increased conduction delays and cellular costs, relatively fewer might be retained during development in larger brains. Large numbers of transient projections are produced during cortical development (LaMantia & Rakic, 1990; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986). Selective pruning eliminates approximately two-thirds of these connections (LaMantia & Rakic, 1990). Selective pruning may be influenced by differences in connection length during development, and the impact of these differences on energy consumption and conduction delay. Conduction speeds are relatively slow in the smaller diameter less well myelinated axons of the developing brain; and the metabolic costs are particularly high: the adult

brain consumes approximately 20% of the total energy used, while the infant brain consumes about 60% (Hofman, 1983). But the magnitude of exuberance may also vary in different species and individuals according to differences in brain size destiny.

To shed light on the developmental aspect of the relation between connection length and degree of connectivity, we investigate this relation in children, and contrast the results with those reported by Lewis *et al* (2008b) in adults.

III.C Methods

III.C.1 Subjects

A total of 19 normal healthy boys ranging between 7 and 11 years of age (mean 9.37; stddev 1.58) participated in the study. All children gave informed assent, the children's' parents gave informed consent, and the study was approved by the ethics committee at the University of California, San Diego.

III.C.2 Imaging and Image Processing

All subjects were scanned at the UCSD Center for fMRI on a GE EXCITE HDx 3.0T short bore scanner with an eight-channel array head coil. The scan protocols were based on those used by Lewis *et al* (2008b), with minor adjustments for use with children. Five types of images were acquired from each subject: (i) one set of 3D T_1-weighted images (Fast Gradient Echo, SPGR; TE = 3.1ms; flip angle = 12°; NEX = 1; FOV = 25cm; matrix=256x256); (ii) one set of 3D T_1-weighted images (Fast Gradient Echo, SPGR; TE = 3.1ms; flip angle = 12°; NEX = 1; FOV = 25cm;

matrix=256x256; ASSETT); (iii) four sets of T_2-weighted images (dual spin-echo, EPI; TR = 15s; TE = 89ms; 45 axial slices; NEX = 1; FOV = 24cm; matrix = 128x128; resolution = 1.875x1.875x3 mm; 3mm interleaved contiguous slices); (iv) four sets of diffusion weighted images isotropically distributed along 15 directions (dual spin-echo, EPI; TR = 15s; TE = 89ms; 45 axial slices; NEX = 1; FOV = 24cm; matrix = 128x128; resolution = 1.875x1.875x3 mm; 3mm interleaved contiguous slices; *b* value = 1,400 s/mm^2); and (v) fieldmaps matched to the diffusion-weighted images.

Note that four sets of diffusion weighted images were acquired. Likewise for the T_2-weighted images, which were acquired together with the diffusion weighted images.

Fieldmaps were acquired before the first and third sets of diffusion-weighted images were acquired, and, in cases where there was between scan motion, additional sets of fieldmaps were acquired as needed.

In cases where within-scan motion rendered the T_1-weighted image set unusable, the ASSETT scan was used in the analysis. Where within-scan motion made the use of a T_2-weighted, diffusion, or fieldmap scan questionable, the scan was aborted and reinitiated.

The T_1-weighted images were converted to AFNI (Cox, 1996) — an open source environment for processing and displaying MRI data — and the resulting volume was AC-PC aligned, *i.e.*, reoriented so that the midsagittal points of the anterior and posterior commisures lie along a horizontal line centered on the right-left axis, and so that the two hemispheres lie on either side of the vertical plane through

that line. The boundary and divisions of the corpus callosum were then identified on the midsagittal slice of the AC-PC aligned T_1-weighted images using the semi-automated procedure described in Lewis *et al* (2008b). That procedure uses an implementation of the active contour algorithm to locate a smoothed boundary at the center of the gradient at the edge of the callosum. The midline of the callosum is then computed and divided into five equal length segments, and the shortest length lines that cut the callosum at the points defined by these segments are the regional boundaries (Clarke, Kraftsik, van der Loos, & Innocenti, 1989). Figure III-1 illustrates the subregions arrived at via this procedure.

Four-dimensional volumes were created from the sets of diffusion-weighted images; software developed by the UCSD Center for fMRI was used to correct the

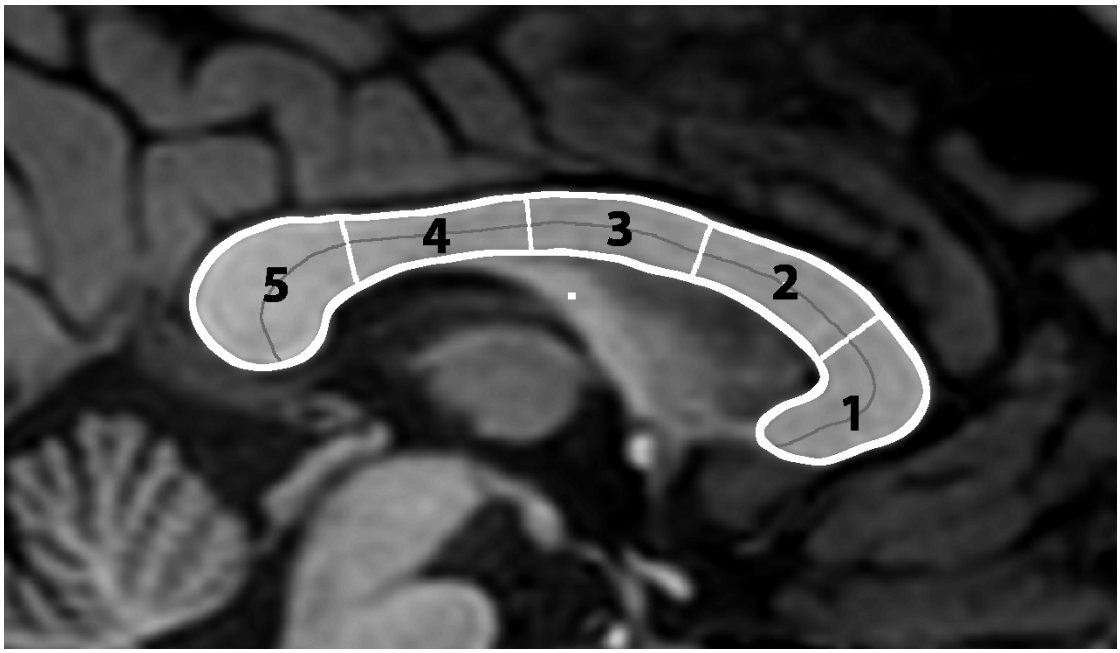

Figure III-1. The divisions of the corpus callosum.

diffusion-weighted images, using the fieldmaps, of distortions caused by inhomogeneities in the magnetic field, and to correct for within-scan motion. Using the 3D Slicer DTMRI module (an Open Source development project begun at the MIT Artificial Intelligence Laboratory and the Surgical Planning Laboratory at Brigham and Women's Hospital), the four 4D diffusion-weighted volumes were then converted to diffusion-tensor volumes, coregistered using non-linear tensor-to-tensor registration (Park et al., 2003), and averaged.

The non-linear transformation used to register the tensor volumes was also used to register the corresponding T_2-weighted volumes. These T_2-weighted volumes were then averaged, and together with the T_1-weighted volume were processed with *freesurfer* (BioMedical Imaging and Cortech Labs) to obtain a segmentation. This segmentation provided the cortical gray-matter measures used in the analyses, and allowed for the creation of a seed region for fiber-tract generation.

The average diffusion-tensor volume was then coregistered with the T_1-weighted volume, and tracts were seeded along the edge of the white-matter where the white-matter was bounded by cortical gray-matter. The average diffusion-tensor volume was coregistered with the T_1-weighted volume by generating a fractional anisotropy volume from the tensors, coregistering the fractional anisotropy volume to the T_1-weighted volume, and applying that transform to the tensor volume. The seed-region along the edge of the white-matter was constructed by dilating a mask of the cortical gray-matter, and retaining the areas that overlapped with the white-matter. Tracts were generated from all voxels within this seed region using a modified version of *3D Slicer*, which allowed tracts to be terminated at the mid-sagittal point of the corpus

callosum, and to be filtered out if they terminated elsewhere. Tracts were further constrained by a radius of curvature limit of 1mm, and a fractional anisotropy threshold of 0.15. The volume in which the subregions of the callosum had been labeled was used to terminate callosal tracts at the mid-line, and to identify the set of tracts that passed through each subregion of the callosum. Figure III-2 shows the set of fiber tracts produced by this method. The tracts are colored in five shades ranging from blue in subregion 1 to red in subregion 5. Temporal cortex poses particular difficulties for tractography, and so, as in Lewis *et al* (2008b), is excluded from the

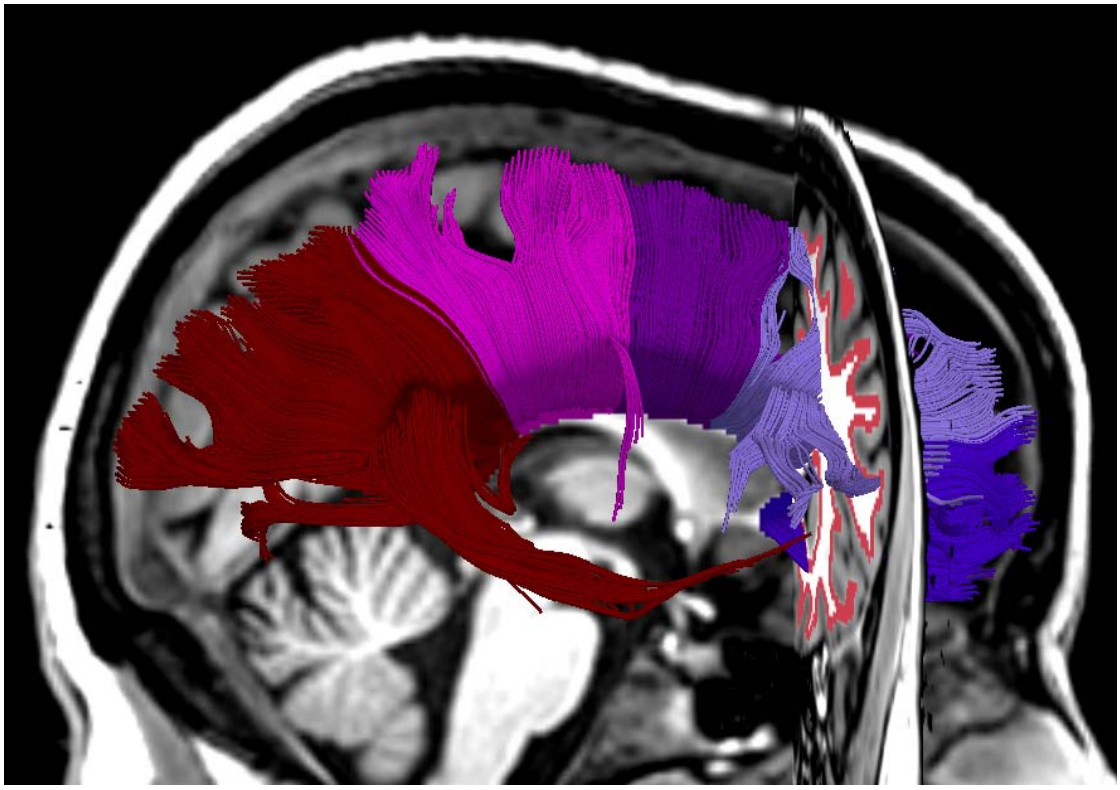

Figure III-2. The set of tracts that pass through the five subregions of the corpus callosum. The seed region for the tracts is visible in the coronal plane.

analysis. This exclusion involves only subregion 5 of the callosum; the estimate of the number of fibers passing through subregion 5 was based on the percentage of subregion 5 that contained fibers that originated from other areas of cortex.

As per Lewis *et al* (2008b), the cortex was divided into areas corresponding to the callosal subregions by using the automatic parcellation of the cortex provided by *freesurfer*. The *freesurfer* cortical labels resulting from the automatic parcellation were then assigned to callosal subregions with weights that reflected their contribution. Their contribution to a given subregion was defined in terms of the fraction of inter-hemispheric connections that originated in the labeled area, and the fraction of such connections that passed through the subregion. The cortical divisions were taken from Lewis *et al* (2008b), and are depicted in Figure III-3 — with colors corresponding to those in Figure III-2 — and detailed in Table III-1.

III.C.3 Data Analysis

The data were analyzed exactly as in Lewis *et al* (2008b). For each subregion of the callosum, the degree of connectivity was calculated as the ratio of an estimate of the number of interhemispheric connections passing through that subregion to an estimate of total cortico-cortical projection neurons in the cortical areas connected by that subregion; and for each subregion, connection length was estimated as the average length of the longest fibers passing through that subregion.

The estimate of the number of fibers passing through each region of the callosum is based on the work of Tomasch (1954) showing that the callosum consists

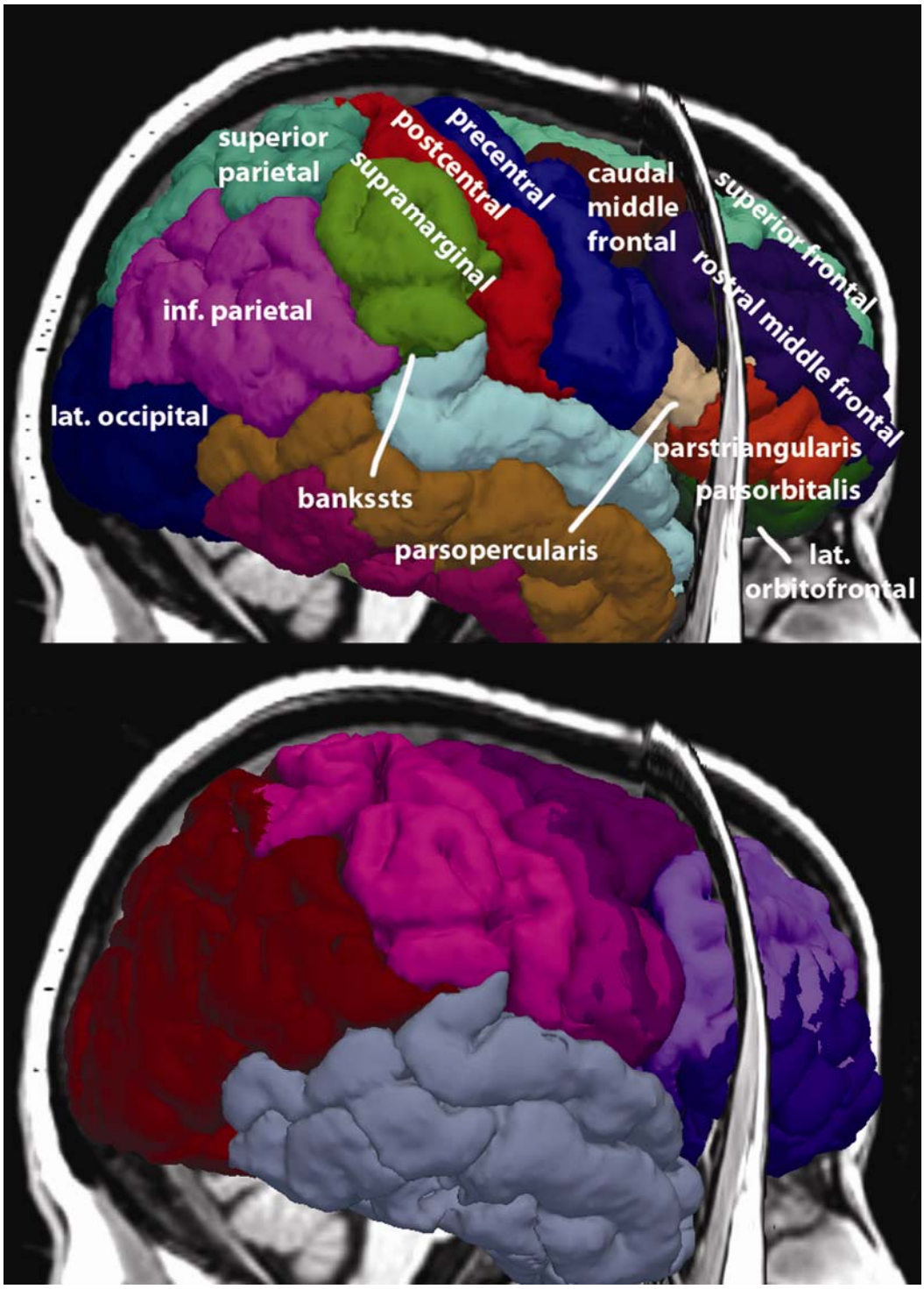

Figure III-3. The cortical divisions corresponding to the five regions of the corpus callosum. The cortical parcellation provided by *freesurfer* is shown in the top figure; the assignment of these labels to cortical regions is illustrated in the bottom figure — with colors corresponding to those in Figure III-2.

Table III-1. The cortical divisions. Cortical labels that were assigned to more than one callosal region are shown centered between those regions; the surface area and volume associated with the cortical label were divided equally between the associated callosal regions. A fraction prefixed to a cortical label indicates that only that much of the surface area and volume will be used**.**

CC1	CC2	CC3	CC4	CC5
frontal pole			¾ postcentral	cuneus
½ lat. orbitofrontal		paracentral		lingual
¼ parstriangularis	caudal middle frontal		precuneus	
¼ parsorbitalis	¾ precentral		superior parietal	
¼ parsopercularis			½ inf. parietal	
rostral middle frontal			¼ supramarginal	½ lat. occipital
superior frontal				¼ bankssts
				pericalcarine

of approximately 190 million fibers, and studies of axon diameter in the corpus callosum showing that, except for the largest approximately 0.1% of the fibers, the distribution of fibers does not vary with brain size (Aboitiz, Scheibel, & Zaidel, 1992; Jerison, 1991; Olivares, Montiel, & Aboitiz, 2001; Schüz & Preissl, 1996). Thus, the number of interhemispheric connections in each region can be estimated to be approximately 190 million times the ratio of the area of that region to the across-subject average total area of the callosum. Tomasch's (1954) subjects were between 50 and 60 years of age, thus, for children, this approach will underestimate the number

of callosal connections, and must be scaled to adjust for the larger number of smaller diameter less well myelinated fibers in the developing brain. Histological data for children are lacking, and so this cannot be done accurately; but only the relative values among the children are important for an analysis of the relation between connection length and degree of connectivity among the children. The callosum also continues to grow throughout this period of development (Thompson et al., 2000), so the area measures of each subregion are adjusted for age effects, and the adjusted measures are used in the estimate of the number of axons that pass through that subregion.

The estimate of the number of projections neurons in each area of cortex is based on the histological work of Pakkenberg and Gundersen (1997). Sampling from the brains of 62 males between 19 and 87 years of age and 32 females between 18 and 93 years of age Pakkenberg and Gundersen (1997) determined that neocortical neuron number can be predicted with a 95% tolerance limit of ±24% based on gender, age, gray matter volume, and cortical surface area. The formula is as follows:

$$N_{neurons} = 10^9 * \exp[-3.406\ (+\ 0.031 \text{ if male}) + (0.00018 * \text{age}) + (0.579 * \ln[Vol_{cortex}]) + (0.379 * \ln[Surf_{cortex}])].$$

This formula was used to estimate the number of projection neurons associated with each of the divisions of cortex, as defined above, assuming that projection neurons scale with the total number of neurons. The measures of cortical gray-matter volume and cortical surface area for each cortical area were provided by *freesurfer*.

The length of the interhemispheric connections was estimated from the tracts emanating from the gray-matter and terminating at the mid-sagittal point of the callosum. The measure of length for each region of the callosum was an average of the lengths associated with each voxel of that region on the midsagittal slice; the length associated with each voxel was calculated as the average of the longest 10% of the tracts terminating at that voxel. This was calculated for each hemisphere separately, and then for each subregion, the length measures for the two hemispheres were summed.

III.D Results

Regressing the degree of connectivity for subregion *i* of the callosum against the average length of the connections passing through subregion *i* yielded a significant relationship in only the most posterior subregion, with r^2 values of 0.180, 0.025, 0.011, 0.058, and 0.516 in subregions 1 through 5, respectively. These results are shown in Figure III-4.

The results reported in Lewis *et al* (2008b) for adults are reproduced here for comparison. Lewis *et al* (2008b) reported significant relationships in adults for all subregions except subregion 4 — roughly the isthmus — with r^2 values of 0.304, 0.390, 0.263, 0.114, and 0.203. Those results are reproduced in Figure III-5.

The significance and r^2 values for both the children and adults are presented together in Table III-2. The mean connection length and mean degree of connectivity for both are presented together in Table III-3.

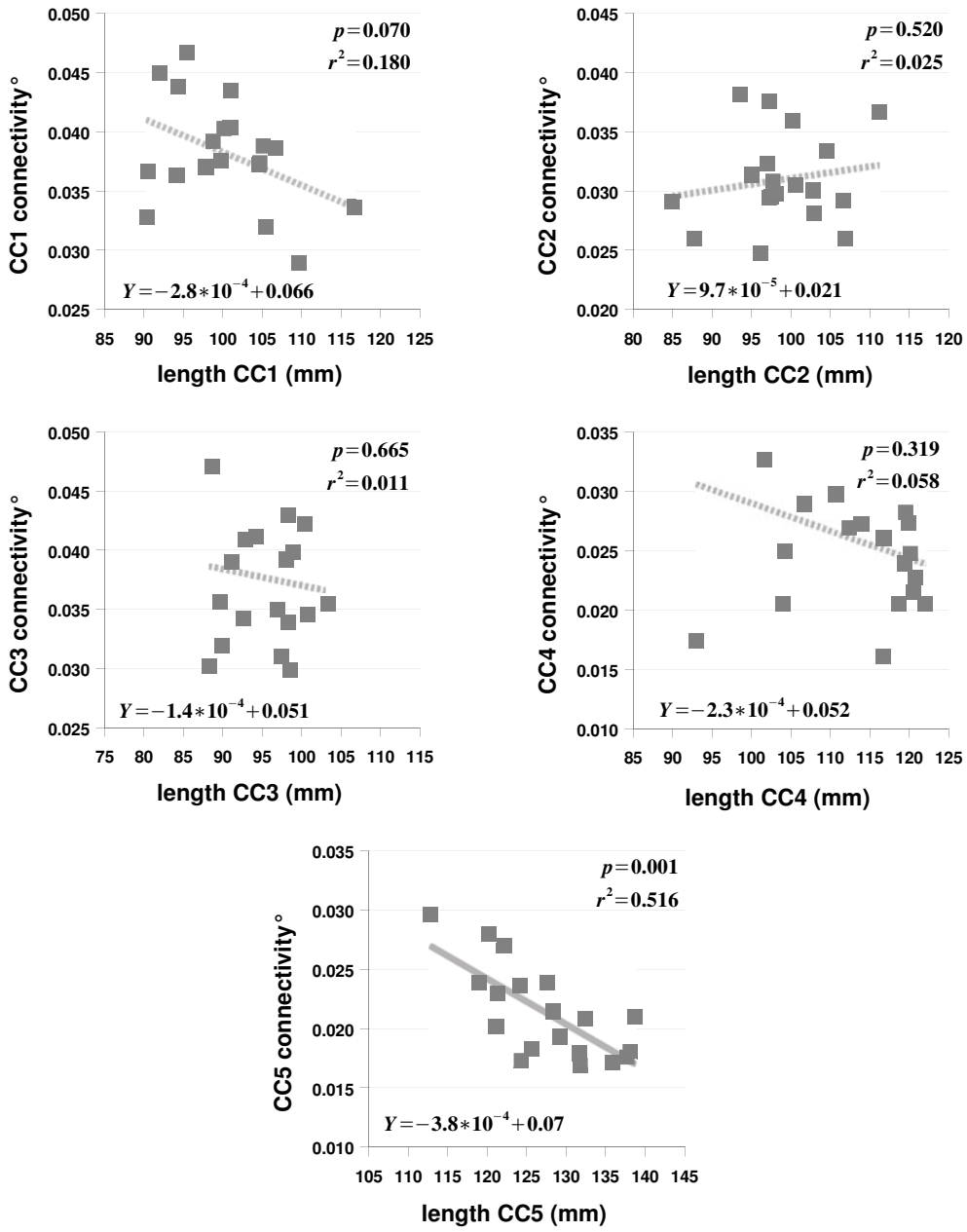

Figure III-4. The relation between degree of connectivity for subregion i of the callosum — indicated as CC_i *connectivity*° — and the average length of the connections passing through subregion *i*, for the children. The solid regression line in subregion 5 indicates that the relationship is significant at $P \leq 0.05$. The relation is not significant in the other four subregions, and the average r^2 value is 0.0685. The significance and r^2 values are given in Table III-2.

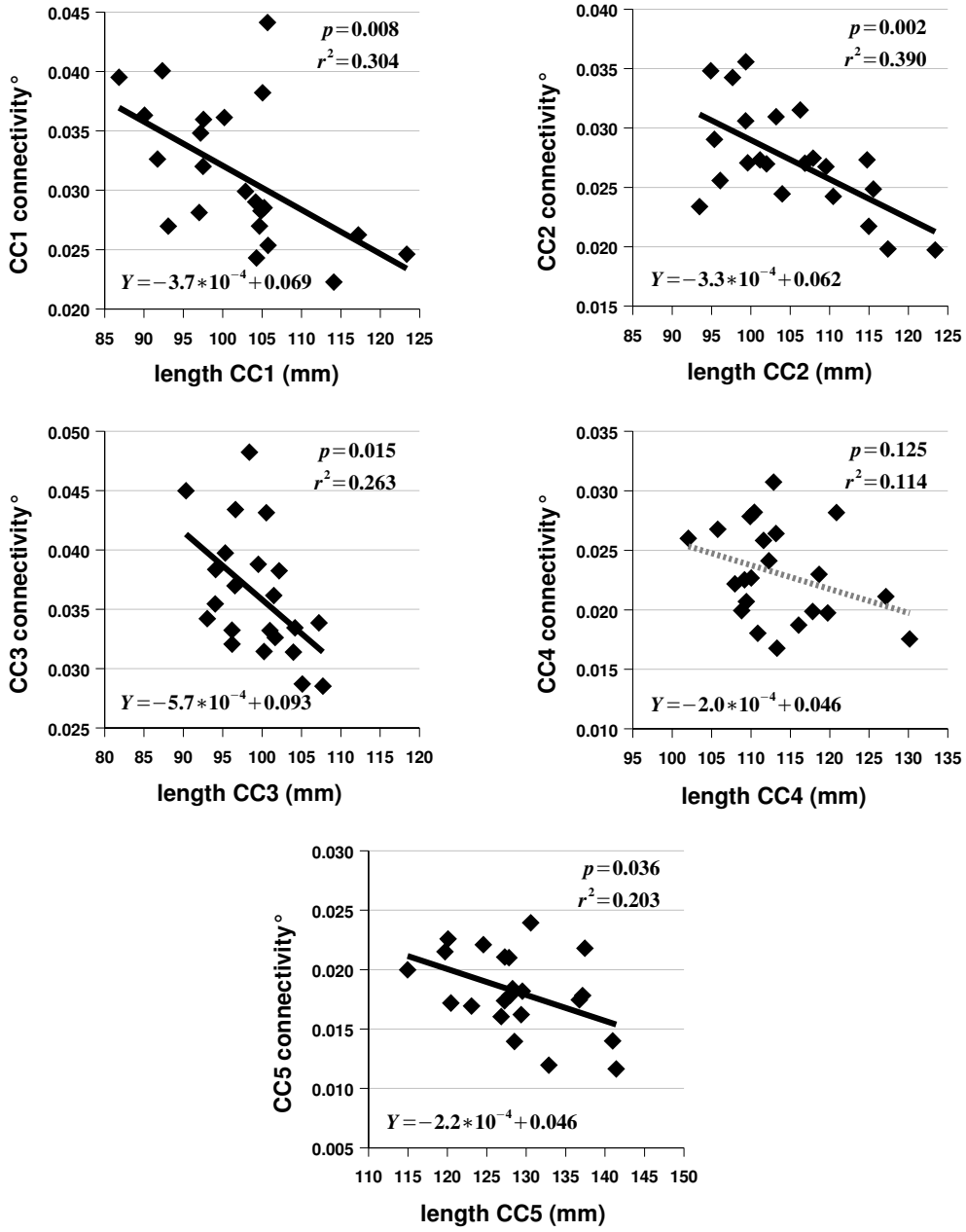

Figure III-5. The relation between degree of connectivity for subregion *i* of the callosum — indicated as CC_i *connectivity*° — and the average length of the connections passing through subregion *i*, for the adults. The solid regression lines in subregions 1,2,3 and 5 indicate that the relationship is significant at $P \leq 0.05$. The significance and r^2 values are given in Table III-2.

Table III-2. The significance and r^2 values for the results for regressions of the degree of connectivity for subregion *i* against the average length of the connections in subregion *i*. The top row provides the values for the children, and correspond to the regression plots in Figure III-4. The bottom row provides the values for the adults, and correspond to the regression plots in Figure III-5. The adult data is reproduced from Lewis *et al* (2008b)**.**

	CC_1		CC_2		CC_3		CC_4		CC_5	
	Sig.	**r^2**	**Sig.**	**r^2**	**Sig.**	**r^2**	**Sig.**	**r^2**	**Sig.**	**r^2**
children	.070	.180	.520	.025	.665	.011	.319	.058	**.001**	**.516**
adults	**.008**	**.304**	**.002**	**.390**	**.015**	**.263**	.125	.114	**.036**	**.203**

Table III-3. The means for connection length and degree of connectivity — indicated as *con°* — for each subregion, for the children and the adults. The adult data is from Lewis *et al* (2008b).

	CC_1		CC_2		CC_3		CC_4		CC_5	
	length	**con°**	**length**	**con°**	**length**	**con°**	**length**	**con°**	**length**	**con°**
children	100.4	.038	98.8	.031	95.3	.038	112.9	.026	127.5	.021
adults	101.9	.031	105.1	.027	99.3	.036	113.5	.023	128.8	.018

III.E Discussion

The results from the children combined with those from Lewis *et al* (2008b) from adults indicate that the negative relation between connection length and degree of connectivity observed in adults develops during childhood and adolescence. The two studies utilized the same methodology: diffusion tensor imaging and tractography to detail the patterns of interhemispheric connectivity and to determine the length of the connections, and formulae based on histological results to estimate degree of

connectivity. The children showed a significant relation between connection length and degree of connectivity only in the posterior-most subregion of the callosum, whereas the adults studied by Lewis *et al* (2008b) showed significant relationships in four of the five subregions — the exception being subregion 4, *i.e.*, the isthmus. Moreover, in the children, averaging over the anterior 4 subregions, connection length accounted for less than 7 percent of the variance in degree of connectivity; in the adults, averaging over these same 4 subregions, connection length accounted for almost 27 percent of the variance in degree of connectivity. Further, in subregion 2, whereas for the adults the negative relation between connection length and degree of connectivity accounted for 39 percent of the variance in degree of connectivity, in the children connection length accounts for less than 3 percent of the variance in degree of connectivity, and the relation is positive rather than negative. Thus, the relation between connection length and degree of connectivity observed in adults is not seen before adolescence, except in the splenium.

This anterior-posterior pattern of differences is also evidence that the relation develops. In our results, though in the anterior four subregions connection length accounts for less than 7 percent of the variance in degree of connectivity — with subregion 2 contributing via a positive rather than negative relation — in subregion 5, connection length accounts for more than 50 percent of the variance in degree of connectivity. The adult results reported by Lewis *et al* (2008b) show no such anterior-posterior difference. And, that it is the posterior of the callosum that shows the relation in children fits with findings that during late childhood the posterior of the callosum experiences the most substantial changes (Giedd et al., 1999; Giedd et al.,

1996; c.f. Keshavan et al., 2002; Rajapakse et al., 1996; Thompson *et al.*, 2000). Notice too, that relative to the adult pattern, the mean degree of connectivity in the posterior is considerably more reduced compared to the anterior, indicating that substantially more pruning has occurred in posterior regions.

The results here thus provide strong evidence that the relation between connection length and degree of connectivity seen in the adults is established during development.

This conclusion directly opposes that of Jäncke *et al* (1999). Using T_1-weighted images, Jäncke *et al* (1999) studied the relation between forebrain volume and corpus callosum size in adults between 18 and 45 years of age (mean 26.7; stddev 4.4), and in children between 3 and 14 years of age (mean 8.4; stddev 2.7). They report significant relationships between $\log_{10}$ FBV and the $\log_{10}$ total CC size for both adults and children, with similar significance, and r^2 values for adults ($r^2 = 0.22$, $p = 0.001$) and children ($r^2 = 0.24$, $p = 0.001$), and similar slopes of these regressions — *i.e.*, a non-significant interaction between group and $\log_{10}$ FBV in a hierarchical polynomial regression model. They conclude that it is "unlikely that biological maturation or environmental factors acting during this period of life alter the aforementioned relationship between CC and FBV."

Note, however, that Jäncke *et al* (1999) compared the relation between CC and FBV only for total CC area, not for subregions of the callosum, and did not control for age effects — though they did report significant age-effects in the splenium, isthmus, and middle third of the callosum in children, and in the middle third in adults. The anterior-posterior differences observed in the current study are not visible to an

analysis which does not subdivide the callosum; such an approach collapses the strong posterior relation in the splenium with the non-significant relations in the anterior. And, the wide-spread age effects in the children, together with the large age range, suggest that the reported relation between CC and FBV might reflect age-related changes in the relation between CC area and FBV, rather than a stable relation that persists from childhood on; and by using total CC area rather than the divisions that were used to assess age-effects, the overall correlation was confounded by the age effects. Moreover, age effects appear to also impact the results for the adults: with the callosum divided into five subregions, and age-adjusted measures of corpus callosum subregion area and forebrain volume, Lewis *et al* (2008b) reported a significant relationship between callosum size and forebrain volume only in subregion 3, and r^2 values of 0.002, 0.055, 0.161, 0.000 and 0.078 in subregions 1 through 5, respectively.

In contrast, regressing the estimate of the degree of inter-hemispheric connectivity associated with subregion *i* of the callosum and the length of the inter-hemispheric connections passing through subregion *i* reveals large differences between children and adults. Lewis *et al* (2008b) reported significant relations between the estimate of the degree of inter-hemispheric connectivity associated with subregion *i* of the callosum and the length of the inter-hemispheric connections passing through subregion *i* in subregions 1,2,3 and 5, with r^2 values of 0.304, 0.390, 0.263 and 0.203, respectively. Across all subregions, an average of 25.5 percent of the variability in degree of inter-hemispheric connectivity associated with each subregion was accounted for by the length of the inter-hemispheric connections. The results here, with a narrow age range of children, and with the same methodology,

show children to almost completely lack this relation between connection length and degree of connectivity. The children showed a significant relation only in subregion 5 of the callosum; in subregion 3 connection length accounted for only about 1 percent of the variance in degree of connectivity; and subregion 2 showed a positive rather than negative relation.

In addition to showing that the relation between connection length and degree of connectivity is established during development, the current data also suggest that the emergence of this relation stems from the impact of the longer long-distance connections of larger brains on known developmental mechanisms, *e.g.*, selective pruning. This relation emerges first in subregion 5, and the connections that pass through subregion 5 are considerably longer than those in the other four subregions. And notice that, whereas for the adults, larger values for mean connection length are associated with smaller values for mean degree of connectivity — *e.g.*, the longest connections and lowest degree of connectivity are in subregion 5, and the shortest connections and highest degree of connectivity are in subregion 3 — for the children this is true only in the posterior of the callosum. The differences in conduction delays and cellular costs associated with differences in connection length are substantially greater in the developing brain than in the mature brain, and so brain size differences during development should be expected to have a considerable impact on the growth and retention of long-distance connections. Unmyelinated axon conduction velocities range from about 0.5 to 10 m/s (Purves et al., 2001). Connection length across subjects differs by as much as 30mm. Thus, the impact on conduction delay will range from a few milliseconds in the largest diameter fibers to about 60 milliseconds

in the smallest. And, the increase in metabolic costs associated with these longer fibers is presumably substantial; larger brains incur greater metabolic costs (Aiello, 1997; Aiello, Bates, & Joffe, 2001; Isler & van Schaik, 2006; Karbowski, 2007; Sherwood et al., 2006), and the glucose metabolic rate is approximately double that of adults at 9 years of age (Chugani, 1998). Brain size differences during development are thus likely to have a considerable impact on the growth and retention of long-distance connections; and so, the shape of the growth trajectory during development likely plays an important role in determining the organization of white-matter.

This concurs with a growing body of evidence that metabolic costs and processing efficiency constrain the way the cortex is organized (Changizi, 2001, 2005; Changizi & Shimojo, 2005; Chklovskii & Koulakov, 2000; Chklovskii, Schikorski, & Stevens, 2002; Harrison, Hof, & Wang, 2002; He, Chen, & Evans, 2007; Kaiser & Hilgetag, 2004; Karbowski, 2001, 2003; Lewis & Elman, 2008; Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994; Schüz & Miller, 2002; Sporns & Honey, 2006; Sporns & Zwi, 2004; Watts & Strogatz, 1998).

A few caveats, however, should be noted. The results here rely on histology done on adult brains. The estimates of total neuron number are based on data from individuals between 18 and 93 years of age. Though brain volume changes little after five years of age (Durston et al., 2001), neuron density may; histological data for the current age range is required to determine the accuracy of the estimates. Also, as with Lewis *et al* (2008b), our results rely on the assumption that the number of cortico-cortical projection neurons scales with the total number of neurons in cortex. The results, however, rely on the relative values among the children, not the actual values,

and the narrow age range of our sample makes it likely that the relative values are reasonable. The estimates of the number of fibers that comprise the callosum are also based on adult histology. These estimates, most likely, are inaccurate. Considerable myelination takes place through adolescence and even into the third decade of life (Pujol, Vendrell, Junqué, Martí-Vilalta, & Capdevila, 1993), there are increases in axon diameter, and selective pruning eliminates a substantial number of fibers (Rakic & Yakovlev, 1968). Again, however, our results rely on the relative values among the children, not the actual values. Moreover, during this age range, changes in the callosum are predominately in posterior regions (Thompson *et al.*, 2000), so the contrast of the existence of the relation between connection and degree of connectivity for the anterior subregions of the adult callosum, and the lack of that relation for the anterior regions of the developing callosum seems reliable. But, a relation between brain size and the spatio-temporal patterns of change in the developing brain could distort even these results.

There are, as well, as discussed in Lewis *et al* (2008b), limitations associated with tractography: crossing fibers, and fibers that come together and then separate again — so called 'kissing fibers' — can cause tractography to fail. Crossing fibers result in reduced fractional anisotropy values, which, if sufficient, will cause tractography to terminate; and so the tract will be discarded. Fibers that come together and then separate again contribute to the same set of tensors while in close proximity, and at the point of separation cannot be distinguished; moreover, at the point of separation, deterministic tractography will follow only one path. The fibers of the callosum originate broadly from cortex, and fan in to the mid-sagittal plane. The

methodology used here, and in Lewis *et al* (2008b), seeds tracts from all points along the edge of cortex, and terminates tracts at the mid-sagittal slice, thus the 'kissing fibers' problem does not exist for the callosal fibers in isolation. The problem does arise, however, in interactions between callosal tracts and others. Fibers originating in the anterior of the temporal lobe, for example, come together with fibers in the inferior longitudinal fasciculus, some of which ascend to the splenium. These 'callosal' tracts are thus unreliable, and may cause large inaccuracies in the estimates of length associated with subregion 5 of the callosum. Thus the temporal lobe was eliminated from the analysis. Callosal fibers projecting to frontal, parietal and occipital lobes may become confused with thalamo-cortical connections, as well. But the longest callosal fibers and the longest thalamo-cortical fibers will both originate/terminate at the outermost point of a gyrus, and so the impact on the estimate of length will be small. These thalamo-cortical fibers, however, also interfere with tractography for callosal fibers projecting to, or coming from, more lateral cortical areas. In this case, the callosal fibers cross with the thalamo-cortical fibers. This will produce low fractional anisotropy values, and so callosal tracts from lateral cortex may be truncated and discarded. This will introduce inaccuracies in the length measurements to the extent that such tracts are among the longest that comprise a subregion of the callosum, and are substantially different in length from tracts for which tractography succeeds.

These estimates of connection length and degree of connectivity are, nonetheless, a considerable improvement over methods which used volumetric measures. The estimates of connection length, though, due to the limitations of

tractography, not completely accurate, are presumably a much better estimate of the length of the inter-hemispheric connections than forebrain volume, or cortical surface area; and the estimates of degree of connectivity, though the histological results need to be extended to this age range, are presumably a considerable improvement over approaches which ignored the histological results altogether. The importance of using meaningful relative measures has been demonstrated elsewhere (Jungers, Falsetti, & Wall, 1995; Lewis, Theilmann, Sereno, & Townsend, 2008b; Smith, 2005).

Assuming that the conclusions here are correct, differences in growth trajectories may account for much of the individual variation in degree of connectivity not accounted for by static connection length alone. Brains that ultimately achieve the same size may do so at very different rates. The data here suggest that these size differences during development may determine the degree of connectivity in the adult brain. Moreover, this may have considerable explanatory value for developmental disorders in which there are early abnormalities in brain size — *e.g.*, autism (Lewis & Courchesne, 2004b; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008; Lewis, Elman, & Courchesne, 2005). Children with autism spectrum disorder have unusually large heads and brains during early childhood (Aylward, Minshew, Field, Sparks, & Singh, 2002; Fombonne, Roge, Claverie, County, & Fremolle, 1999; Lainhart et al., 1997; Sparks et al., 2002), arrived at via abnormally rapid growth during the first years of life (Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Dementieva et al., 2005; Hazlett et al., 2005; Lainhart et al., 1997). Computational modeling of this early brain overgrowth has shown that the increased conduction delays presumably accompanying this

increased brain size lead to decreased functional and structural connectivity (Lewis & Elman, 2008). Magnetic resonance imaging studies of children with autism have related brain size to the relative size of the corpus callosum (Lewis & Courchesne, 2004a; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004), and to changes in the relative size of the callosum (Lewis, Elman, & Courchesne, 2005). And adolescents and adults with autism show reduced structural and functional connectivity (Belmonte et al., 2004; Egaas, Courchesne, & Saitoh, 1995; Herbert, 2005; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Just, Cherkassky, Keller, & Minshew, 2004; Lewis, Theilmann, Sereno, & Townsend, 2008a; Murias, Webb, Greenson, & Dawson, 2007; Piven, Bailey, Ranson, & Arndt, 1997).

A number of other factors, of course, might impact degree of connectivity — *e.g.*, experience, environment, and genetics (Lee, Chen, & Schlaug, 2003; Öztürk, Tasçioglu, Aktekin, Kurtoglu, & Erdin, 2002; Pfefferbaum, Sullivan, Swan, & Carmelli, 2000; Scamvougeras, Kigar, Jones, Weinberger, & Witelson, 2003). It remains to future research to determine to what extent connection length during development determines the degree of connectivity in the mature individual. The current research, however, shows that this relation is established during childhood and adolescence.

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Chapter IV
Growth-Related Neural Reorganization and the Autism Phenotype: A Test of the Hypothesis that Altered Brain Growth Leads to Altered Connectivity

IV.A Abstract

Theoretical considerations, and findings from computational modeling, comparative neuroanatomy and developmental neuroscience, motivate the hypothesis that a deviant brain growth trajectory will lead to deviant patterns of change in cortico-cortical connectivity. Differences in brain size during development will alter the relative cost and effectiveness of short and long-distance connections, and should thus impact the growth and retention of connections. Reduced brain size should favor long-distance connectivity; brain overgrowth should favor short-distance connectivity; and inconsistent deviations from the normal growth trajectory — as occurs in autism — should result in potentially disruptive changes to established patterns of functional and physical connectivity during development. To explore this hypothesis, neural networks which modeled inter-hemispheric interaction were grown at the rate of either typically developing children or children with autism. The influence of the length of the inter-hemispheric connections was analyzed at multiple developmental time points. The networks that modeled autistic growth were less affected by removal of the inter-hemispheric connections than those that modeled normal growth — indicating a reduced reliance on long-distance connections — for short response times, and this difference increased substantially at approximately 24 simulated

months of age. The performance of the networks showed a corresponding decline during development. And direct analysis of the connection weights showed a parallel reduction in connectivity. These modeling results support the hypothesis that the deviant growth trajectory in autism spectrum disorders may lead to a disruption of established patterns of functional connectivity during development, with potentially negative behavioral consequences, and a subsequent reduction in physical connectivity. The results are discussed in relation to the growing body of evidence of reduced functional and structural connectivity in autism, and in relation to the behavioral phenotype, particularly the developmental aspects.

IV.B Introduction

Brain size has been found to be strongly correlated with relative long-distance cortico-cortical connectivity across species (Rilling & Insel, 1999; Zhang & Sejnowski, 2000), and also, though less strongly, within species (Jancke, Staiger, Schlaug, Huang, & Steinmetz, 1997). Evidence that such a relationship also holds developmentally (Jancke, Preis, & Steinmetz, 1999; Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004) suggests a link between findings of deviant brain growth trajectories in developmental disorders (Bailey et al., 1998; Bauman & Kemper, 1985; Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Hagberg, Stenbom, & Engerström, 2001; Hazlett et al., 2005) and findings of abnormalities in cortico-cortical connectivity in these disorders (Barnea-Goraly et al., 2004; Baron-Cohen, Knickmeyer, & Belmonte, 2005; Egaas, Courchesne, & Saitoh, 1995; Lewis & Courchesne, 2004; Lewis, Courchesne, &

Elman, 2003; Lewis, Courchesne, & Elman., 2004; Piven, Bailey, Ranson, & Arndt, 1997; Vidal et al., 2006; Waiter et al., 2005) — and possibly between these findings and behavior (Belmonte et al., 2004; Castelli, Frith, Happe, & Frith, 2002; Deutsch & Joseph, 2003a, 2003b; Just, Cherkassky, Keller, & Minshew, 2004; Pelphrey, Morris, & McCarthy, 2005; Tager-Flusberg & Joseph, 2003). Brain size is inversely correlated with the ratio of inter-hemispheric white-matter to gray-matter (Jancke, Preis, & Steinmetz, 1999; Jancke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Rilling & Insel, 1999), and presumably with the ratio of long-distance cortico-cortical connections, in general, to gray-matter (Zhang & Sejnowski, 2000). Thus developmental disorders in which brain size is abnormally small throughout development should show increased long-distance connectivity; and those in which brain size is abnormally large should show decreased long-distance connectivity. In cases in which brain size abnormalities are not consistent throughout development, more complex and possibly more detrimental effects on connectivity might be expected.

The relation between brain size and connectivity has been hypothesized to stem from the relations between brain size and conduction delay and between brain size and the cellular costs associated with long-distance connections (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Ringo, Doty, Demeter, & Simard, 1994). The conduction delay associated with either a myelinated or an unmyelinated axon is primarily a function of its diameter and length (Waxman, 1977); and differences in brain size necessarily correlate with differences in the lengths of long-distance connections, but appear to

correlate only weakly with differences in axon diameters (Olivares, Montiel, & Aboitiz, 2001). Thus, differences in brain size should alter the relative usefulness of short and long-distance connections for tasks that require rapid responses. The cell maintenance costs associated with long-distance connections should also correlate with brain size, and so differences in brain size should also alter the relative costs of short and long-distance connections.

Both intra- and inter-hemispheric connectivity appear to be arrived at via prenatal exuberance followed by postnatal pruning (LaMantia & Rakic, 1990; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986), the latter of which is thought to be moderated by an activity dependent competition for neurotrophins (Barres & Raff, 1993; Callaway, Soha, & Van Essen, 1987; Van Ooyen & Willshaw, 1999). Brain-size differences during development should impact this competition, and so the growth and retention of connections (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004). In abnormal development, in periods of time in which brain size is abnormally small, long-distance connections should be favored, and during periods of time in which brain size is abnormally large, short-distance connections should be favored. Brain development is not spatio-temporally homogenous — evidence supports heterochronous development in typically developing children (Giedd et al., 1999; Thompson et al., 2000) — and so the effects of brain-size abnormalities on connectivity should be expected to be temporally and spatially linked. A growth trajectory in which there is a developmentally inconsistent brain-size abnormality should thus show a corresponding fluctuation in the pattern of connectivity in spatial accord with the

temporal aspects of the brain-size abnormalities. And a very rapid change in the growth trajectory might be expected to alter established patterns of connectivity within a given brain area — abandoning connections in which early learning has been represented, potentially giving rise to abnormalities in the behaviors that relied on those connections.

There is now consistent evidence from post mortem studies (Bailey et al., 1998; Bauman & Kemper, 1985; Kemper & Bauman, 1998), head circumference measures (Aylward, Minshew, Field, Sparks, & Singh, 2002; Bailey et al., 1993; Courchesne, Carper, & Akshoomoff, 2003; Davidovitch, Patterson, & Gartside, 1996; Dementieva et al., 2005; Fombonne, Roge, Claverie, County, & Fremolle, 1999; Hazlett et al., 2005; Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000; Woodhouse et al., 1996) and MRI volumetric analyses (Aylward, Minshew, Field, Sparks, & Singh, 2002; Courchesne et al., 2001; Piven et al., 1995; Sparks et al., 2002) that individuals with autism spectrum disorders have abnormally large brains after the second or third year of life, and that, early in development, this size difference can be multiple standard deviations above the norm (Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Dementieva et al., 2005; Hazlett et al., 2005; Sparks et al., 2002). Children later diagnosed with autism spectrum disorders, however, have head circumference measures at birth that are normal (Hazlett et al., 2005; Hultman, Sparen, & Cnattingius, 2002), or even slightly smaller than normal (Courchesne, Carper, & Akshoomoff, 2003; Redcay & Courchesne, 2005). That these results stem from accelerated growth over the first years of life is supported by longitudinal data (Courchesne, Carper, & Akshoomoff, 2003; Dementieva et al.,

2005; Hazlett et al., 2005). Thus autism appears to be an example of a developmental disorder showing an abrupt increase in brain size after a period of normal or slightly reduced growth.

This pattern of growth is predicted to show disruptions in the initially established patterns of functional connectivity, abnormalities in the behaviors associated with these disruptions, and a subsequent reduction in physical connectivity.

There is a growing body of evidence of reduced large-scale functional and structural connectivity in adults with autism spectrum disorders (Castelli, Frith, Happe, & Frith, 2002; Egaas, Courchesne, & Saitoh, 1995; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; Koshino et al., 2005; Manes et al., 1999; Piven, Bailey, Ranson, & Arndt, 1997; Ring et al., 1999; Vidal et al., 2006). And it has been proposed that the deficits in autism are a result of reduced integration of information due to this under-connectivity (Herbert, 2005; Just, Cherkassky, Keller, & Minshew, 2004). But there are no studies of the developmental changes in functional connectivity, and the relations between the trajectory of brain growth and the behavioral phenotype, and physical connectivity, are almost unknown. The growth of inter-hemispheric connectivity in children with autism spectrum disorders appears to be inversely related to brain size between 4 and 10 years of age (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman., 2004), and by late childhood or adolescence, individuals with autism spectrum disorders show abnormal increases in gray-matter (Waiter et al., 2004), decreases in inter-hemispheric white-matter (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman., 2004; Waiter et al., 2005), and increased short-distance connectivity (Herbert et al., 2004). And there

is also some indication that the degree of abnormality in the rate of brain growth is related to the severity of the outcome (Akshoomoff et al., 2004; Courchesne, Carper, & Akshoomoff, 2003; Deutsch & Joseph, 2003b; c.f. Sparks et al., 2002; Tager-Flusberg & Joseph, 2003). But there is essentially no research that relates the shape of the brain growth trajectory in the first years of life to developmental changes in functional connectivity, structural connectivity, or to the particular aspects of the behavioral phenotype that might be vulnerable to reorganization.

This paper reports on a computational study of the possibility of such effects of brain-growth on developmental patterns of connectivity and performance. Neural networks 'grown' in accord with either the brain-growth patterns of typically developing children or children with autism were used to explore this possibility.

IV.C Methods

IV.C.1 Architecture and Training

The simple two-hemisphere model shown in Figure IV-1 was used to explore this hypothesis. This architecture was based on that used by Ringo et al. (Ringo, Doty, Demeter, & Simard, 1994). The network comprised two 'hemispheres' of ten units each, five input units and five output units for each hemisphere, and a number of units used to implement conduction delay in inter- and intra-hemispheric connections. Each unit in both hemispheres was fully connected with the 9 other units in that hemisphere, and all of these units were recurrent. Two units in each hemisphere also had afferent and efferent connections with two units in the other hemisphere. The five

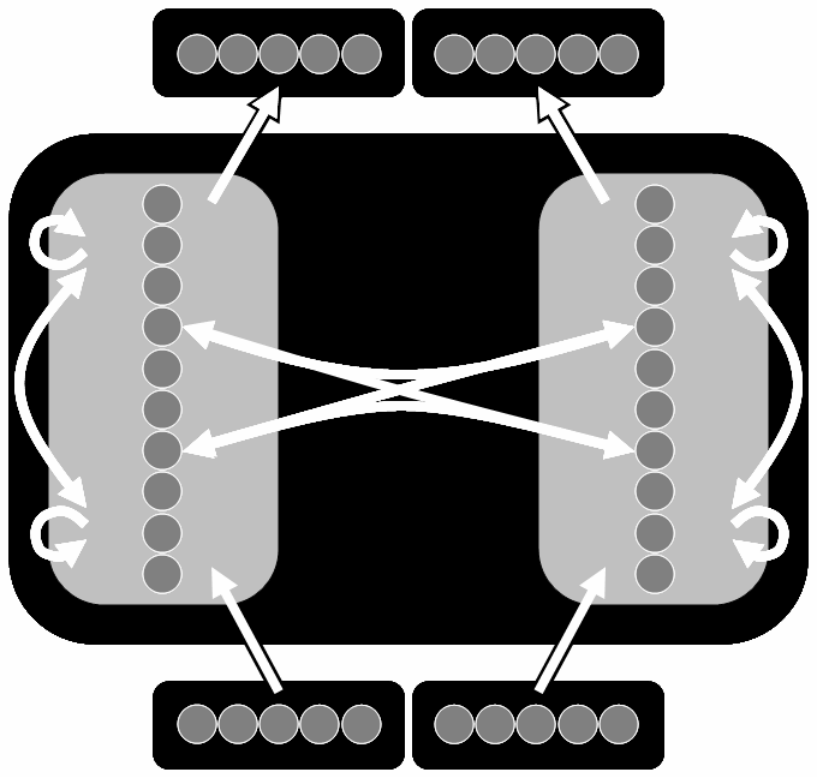

Figure IV-1. The network architecture. Five input units are fully connected to either 'hemisphere', and either hemisphere is fully connected to five output units. A hemisphere comprises ten units and is fully recurrent. Two units from each hemisphere are used for inter-hemispheric connections; each of the two units in one hemisphere is connected to both units in the other hemisphere.

input units for a hemisphere were fully connected with that hemisphere; and each hemisphere was fully connected with five output units.

Both inter- and intra-hemispheric connections were associated with conduction delays, implemented by constructing these connections as chains of copy units. The conduction delay was the number of links in an inter- or intra-hemispheric chain. The delay associated with an inter-hemispheric connection was a function of age based on

the head circumference growth trajectories for either typically developing children or children with autism. The delay function was:

$$Delay_{INTER}(age, diagnosis) = {}^{2}/_{3} * (HC(age, diagnosis)/\pi) / ConductionVelocity(age)$$

where *HC(age, diagnosis)* is the head circumference at the given age for the given diagnosis, and *ConductionVelocity(age)* is an increasing linear function of age. The inter-hemispheric delay was thus $^{2}/_{3}$ of the diameter of a spherical head corresponding to *HC(age, diagnosis)* — a crude approximation of the length of the inter-hemispheric connections taking scalp, skull, cortical thickness, and cortical folding into account — divided by *ConductionVelocity(age)* — a crude approximation of the increases in axon diameter and myelination that occur over development. The delay associated with an intra-hemispheric connection was identical for both the networks modeling typical brain growth and the networks modeling autistic brain growth; it was $^{3}/_{8}$ of the inter-hemispheric delay associated with the typical brain growth pattern. These functions are plotted in Figure IV-2. The developmental changes in the conduction delays associated with inter- and intra-hemispheric connections are, of course, a far more complex combination of non-linear functions which differ between regions; the connections may follow complex paths that are substantially greater than $^{2}/_{3}$ of the diameter of the head; and heads are not spherical. But these functions are plausibly an index of the actual average conduction delays associated with the two types of connections.

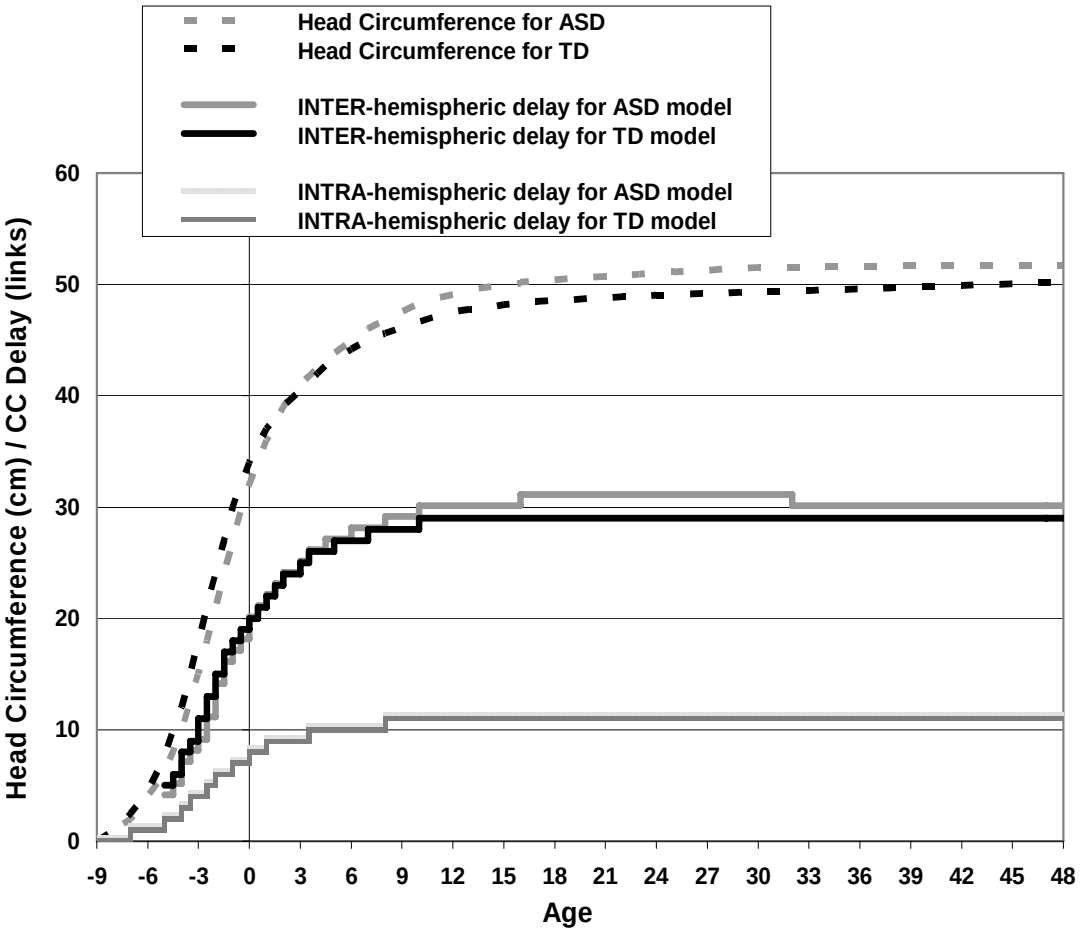

Figure IV-2. The growth trajectories of the networks modeling typically developing children and children with autism spectrum disorders. The head circumference growth trajectories are based on reported data. The inter-hemispheric conduction delay for the networks was a discretized function of age based on the head circumference growth trajectories. The delay function was:

$$Delay_{\mathrm{INTER}}(age, diagnosis) = {}^{2}/_{3} * (HC(age, diagnosis)/\pi) / ConductionVelocity(age)$$

where *HC(age, diagnosis)* is the head circumference at the given age for the given diagnosis, and *ConductionVelocity(age)* is an increasing linear function of age. The delay associated with an *intra*-hemispheric connection was identical for both the networks modeling typical brain growth and the networks modeling autistic brain growth; the delay was ${}^{3}/_{8}$ of the *inter*-hemispheric delay associated with the model of typical brain growth.

The growth trajectory for networks modeling typical development was based on head circumference measures from standardized growth charts (Kuczmarski et al., 2002; Nellhaus, 1968) and on prenatal measures taken by ultrasound (Kurmanavicius et al., 1999.; Schwärzler, Bland, Holden, Campbell, & Ville, 2004). The growth trajectory for the networks modeling development in autism was derived from a meta-analysis of brain growth in children with autism (Redcay & Courchesne, 2005). Gompertz curves were fitted to these data to estimate the prenatal trajectories (Luecke, Wosilait, & Young, 1995; Winsor, 1932; Wosilait, Luecke, & Young, 1992).

As shown in Figure IV-2, network growth was discretized — *i.e.*, the delay functions were approximated with step functions. Copy units were added to or subtracted from each of the inter- and intra-hemispheric connections in accord with the delay functions at the beginning of each simulated half-month. The network architecture was then held static for the duration of that simulated half-month. Training for 500 epochs constituted a simulated half-month. As shown in Figure IV-2, as well, the inter-hemispheric connections were connected at 5 months before birth; this is approximately the timing of the establishment of inter-hemispheric connections in prenatal development (Rakic & Yakovlev, 1968). Network training begins 5 months before birth, as well.

The networks were trained to enumerate a set of input strings. The networks were provided with 32 input-output patterns, and were trained to associate each input pattern with its corresponding output pattern. The input patterns were randomly generated binary strings. The output patterns were the base 2 encodings of unique numbers assigned to the input patterns, duplicated for the output units of either

hemisphere, *e.g.* the output for pattern number 1 was 00001 00001. The input patterns for both hemispheres together always corresponded to a unique output for all 32 input patterns. But, in order to explore the potential impact of the different growth trajectories on aspects of task performance that rely on inter-hemispheric communication and aspects that do not, half of the input-output pairs were unique within either hemisphere, and half of the input patterns for either hemisphere alone each corresponded to four different outputs. Thus, 16 of the input patterns could be associated with their outputs without inter-hemispheric communication; and the other 16 were 4-way ambiguous within either hemisphere, and so to generate the correct output, the network had to make use of the inter-hemispheric connections. Each of these 32 inputs was randomly assigned a number between 0 and 31, and paired with the binary string comprised of the five digit base 2 encoding of that number concatenated with itself. Table IV-1 and Table IV-2 show the two sorts of input-output patterns. Examples were drawn randomly from such training sets.

The networks were constructed and trained on LENS (Rhode, 1999) using the backpropagation of error algorithm (Rumelhart, Hinton, & Williams, 1986) and gradient descent with a learning rate of 0.01 and a momentum value of 0.9. A cross-entropy error function was used so that the activation levels of the output units could be interpreted as probabilities as well as confidence estimates.

To ensure the generality of the results, networks were trained on ten different training sets, and for each training set were trained 20 times with different initial random connection weights. Additionally, the impact of the time between presenta-

Table IV-1. 16 example input-target patterns which are 4-way ambiguous within each hemisphere. One half of one of the training sets comprises these examples. The four examples which are bolded are identical with respect to the inputs to the left hemisphere. The corresponding inputs to the right hemisphere are, however, unique. The left and right inputs together thus uniquely specify the outputs for both hemispheres. Note that this same within-hemisphere ambiguity exists for each of these 16 examples.

Left Hemisphere			**Right Hemisphere**		
Input		**Target**	**Input**		**Target**
1 0 0 0 1	→	**0 0 0 0 1**	**0 1 0 0 0**	→	**0 0 0 0 1**
0 1 0 0 0	→	0 1 1 1 0	0 0 1 0 0	→	0 1 1 1 0
1 1 1 1 0	→	1 0 0 0 1	1 0 1 0 1	→	1 0 0 0 1
1 0 0 0 1	→	**0 1 0 1 1**	**1 0 1 0 1**	→	**0 1 0 1 1**
1 1 0 1 1	→	1 0 0 1 1	0 0 1 0 0	→	1 0 0 1 1
1 1 1 1 0	→	1 0 1 1 0	0 1 0 0 0	→	1 0 1 1 0
0 1 0 0 0	→	1 0 1 1 1	1 0 1 0 1	→	1 0 1 1 1
1 1 1 1 0	→	1 1 0 0 1	0 0 0 0 0	→	1 1 0 0 1
1 1 0 1 1	→	1 1 0 1 0	0 1 0 0 0	→	1 1 0 1 0
1 0 0 0 1	→	**0 1 0 0 0**	**0 0 1 0 0**	→	**0 1 0 0 0**
1 1 0 1 1	→	1 1 1 0 0	1 0 1 0 1	→	1 1 1 0 0
0 1 0 0 0	→	1 1 1 0 1	0 1 0 0 0	→	1 1 1 0 1
1 0 0 0 1	→	**0 1 0 0 1**	**0 0 0 0 0**	→	**0 1 0 0 1**
0 1 0 0 0	→	1 1 1 1 1	0 0 0 0 0	→	1 1 1 1 1
1 1 1 1 0	→	0 0 1 0 0	0 0 1 0 0	→	0 0 1 0 0
1 1 0 1 1	→	0 0 1 1 0	0 0 0 0 0	→	0 0 1 1 0

tion of the input and evaluation of the response — *i.e.*, the settling time — was of the input and evaluation of the response — *i.e.*, the settling time — was assessed for each training set and each weight initialization. Settling time and conduction delay, together, determine how quickly, and for how long, the inter-hemispheric connections can influence the dynamics of the network, and so settling time was expected to have a

Table IV-2. The other half of the training set shown in Table IV-1. In these examples, the inputs to each hemisphere uniquely specify the outputs.

Left Hemisphere			Right Hemisphere		
Input		**Target**	**Input**		**Target**
0 0 0 1 0	→	0 0 0 0 0	0 0 0 1 0	→	0 0 0 0 0
0 1 0 1 0	→	0 0 0 1 0	1 0 1 1 0	→	0 0 0 1 0
0 0 0 0 0	→	0 0 0 1 1	1 0 0 0 1	→	0 0 0 1 1
1 0 0 1 1	→	0 0 1 0 1	0 0 0 1 1	→	0 0 1 0 1
0 1 1 0 1	→	0 0 1 1 1	1 1 0 1 0	→	0 0 1 1 1
1 1 0 1 0	→	0 1 0 1 0	0 0 1 1 1	→	0 1 0 1 0
0 0 0 0 1	→	0 1 1 0 0	0 1 0 1 0	→	0 1 1 0 0
1 1 1 0 1	→	0 1 1 0 1	1 1 1 0 1	→	0 1 1 0 1
0 1 1 0 0	→	0 1 1 1 1	1 0 0 1 1	→	0 1 1 1 1
1 1 0 0 0	→	1 0 0 0 0	0 1 0 1 1	→	1 0 0 0 0
1 0 1 1 1	→	1 0 0 1 0	1 0 0 0 0	→	1 0 0 1 0
1 0 0 0 0	→	1 0 1 0 0	1 1 1 0 0	→	1 0 1 0 0
0 0 1 0 0	→	1 0 1 0 1	0 1 1 0 1	→	1 0 1 0 1
0 0 1 1 0	→	1 1 0 0 0	0 0 1 0 1	→	1 1 0 0 0
0 1 0 0 1	→	1 1 0 1 1	0 1 0 0 1	→	1 1 0 1 1
1 0 1 0 1	→	1 1 1 1 0	1 1 0 0 1	→	1 1 1 1 0

strong influence on the development of functional and physical connectivity, and on performance. Each network was trained once with a short settling time, and once with a long settling time. The short settling time was 10 sweeps greater than the time required for activation to spread from one hemisphere to the other in the networks following the brain growth trajectory of typically developing children. The long settling time was 20 sweeps greater than the short settling time.

IV.C.2 Measures of Connectivity and Performance

The impact of the difference in the two growth trajectories was analyzed for each network at multiple points during training: at the simulated equivalent of birth, 12, 24, 36, and 48 months of age. The impact on inter-hemispheric functional connectivity was measured. The impact on performance was measured. And the impact on inter-hemispheric physical connectivity was measured.

The functional analysis was done by removing all of the inter-hemispheric connections and measuring the impact of these lesions on the network's performance on the training set. The measure of performance was the cross-entropy error. The difference between the pre and post-lesion cross-entropy error — *i.e.*, the increase in error caused by the lesion — was calculated. This will be referred to as the *lesion induced error*. This measure was taken as an indication of the functional role of the inter-hemispheric connections. A greater increase in the lesion induced error was assumed to indicate a greater reliance on inter-hemispheric connections. This was assessed separately for the two sorts of input patterns — the 16 binary strings that were unique within either hemisphere, and the 16 that were 4-way ambiguous within either hemisphere.

The analysis of performance was done by measuring the cross-entropy error for the intact network on the training set, and on a version of the training set in which all targets were inverted. The network's performance was taken to be the percent correct, calculated as the error produced on the inverted version of the training set as a percentage of the total possible error. As with the functional measure, this was assessed separately for the two sorts of input patterns — the 16 binary strings that

were unique within either hemisphere, and the 16 that were 4-way ambiguous within either hemisphere.

The analysis of the impact of the difference in the growth trajectories on inter-hemispheric physical connectivity was done by measuring connection weights. The analysis used the mean of the absolute value of the inter-hemispheric connection weights — *i.e.*, $(\Sigma_{i,j} | w_{ij} |)/N$, where w_{ij} is the weight associated with the link between the i^{th} and j^{th} units, and the i^{th} and j^{th} units are in different hemispheres, and N is the number of such links — relative to the mean of the absolute value of the intra-hemispheric connection weights. This gave a measure of the physical connectivity across hemispheres relative to the physical connectivity within hemispheres.

To evaluate the effect of the growth trajectory on these measures, four sorts of analyses were conducted: (i) the estimated marginal means were computed for both growth conditions at each measured time point; (ii) the estimated marginal means were compared between the two groups at each time point; (iii) interactions between group and age were computed for successive pairs of time points; and (iv) where the estimated marginal means decreased across time within a group, they were compared to assess the reduction. To compare the estimated marginal means, for each time point and settling time, repeated measures ANOVAs were done with group and training set as within-subject factors — the different random initializations of a network being taken as different subjects. To evaluate interactions between the type of growth trajectory and age, for successive pairs of these time points, repeated measures ANOVAs were done with group, training set, and age as within-subject factors. And to assess the possibility of a reduction in functional or physical connectivity, or a

decline in performance, repeated measures ANOVAs were done for the group in question, for successive pairs of time points, with training set, and age as within-subject factors.

IV.D Results

The results of the analysis of the impact of removing the inter-hemispheric connections show an overall reduction in functional connectivity at approximately '24 months' in the networks that modeled autistic growth with short settling times, with considerable individual variation, and variation across training sets. The results of the analysis of performance show a corresponding decline in performance, with similar variability across individuals and training sets. And the results of the analysis of relative inter-hemispheric weight show a parallel reduction in physical connectivity. The results of the functional analyses are presented in Figure IV-3 and Figure IV-4, and in Table IV-3 and Table IV-4; the results of the analysis of performance during learning are presented in Figure IV-5 and Figure IV-6, and in Table IV-5 and Table IV-6; and the results of the analyses of the relative inter-hemispheric connection weight are presented in Figure IV-7 and Table IV-7.

Averaging over individual variation, and different outcomes for different training sets, the networks with short settling times grown at the rate of children with autism showed a reduction in functional connectivity — in terms of the impact of removing the inter-hemispheric connections — at approximately the simulated equivalent of 24 months of age. These networks showed less impact of the lesions

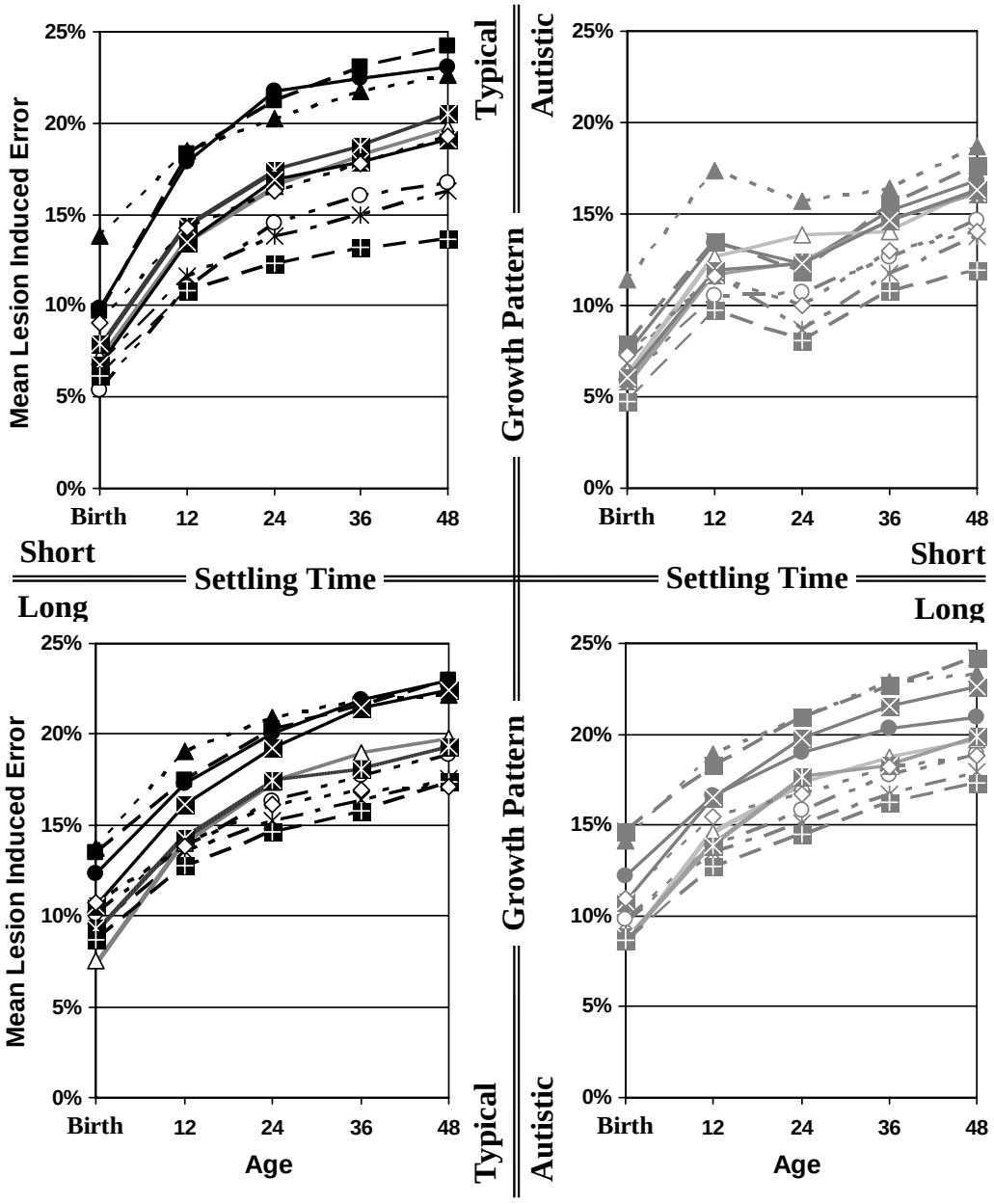

Figure IV-3. The impact of disconnecting the inter-hemispheric connections on the portion of the task which required inter-hemispheric communication. The left and right columns show the impact on the networks following the growth pattern in typical development and in autism, respectively. The top and bottom rows show the outcome for short and long settling times, respectively. Each curve represents the mean lesion induced error for a single training set.

Table IV-3. The impact of removing the inter-hemispheric connections on the portion of the task which required inter-hemispheric communication. Three statistics are reported for both short and long settling times: (i) the estimated marginal means at each of the time points; (ii) the main effect of group at each time point; (iii) the interactions of group and age between successive pairs of time points. These statistics complement the results graphed in Figure IV-3.

		Birth	12	24	36	48
i	μ_{ASD}	6.9	12.4	11.7	13.8	15.6
	μ_{TD}	8.1	14.1	16.8	18.1	19.3
ii	$F(1,19)$	74.235	59.767	109.932	49.361	31.996
	p	<0.001	<0.001	<0.001	<0.001	<0.001
	partial-η^2	0.796	0.759	0.853	0.722	0.627
iii	$F(1,19)$		4.913	68.224	4.102	4.224
	p		0.039	<0.001	0.057	0.054
	partial-η^2		0.205	0.782	0.178	0.182
Short						
Long			**Settling Time**			
i	μ_{ASD}	10.6	15.3	17.7	19.3	20.3
	μ_{TD}	10.7	15.1	17.5	17.9	19.1
ii	$F(1,19)$	0.175	0.178	0.138	15.778	11.190
	p	0.681	0.678	0.714	0.001	0.003
	partial-η^2	0.009	0.009	0.007	0.454	0.371
iii	$F(1,19)$		1.283	0.012	22.790	1.434
	p		0.271	0.913	<0.001	0.246
	partial-η^2		0.063	0.001	0.545	0.070

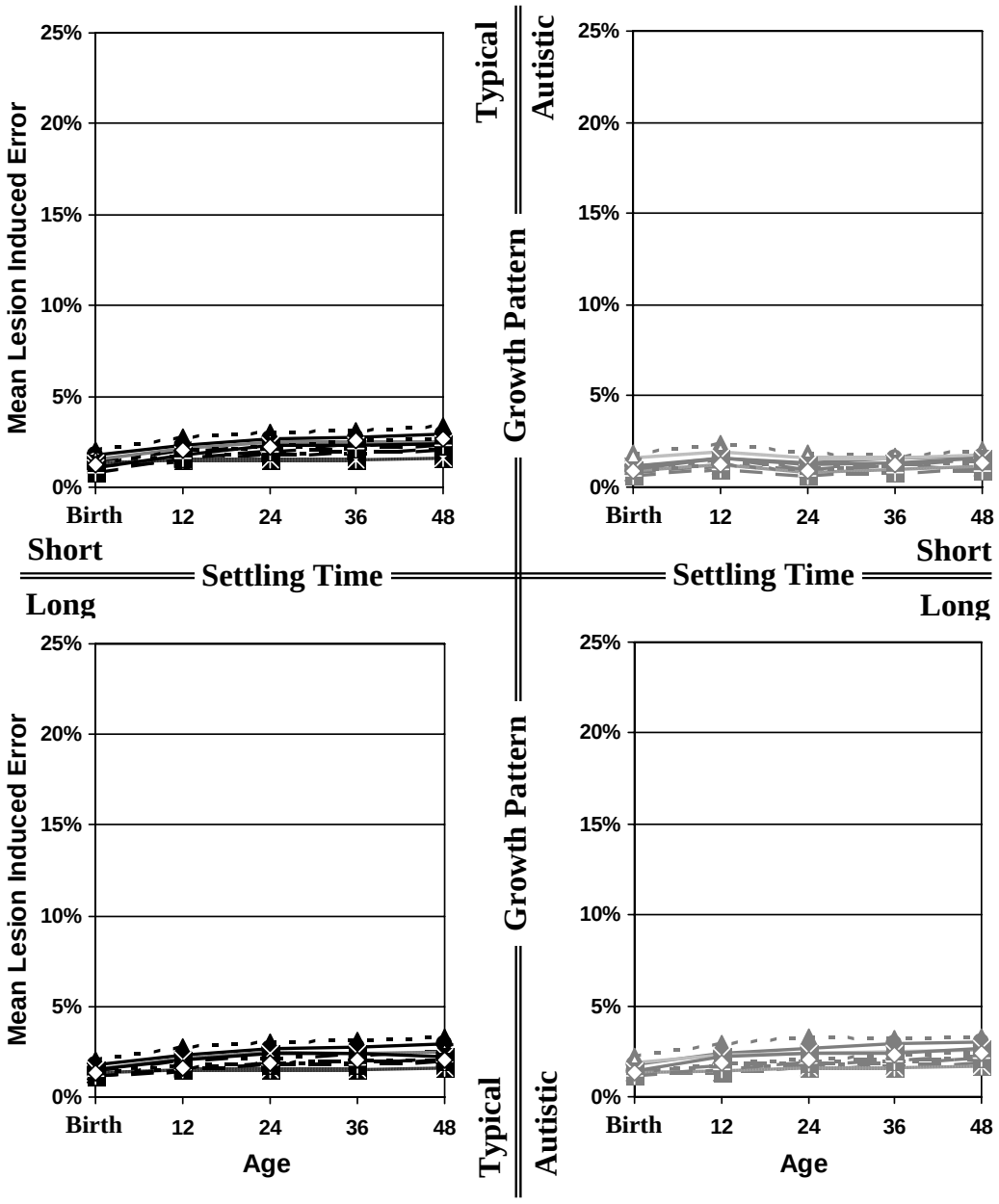

Figure IV-4. The impact of disconnecting the inter-hemispheric connections on the portion of the training set for which the inputs for either hemisphere uniquely specify the outputs for that hemisphere. The left and right columns show the impact on the networks following the growth pattern in typical development and in autism, respectively. The top and bottom rows show the outcome for short and long settling times, respectively. Each curve represents the mean lesion induced error for a single training set.

Table IV-4. The impact of removing the inter-hemispheric connections on the portion of the training sets comprised of examples that do not require inter-hemispheric communication. Three statistics are reported for both short and long settling times: (i) the estimated marginal means at each of the time points; (ii) the main effect of group at each time point; (iii) the interactions of group and age between successive pairs of time points. These statistics complement the results graphed in Figure IV-4.

		Birth	12	24	36	48
i	μ_{ASD}	1.0	1.5	1.1	1.2	1.4
	μ_{TD}	1.3	2.1	2.6	2.8	3.0
ii	$F(1,19)$	23.613	50.316	103.864	106.377	98.270
	p	<0.001	<0.001	<0.001	<0.001	<0.001
	partial-η^2	0.554	0.726	0.845	0.848	0.838
iii	$F(1,19)$	20.858	89.721	2.333	0.203	
	p	<0.001	<0.001	0.143	0.658	
	partial-η^2	0.523	0.825	0.109	0.011	
Short			**Settling Time**			
Long						
i	μ_{ASD}	1.5	2.0	2.1	2.2	2.3
	μ_{TD}	1.4	1.9	2.1	2.2	2.3
ii	$F(1,19)$	3.851	1.560	0.033	<0.001	0.049
	p	0.065	0.227	0.858	0.989	0.827
	partial-η^2	0.169	0.076	0.002	<0.001	0.003
iii	$F(1,19)$	0.027	3.269	0.397	0.407	
	p	0.872	0.087	0.536	0.532	
	partial-η^2	0.001	0.154	0.022	0.022	

than their typically developing instantiations at all measured time-points, but the difference was smaller at 'birth' than at '12 months', and much smaller at '12 months' than thereafter. This is reflected in the differences in the estimated marginal means (Table IV-3 and Table IV-4), and in the fact that there were significant interactions between group and age for these time points (Table IV-3 and Table IV-4). This reduction occurred both for the portion of the task which required inter-hemispheric communication, and for the portion that did not — the latter presumably due to reorganization caused by the former. And, as is evident from the estimated marginal means and the graphs of the mean lesion induced error for each training set (Figure IV-3 and Figure IV-4), the interaction between group and age between '12 months' and '24 months' indicates not just a decrease relative to the networks following the growth pattern in typical development, but an actual decrease in functional connectivity. A repeated measures ANOVA on the lesion impact measures from the networks grown at the rate of children with autism yielded a marginal main effect of age ($F(1,19)=3.264$, $p=0.087$, partial $\eta^2=0.147$) for the portion of the task that requires inter-hemispheric communication. But there was considerable variation in the timing of the reduction in functional connectivity. Adjusting for the latency of this reduction by taking, for each network, either the period from '12 months' to '24 months', or '24 months' to '36 months', whichever showed the greater decrease in functional connectivity, yielded a significant main effect of age ($F(1,19)=29.016$, $p<0.001$, partial $\eta^2=0.604$). For the portion of the task that does not require inter-hemispheric communication, a repeated measures ANOVA on the lesion impact measures from the networks grown at the rate of children with autism yielded a

significant main effect of age for this time period ($F(1,19)=30.331$, $p<0.001$, partial $\eta^2=0.615$). In both cases, however, there was substantial individual variation, with some networks showing a continual increase in functional connectivity, some showing a period of little change, and others showing substantial reductions. And, as is evident from the estimated marginal means for individual training sets (Figure IV-3 and Figure IV-4), some training sets also resulted in continual increases in functional connectivity, overall, some in a period of little change, and others in reductions.

The networks with long settling times grown at the rate of children with autism showed no such reduction in functional connectivity. Rather, these networks showed greater functional connectivity at the simulated equivalent of 36 and 48 months of age for the portion of the task that required inter-hemispheric communication (Table IV-3), though the effect was small. It is unclear why this occurred, but perhaps it indicates that the longer settling times allowed the networks to compensate for the increased conduction delay in the networks following the growth trajectory in autism — a difference which is maximal between 16 and 32 simulated months of age, and is thus diminished at 36 and 48 simulated months of age.

The performance of the networks grown at the rate of children with autism shows a similar pattern of development. On the portion of the task which required inter-hemispheric communication, averaging over individual variation, and different outcomes for different training sets, the networks with short settling times grown at the rate of children with autism showed a fall-off in performance — *i.e.*, an increase in cross-entropy error — at approximately the simulated equivalent of 24 months of age (Figure IV-5 and Table IV-5). These networks, overall, performed worse on that

portion of the task than their typically developing counterparts at all measured time-points, but the difference was smaller at ‘birth’ than at ‘12 months’, and much smaller at ‘12 months’ than thereafter. This is reflected in the differences in the estimated marginal means (Table IV-5), and in the fact that there was a significant interaction between group and age between ‘12 months’ and ‘24 months’ ($F(1,19)=181.463$, $p<0.001$, partial $\eta^2=0.905$). As indicated by the greater estimated marginal mean at ‘12 months’ than at ‘24 months’, this is a decline in performance paralleling the reduction in functional connectivity. Due to variation in the timing of the decline in performance, a main effect of age was not significant ($F(1,19)=2.073$, $p<0.166$, partial $\eta^2=0.098$). But adjusting for the latency of the decline by taking, for each network, either the period from ‘12 months’ to ‘24 months’, or ‘24 months’ to ‘36 months’, whichever showed the greater increase in performance error, yielded a significant main effect of age ($F(1,19)=43.515$, $p<0.001$, partial $\eta^2=0.696$).

As with functional connectivity, however, there was substantial individual variation, with some networks showing a continual increase in performance, some showing a period of little change, and others showing substantial declines in performance. And, as is evident from the estimated marginal means for individual training sets (Figure IV-5), some training sets also resulted in continual improvement in performance, overall, some in a period of little change, and others in overall declines in performance.

On the portion of the task which does not require inter-hemispheric communication (Figure IV-6 and Table IV-6), the networks with short settling times grown at the rate of children with autism showed significantly inferior performance at

‘12 months’ ($F(1,19)=36.465$, $p<0.001$, partial $\eta^2=0.657$) and at ‘24 months’ ($F(1,19)=54.152$, $p<0.001$, partial $\eta^2=0.740$) in comparison to the networks grown at the rate of typically developing children. But there was no actual decline in performance over time. Rather, following this initial inferior performance, the performance of the networks grown at the rate of children with autism improved rapidly, and by ‘48 months’, was comparable to the performance of the networks grown at the rate of typically developing children.

The networks with long settling times grown at the rate of children with autism showed no such fall-off in performance, neither for the portion of the task that required inter-hemispheric interaction (Figure IV-5 and Table IV-5), nor for the portion of the task that did not (Figure IV-6 and Table IV-6).

This pattern of development of functional connectivity, and of performance, is directly reflected in the patterns of development of physical connectivity as measured by relative inter-hemispheric connection weight (Figure IV-7 and Table IV-7). Averaging over individual variation, and different outcomes for different training sets, the networks with short settling times grown at the rate of children with autism showed a reduction in physical connectivity at approximately the simulated equivalent of 24 months of age. These networks, overall, had reduced relative inter-hemispheric connection weights at all measured time-points, but the difference increases substantially at ‘12 months’. This is reflected in the differences in the estimated marginal means (Table IV-7), and in the fact that there was a significant interaction between group and age between ‘12 months’ and ‘24 months’ (Table IV-7). And, as

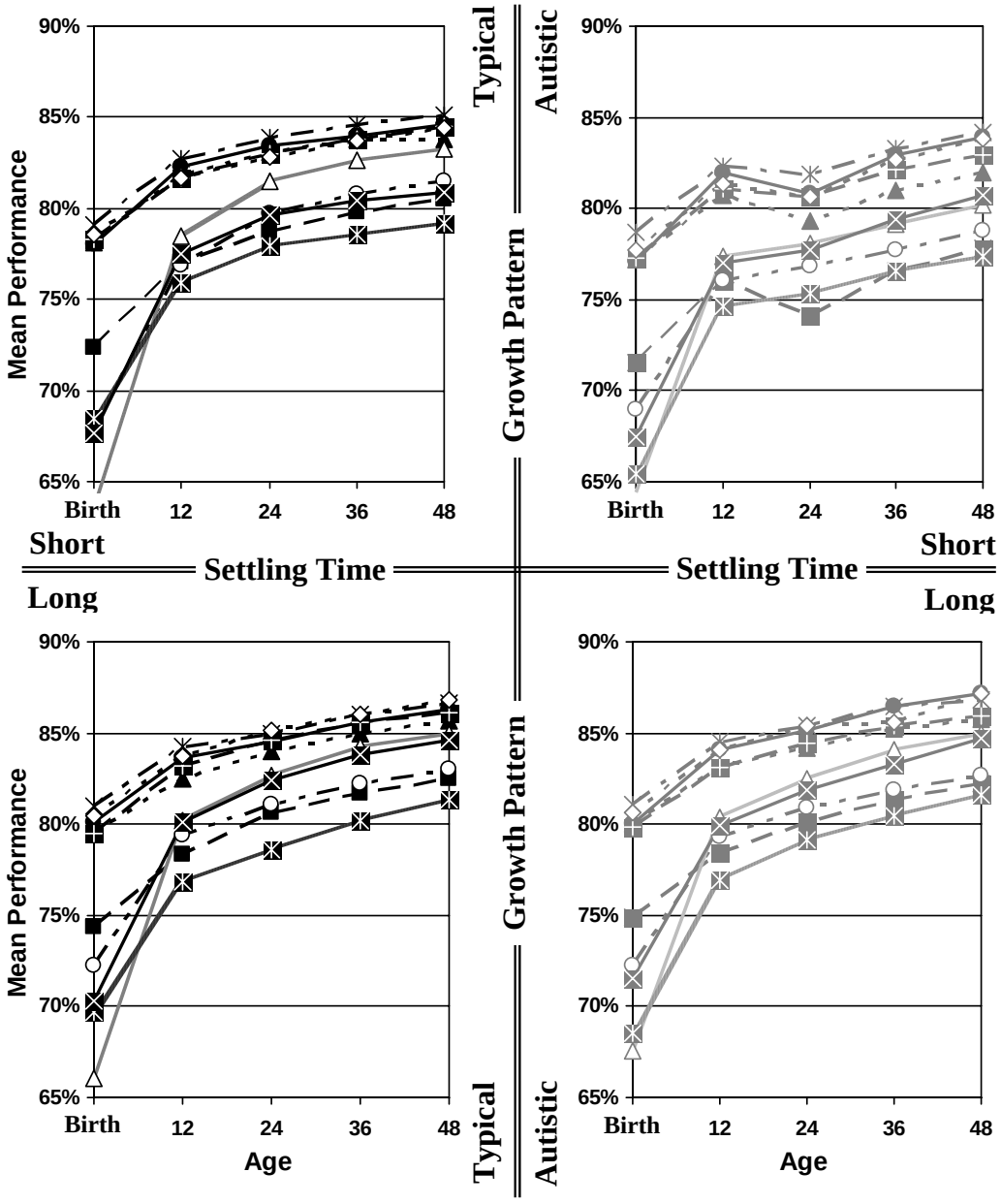

Figure IV-5. The impact of the different patterns of growth on performance on the portion of the task which required inter-hemispheric communication. The left and right columns show the values for the networks following the growth pattern in typical development and in autism, respectively. The top and bottom rows show the outcome for short and long settling times, respectively. Each curve represents the mean performance for a single training set.

Table IV-5. Performance on the portion of the task which required inter-hemispheric communication. Three statistics are reported for both short and long settling times: (i) the estimated marginal means of the performance error at each of the time points; (ii) the main effect of group at each time point; (iii) the interactions of group and age between successive pairs of time points. These statistics complement the results graphed in Figure IV-5.

		Birth	12	24	36	48
i	μ_{ASD}	72.6	78.8	78.5	80.1	81.2
	μ_{TD}	73.2	79.6	81.4	82.2	82.8
ii	$F(1,19)$	9.060	21.364	193.165	101.767	67.116
	p	0.007	<0.001	<0.001	<0.001	<0.001
	partial-η^2	0.323	0.529	0.910	0.843	0.779
iii	$F(1,19)$		0.556	181.463	18.721	35.910
	p		0.465	<0.001	<0.001	<0.001
	partial-η^2		0.028	0.905	0.496	0.654
Short Settling Time						
Long						
i	μ_{ASD}	75.6	81.4	82.9	84.1	84.9
	μ_{TD}	75.3	81.2	82.9	84.0	84.8
ii	$F(1,19)$	3.361	3.823	0.112	0.382	0.969
	p	0.082	0.065	0.741	0.544	0.337
	partial-η^2	0.150	0.168	0.006	0.020	0.049
iii	$F(1,19)$		0.373	7.277	0.286	0.881
	p		0.548	0.014	0.599	0.360
	partial-η^2		0.019	0.277	0.015	0.044

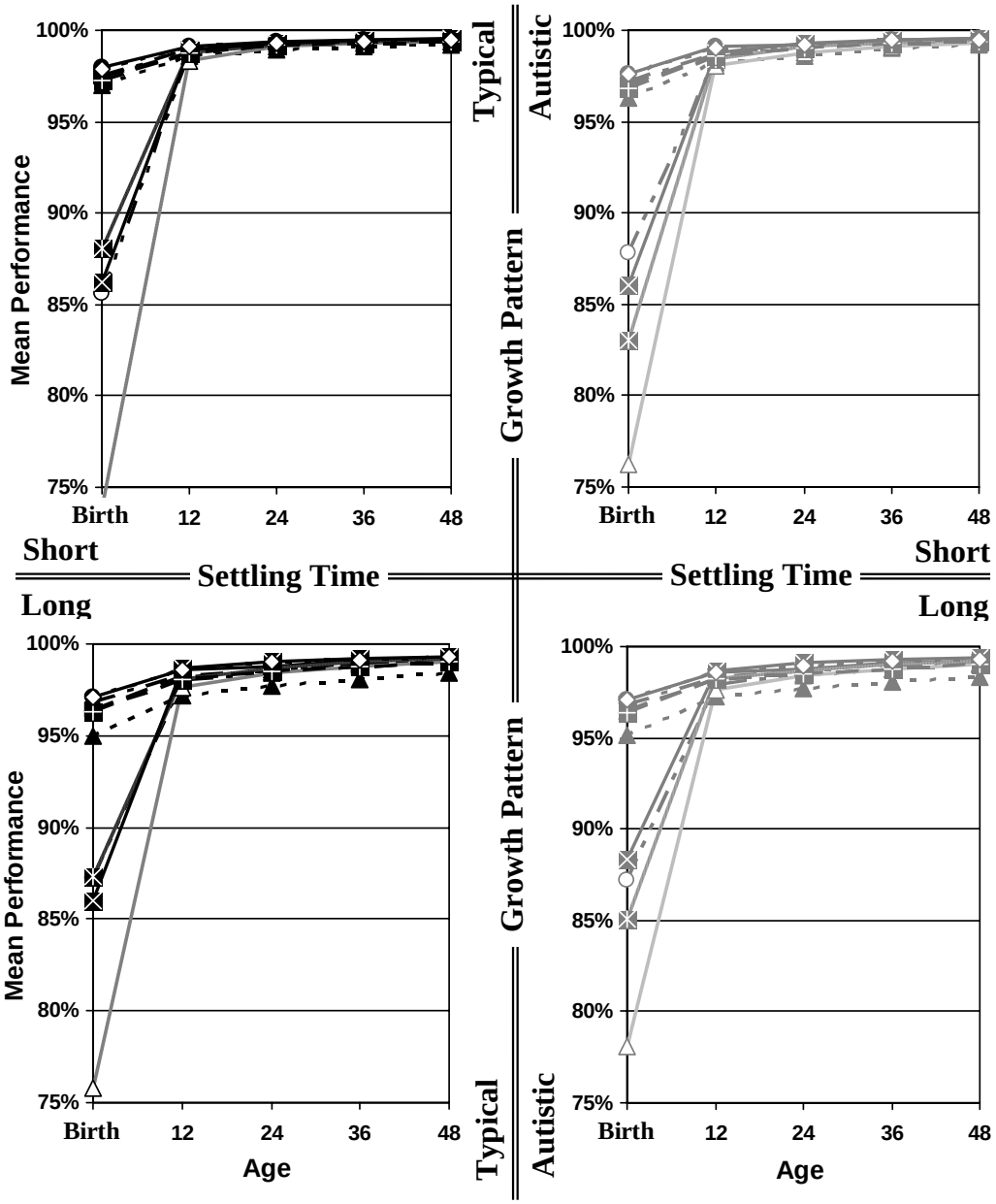

Figure IV-6. The impact of the different patterns of growth on performance on the portion of the training set comprised of examples for which the inputs for either hemisphere uniquely specify the outputs for that hemisphere. The left and right columns show the values for the networks following the growth pattern in typical development and in autism, respectively. The top and bottom rows show the outcome for short and long settling times, respectively. Each curve represents the mean performance for a single training set.

Table IV-6. Performance on the portion of the training sets comprised of examples that do not require inter-hemispheric communication. Three statistics are reported for both short and long settling times: (i) the estimated marginal means of the performance error at each of the time points; (ii) the main effect of group at each time point; (iii) the interactions of group and age between successive pairs of time points. These statistics complement the results graphed in Figure IV-6.

		Birth	12	24	36	48
i	μ_{ASD}	91.5	98.6	99.0	99.3	99.4
	μ_{TD}	91.9	98.8	99.2	99.4	99.4
ii	***F*(1,19)**	0.884	36.465	54.152	3.145	0.144
	p	0.359	<0.001	<0.001	0.092	0.709
	partial-η^2	0.044	0.657	0.740	0.142	0.007
iii	***F*(1,19)**	0.221	0.876	98.760	24.273	
	p	0.644	0.361	<0.001	<0.001	
	partial-η^2	0.011	0.044	0.839	0.561	
Short			**Settling Time**			
Long						
i	μ_{ASD}	91.8	98.2	98.6	98.9	99.1
	μ_{TD}	91.5	98.1	98.6	98.9	99.0
ii	***F*(1,19)**	1.208	2.477	0.121	0.963	0.289
	p	0.285	0.132	0.732	0.339	0.597
	partial-η^2	0.060	0.115	0.006	0.048	0.015
iii	***F*(1,19)**	1.027	8.124	5.595	2.519	
	p	0.324	0.010	0.029	0.129	
	partial-η^2	0.051	0.300	0.227	0.117	

with the pattern of development of functional connectivity, and of performance, the interaction between group and age between '12 months' and '24 months' indicates not just a decrease relative to the networks following the growth pattern in typical development, but an actual reduction in physical connectivity. A repeated measures ANOVA on the relative inter-hemispheric weight measures from the networks trained with short settling times and grown at the rate of children with autism yielded a significant main effect of age for this time period ($F(1,19)=68.470$, $p<0.001$, partial $\eta^2=0.783$).

As with functional connectivity, and performance, however, there was substantial individual variation, with some networks showing a continual increase in physical connectivity, some showing a period of little change, and others showing reductions. As is evident from the estimated marginal means for individual training sets (Figure IV-7), however, the input did not have the same sort of influence on physical connectivity that it did on performance and functional connectivity. This may indicate that there was reorganization in all cases, but that some training sets posed greater problems for this process than did others, and so the physical changes resulted in better functional recovery in some cases than in others.

The networks with long settling times grown at the rate of children with autism showed no such reduction in physical connectivity. Rather, similar to the pattern of development in functional connectivity, these networks showed a small increase in physical connectivity at 48 simulated months of age (Table IV-7). This increase in relative inter-hemispheric weight reflects only an increase in the inter-hemispheric

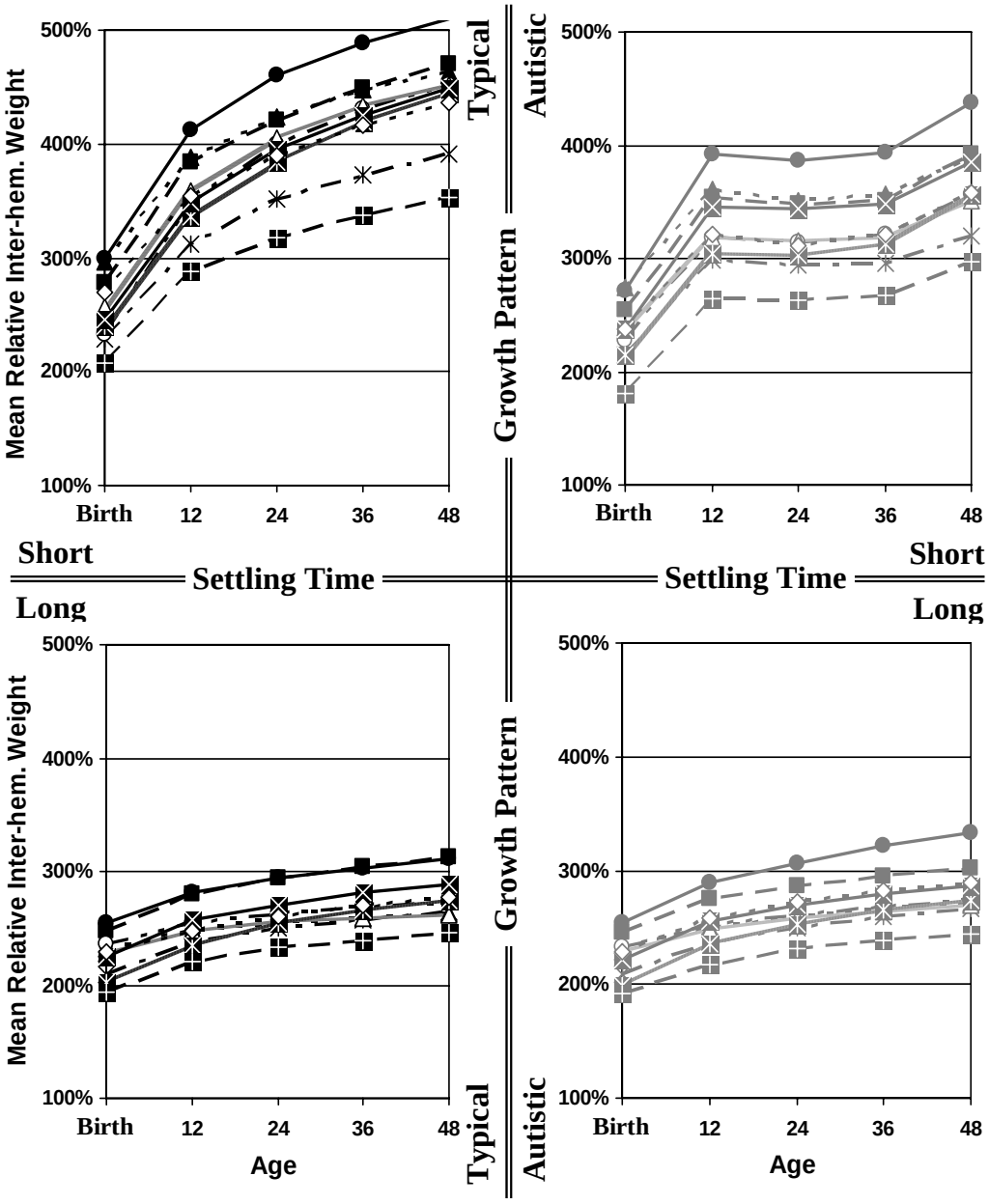

Figure IV-7. The mean inter-hemispheric connection weight as a percentage of the mean intra-hemispheric connection weight. The left and right columns show the values for the networks following the growth pattern in typical development and in autism, respectively. The top and bottom rows show the outcome for short and long settling times, respectively. Each curve represents the mean relative inter-hemispheric weight for a single training set.

Table IV-7. Relative inter-hemispheric connection weight. Three statistics are reported for both short and long settling times: (i) the estimated marginal means at each of the time points; (ii) the main effect of group at each time point; (iii) the interactions of group and age between successive pairs of time points. These statistics complement the results graphed in Figure IV-7.

		Birth	**12**	**24**	**36**	**48**
i	μ_{ASD}	235.2	327.8	323.2	328.5	364.2
	μ_{TD}	255.5	353.3	394.9	422.1	442.2
ii	***F*(1,19)**	91.287	40.725	203.527	272.155	182.560
	p	<0.001	<0.001	<0.001	<0.001	<0.001
	partial-η^2	0.828	0.682	0.915	0.935	0.906
iii	***F*(1,19)**		2.758	690.058	302.471	132.939
	p		0.133	<0.001	<0.001	<0.001
	partial-η^2		0.127	0.973	0.941	0.875
Short						
Long			**Settling Time**			
i	μ_{ASD}	224.8	252.1	265.0	274.2	281.2
	μ_{TD}	225.7	251.2	262.9	270.9	277.3
ii	***F*(1,19)**	0.624	0.635	2.118	3.748	4.388
	p	0.439	0.435	0.162	0.068	0.050
	partial-η^2	0.032	0.032	0.100	0.165	0.188
iii	***F*(1,19)**		3.539	2.653	4.447	1.544
	p		0.075	0.120	0.048	0.229
	partial-η^2		0.157	0.123	0.190	0.075

weights; the mean intra-hemispheric weights are virtually identical to the networks following the typical growth trajectory. Again, it is unclear why this occurred, but perhaps the longer settling times allowed the networks to compensate for the increased conduction delay in the networks following the growth trajectory in autism.

IV.E Discussion

Autism is a developmental disorder defined by impairments in reciprocal social interactions, impairments in verbal and nonverbal communication, and a restricted repertoire of activities and interests [American Psychiatric Association, 1994]. In addition to these core symptoms, however, there are usually deficits in multiple other areas, *e.g.*, imitation (Aldridge, Stone, Sweeney, & Bower, 2000; Charman et al., 1997; DeMyer et al., 1972; Hobson & Lee, 1999; V. Jones & Prior, 1985; Rogers, Bennetto, McEvoy, & Pennington, 1996; Royeurs, Van Oost, & Bothuyne, 1998; Sigman & Ungerer, 1984; Smith & Bryson, 1998; Stone, Lemanek, Fishel, Fernandez, & Altemeier, 1990; Stone, Ousley, & Littleford, 1997), motor coordination (Dawson, Osterling, Meltzoff, & Kuhl, 2000; Kanner, 1943; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998), perception of rapid auditory transitions (Oram Cardy, Flagg, Roberts, Brian, & Roberts, 2005), and of visual motion (Bertone, Mottron, Jelenic, & Faubert, 2003; Gepner & Mestre, 2002; Gepner, Mestre, Masson, & de Schonen, 1995; Milne et al., 2002; Spencer et al., 2000). There are also areas of strength, *e.g.*, discrimination and detection of simple perceptual patterns, and analysis of visuo-spatial details (Bonnel et al., 2003; Happé, 1999; Jolliffe & Baron-Cohen, 1997; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001; Plaisted, O'Riordan, &

Baron-Cohen, 1998; Shah & Frith, 1983). But autism is heterogeneous in its presentation — six of the twelve aspects of the three core symptoms suffice for a diagnosis of autism, so individuals present with different sets of behaviors. There is also substantial variation in terms of the subsets of non-core deficits that are present, and strengths that are present. And individuals show differing degrees of superiority in their strengths, and differing degrees of severity in both core and non-core deficits. Additionally, the onset of the disorder varies: some children exhibit a failure to progress appropriately and show gradual development of any aberrant behaviors, others appear to develop normally for one or two years and then show sudden losses in acquired behaviors and the appearance of aberrant behaviors (Bailey, Phillips, & Rutter, 1996; Filipek et al., 1999; Kolvin, 1971; Lainhart et al., 2002; Luyster et al., 2005; Short & Schopler, 1988; Siperstein & Volkmar, 2004).

Associated with this behavioral profile are findings of increased head and brain size (Aylward, Minshew, Field, Sparks, & Singh, 2002; Bailey et al., 1993; Bailey et al., 1998; Bauman & Kemper, 1985; Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Davidovitch, Patterson, & Gartside, 1996; Dementieva et al., 2005; Fombonne, Roge, Claverie, County, & Fremolle, 1999; Hazlett et al., 2005; Hultman, Sparen, & Cnattingius, 2002; Kemper & Bauman, 1998; Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000; Piven et al., 1995; Redcay & Courchesne, 2005; Sparks et al., 2002; Waiter et al., 2004; Woodhouse et al., 1996), and reduced large-scale functional connectivity (Castelli, Frith, Happe, & Frith, 2002; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; Koshino et al., 2005; Ring et al., 1999) and structural connectivity (Chung,

Dalton, Alexander, & Davidson, 2004; Egaas, Courchesne, & Saitoh, 1995; Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Manes et al., 1999; Piven, Bailey, Ranson, & Arndt, 1997; Vidal et al., 2006; Waiter et al., 2005).

The modeling results presented here suggest that the abnormal brain-growth trajectory in autism, via the influence of conduction delay, may provide an explanation for the findings of reduced large-scale functional and structural connectivity, and perhaps even for several aspects of the behavioral phenotype.

The decline in inter-hemispheric functional connectivity seen in the models with short settling times grown at the rate of children with autism provides almost directly for the findings of reduced large-scale functional connectivity in autism (Castelli, Frith, Happe, & Frith, 2002; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; Koshino et al., 2005; Ring et al., 1999). These reductions have been found in language tasks (Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006), visual motion processing tasks (Castelli, Frith, Happe, & Frith, 2002), and tasks involving working memory (Koshino et al., 2005). Language requires very rapid integration of prosodic and syntactic information in the acoustic signal, and possibly also the dynamic visual information in the face and in gesture. Working memory appears to rely on verbal rehearsal (Baddeley & Hitch, 1974). And motion processing utilizes delay circuits, which are inherently dependent on temporal precision. These temporal processing demands for language and motion processing tasks, make it reasonable to speak of

such networks as having short settling times. There are, however, no longitudinal data on functional connectivity in children with autism, or even cross-sectional data.

The decline in inter-hemispheric physical connectivity seen in the models with short settling times grown at the rate of children with autism, similarly, provides almost directly for the findings of reduced large-scale structural connectivity in autism (Chung, Dalton, Alexander, & Davidson, 2004; Egaas, Courchesne, & Saitoh, 1995; Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Manes et al., 1999; Piven, Bailey, Ranson, & Arndt, 1997; Vidal et al., 2006; Waiter et al., 2005). Cross-sectional and longitudinal data indicate that this is a reduction that occurs developmentally (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman., 2004), and is related to brain-size (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman., 2004). But the functionality of the networks involved, and their temporal demands, must be inferred from the correspondence with the findings of functional reductions.

The fall-off of functional and physical connectivity seen in some of the models with short settling times grown at the rate of children with autism indicates that the brain growth trajectory in autism may result in an initial near-normal commitment to representations involving long-distance connections, followed by substantial reorganization that abandons these large-scale networks in favor of functionally localized representations. This process of reorganization is plausibly extremely functionally disruptive, and as suggested by the increase in performance error seen in these models, might be expected to have negative behavioral consequences. The modeling results indicate that, via such a process of reorganization, the brain

overgrowth in autism may explain a number of aspects of the phenotype: the timing of the onset of the behavioral symptoms, the possibility of regression, the sorts of behaviors that are affected, and the heterogeneity.

Autism is generally reported to have a gradual onset with subtle signs presenting over the first year, and more obvious behavioral symptoms usually appearing late in the second year, or early in the third (Lord et al., 1989; Volkmar, Stier, & Cohen, 1985). But children later diagnosed with autism may, until around 18 to 30 months develop normally, or with subtle abnormalities, and then simply fail to progress, or may even regress — *i.e.*, lose skills that they had already acquired (Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Fombonne & Chakrabarti, 2001; Goldberg et al., 2003; Kurita, 1985; Lainhart et al., 2002; Lord, Shulman, & DiLavore, 2004; Luyster et al., 2005; Rapin & Katzman, 1998; Rogers, 2004; Rutter & Lord, 1987; Shinnar et al., 2001; Simons & Oishi, 1987; Wilson, Djukic, Shinnar, Dharmani, & Rapin, 2003). Both patterns of development thus show a decline in performance during the latter part of the second year, or early in the third. At all simulated ages, the networks with short settling times grown at the rate of children with autism showed a reduction in performance in comparison to their typically developing counterparts. This difference, however, became much greater between 12 and 24 simulated months of age, or in some cases, between 24 and 36 simulated months of age. The correspondence, in terms of the age at which performance is most affected, between the modeling results and the patterns of development in autism suggests that the brain overgrowth in autism may force reorganization, and thereby bring about the appearance of the behavioral symptoms.

In the models following the growth trajectory in autism, inter-hemispheric conduction delay is maximal between 16 and 32 months.

Regression occurs in twenty to fifty percent of children with autism, and is characterized by a significant loss of language and nonverbal communication skills (Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Goldberg et al., 2003; Kurita, 1985; Rapin & Katzman, 1998; Rutter & Lord, 1987; Tuchman, Rapin, & Shinnar, 1991). Many of these children show significant cognitive impairments, and many become nonverbal (Volkmar & Cohen, 1989; Wilson, Djukic, Shinnar, Dharmani, & Rapin, 2003). There is generally gradual abatement of behavioral abnormalities in autism (DeMyer et al., 1973; Gillberg, 1991; Kanner, 1943; Kobayashi, Murata, & Yoshinaga, 1992; Lotter, 1978; Wolf & Goldberg, 1986), but the prognosis seems to be at least partially determined by the severity of the early symptoms (Coplan & Jawad, 2005). Children with late onset autism with regression generally show limited recovery (Volkmar & Cohen, 1989; Wilson, Djukic, Shinnar, Dharmani, & Rapin, 2003). The modeling results suggest that cases of autism with regression may have the same etiology as cases of autism in which there is a failure to progress, or in which the onset is more gradual — *i.e.*, the reorganization driven by brain overgrowth. The reduction in performance at around 24 simulated months of age for the networks grown at the rate of children with autism was, in some cases, just a reduction relative to the typically developing networks; on average there was a slight decline in performance — perhaps akin to a failure to progress in autism; and in some cases, this decline was substantial. Some of the networks showed a fall-off in performance of almost 10% — or, in terms of performance above chance, a decline of almost 25%.

And this decline in performance would most likely be substantially larger if the networks followed the more extreme growth trajectory of some children with autism; and the impact on performance would most likely be larger still, if the training sets increased in complexity over time — more in keeping with, for example, the problem of language acquisition. With a more extreme growth trajectory and more complex input, the number of networks showing such declines would also probably increase. A lesser degree of recovery would probably be seen, as well, though realistic recovery results would probably, at a minimum, require the models to become less plastic over time, and to include pruning; the models used here have the same capacity to learn at all points in development, and permit weights to be reduced to zero, and then become non-zero again.

The characteristic loss of language and communication skills in cases of autism with regression may be in part due to the complexity of the input for those particular tasks, but the modeling results suggest that the rapid temporal demands of tasks such as these, and their reliance on inter-hemispheric connectivity, will make them particularly likely to be affected. As suggested by the far smaller impact on functional and physical connectivity, and on performance, for the models with long settling times, or for the portion of the task for which inter-hemispheric communication was not necessary, the consequences of the growth trajectory depend on the nature of the task. Networks should be expected to be negatively effected to the extent that those networks must rapidly integrate their inputs, to the extent that those networks comprise connections with substantially different conduction delays, and to the extent that the rapidity of the brain growth outpaces the ability of the

system to compensate for the changes. The failure of such networks may underlie many of the behavioral deficits in autism, either directly or indirectly — indirectly in that behaviors that rely developmentally on the functioning of affected circuits cannot be expected to develop normally. Some of the core behavioral symptoms of autism, as well as many of the other associated abnormalities, may simply reflect network disruptions caused by unequal changes in conduction delay as a result of rapid changes in brain size.

Language abilities, for example, rely on the rapid integration of syntactic and prosodic information in the acoustic signal, as well, as the information available in facial dynamics and gesture. These networks span the brain. And the long-distance interactions may be particularly important in language acquisition. Language acquisition appears to make substantially greater use of long-distance connections than does the adult system. Language acquisition, for instance, appears to rely on prosodic cues to a much greater extent than does adult language processing (Gerken, 1996; Hirsh-Pasek et al., 1987), and so on the interactions between the hemispheres. Studies of language processing show more bi-lateral activation in infants than in adults (Dehaene-Lambertz, 2000; Dehaene-Lambertz & Dehaene, 1994; Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Sachs & Gaillard, 2003). Moreover, disruptions in the networks responsible for processing any of the linguistic, and supra-linguistic, input — *e.g.*, the networks responsible for low-level auditory or visual processing, for integration of low-level information, or for processing at more abstract levels — may contribute to a language deficit.

The networks that underlie auditory speech perception extend from the cochlea to the brain stem to anterior and posterior regions of the temporal cortex (Belin, Zatorre, LaFaille, Ahad, & Pike, 2000; Binder et al., 2000; Wise et al., 2001), prefrontal areas (Fiez et al., 1995; Schubotz & von Cramon, 2001), the cerebellum (Hazeltine, Grafton, & Ivry, 1997; Ivry & Keele, 1989), and the basal ganglia (Meck & Benson, 2002; Rammsayer & Classen, 1997). The rapid temporal processing demands of speech (Benasich, Thomas, Choudhury, & Leppänen, 2002) place high demands on such a widely distributed system. Thus auditory speech perception should be expected to be impacted by the early brain overgrowth in autism. Results from EEG studies of auditory brain stem responses to acoustic stimuli indicate that there are increased conduction times from the cochlear nerve to the contralateral lateral lemniscus and inferior colliculus in individuals with autism (Maziade et al., 2000; Rosenhall, Nordin, Brantberg, & Gillberg, 2003; Wong & Wong, 1991); and delayed cortical responses to sinusoidal tones have been found in MEG studies (Gage, Siegel, & Roberts, 2003). The question of whether or not these abnormalities translate into deficits in acoustic speech perception in autism is largely unaddressed, but deficits in rapid temporal processing have been reported (Oram Cardy, Flagg, Roberts, Brian, & Roberts, 2005), and tone and phoneme changes have been found to evoke a delayed cortical response compared to normal controls (Kasai et al., 2005), with a significant positive relation between this latency delay and symptom severity. The ability to process brief acoustic transitions is critical for speech perception, and such impairments in this ability during development are likely to interfere with language acquisition. And deficits elsewhere may also interfere.

Visual and auditory integration is also likely important in early language acquisition. In typically developing children, and in adults, pairing visually presented speech — *i.e.*, an image sequence of a face that is mouthing words — with noisy auditory stimuli results in improved perceptual accuracy in comparison to performance on either modality alone (Calvert, Brammer, & Iversen, 1998; Massaro, 1998; Summerfield & McGrath, 1984). And visually presented speech has been found to activate both visual cortex and auditory cortex (Calvert et al., 1997; Calvert & Campbell, 2003; Campbell et al., 2001; MacSweeney et al., 2000; Pekkola et al., 2005; Santi, Servos, Vatikiotis-Bateson, Kuratate, & Munhall, 2003). But this integration relies on long-distance connections, and must occur rapidly, and so is likely to be impacted by the brain overgrowth in autism. Children with autism show the expected effect: they show a much smaller influence of visually presented speech on their performance in identifying noisy auditory stimuli (Massaro, 1987; Massaro & Bosseler, 2003). And visual speech processing may be particularly important for language acquisition in the context of impairments in speech-related auditory processing abilities.

The integration of visual and auditory information, moreover, involves the amygdala (E. G. Jones & Powell, 1970; Turner, Mishhkin, & Knapp, 1980; Webster, Ungerleider, & Bachevalier, 1991), which has been reported as a possible neural basis of the affect deficits in autism (Aylward et al., 1999; Baron-Cohen et al., 2000; Bauman & Kemper, 1985; Schumann et al., 2004).

The processing of visually presented speech also relies on visual motion processing, which should also be expected to negatively impacted by the early brain

overgrowth in autism. The visual system extends from the retina to the lateral geniculate nucleus to striate cortex, and then to higher level processing areas in occipital, parietal, and temporal cortex, and to frontal cortex and numerous subcortical areas (Van Essen & Gallant, 1994). Delay circuits are at the core of visual motion processing networks, and at multiple levels of processing, the precisely timed activation of pools of neurons is critical. These delay circuits calculate the difference in the timing of the activation of the receptive fields corresponding to two different spatial locations on the retina. Uneven alterations to the conduction delays of the axons that comprise such delay circuits will alter the motion that is detected and the delay with which the detector fires. So the pools of neurons that detect any given motion will be negatively affected in two ways. And the neurons that integrate the outputs of these delay circuits will be similarly vulnerable. The early brain overgrowth in autism should thus be expected to impact visual motion perception, and the effect should be greater for faster motion and complex patterns. Children with autism are reported to be less sensitive to visual full-field radiating flow fields than typically developing children (Gepner, Mestre, Masson, & de Schonen, 1995), and the deficit is reported to increase with speed (Gepner & Mestre, 2002). And children with autism are reported to have significantly higher motion coherence thresholds with global motion stimuli (Spencer et al., 2000), random dot kinematograms (Milne et al., 2002) and texture-defined motion stimuli (Bertone, Mottron, Jelenic, & Faubert, 2003) than typically developing children, but not for luminance-defined motion stimuli (Bertone, Mottron, Jelenic, & Faubert, 2003).

Visual motion processing is, moreover, required to process social cues such as dynamic emotional expressions, eye gaze shifts, and gesture. Children with autism are reported to perform significantly worse than typically developing children on tasks involving the processing of facial dynamics, such as emotional expressions and movements of the lips and eyes (Gepner, Deruelle, & Grynfeltt, 2001). And this performance difference is reported to be substantially reduced when the stimuli are displayed more slowly (Gepner, Deruelle, & Grynfeltt, 2001).

Deficits in motion processing should also be expected to impact an individual's ability to learn about, and respond to, the dynamic properties of the environment. Motor skills show the expected effect: in the first description of autism, Kanner (Kanner, 1943) described children with autism as "clumsy in gait and gross motor performances"; and subsequent research has established that motor deficits are, perhaps reliably, present in children with autism (Dawson, Osterling, Meltzoff, & Kuhl, 2000; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998).

And deficits in motion processing should also be expected to impair an individual's ability to perceive the actions of others. Autistic children are reported to be impaired in the perception of biological motion presented as point-light animations (Blake, Turner, Smoski, Pozdol, & Stone, 2003). This deficit might in turn be expected to lead to an impaired ability to learn motor behaviors which are modeled by others.

Additionally, the long-distance connections that link visual cortex with pre-motor cortex — the mirror neuron system (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996) — should be negatively

effected by the early brain overgrowth in autism. Neurons in premotor cortex that discharge when executing an action also discharge when observing that action (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996; Rizzolatti, Fogassi, & Gallese, 2001). The ability to carry out such internal simulation may play a critical role in the ability to understand other individuals' movements, and the ability to understand social interactions (Rizzolatti & Craighero, 2004; Williams, Whiten, & Singh, 2004). Thus imitation, and imitation learning, should be negatively effected in autism. Individuals with autism spectrum disorders have been reported to lack a *mu* rhythm response when observing another performing an action (Oberman et al., in press) — carrying the implication of a dysfunctional mirror neuron system. Imitation ability in autism is well researched, and support for a deficit in autism is unequivocal. Toddlers with autism have been found to have a deficit in meaningful and non-meaningful action imitation compared to typically developing toddlers (Charman et al., 1997; Stone, Ousley, & Littleford, 1997). Young children with autism show clear deficits on body and motor-object imitation tasks (DeMyer et al., 1972), on simple imitation tasks from the Motor Imitation Scale (Sigman & Ungerer, 1984), on motor imitation tasks (V. Jones & Prior, 1985), on imitative "pretend" actions and body movements (Stone, Lemanek, Fishel, Fernandez, & Altemeier, 1990), and on gestural (Aldridge, Stone, Sweeney, & Bower, 2000; Royeurs, Van Oost, & Bothuyne, 1998) and procedural imitation (Royeurs, Van Oost, & Bothuyne, 1998). And adolescents continue to show deficits in symbolic and non-symbolic imitation (Rogers, Bennetto, McEvoy, & Pennington, 1996; Smith & Bryson, 1998), pantomime tasks (Rogers, Bennetto, McEvoy, &

Pennington, 1996), and the imitation of the style in which an action is performed (Hobson & Lee, 1999).

Disruptions to networks such as these, which operate at a relatively low level, may also interfere with higher-level processing. And as suggested by the modeling results, the reorganization required for one task may have negative consequences for others. But this reorganization may also underlie some of the areas of strength seen in autism. Individuals with autism perform well on visual search tasks (O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001; Plaisted, O'Riordan, & Baron-Cohen, 1998), the block design and object assembly subtests of the Wechsler Intelligence Scale (Frith, 1989; Shah & Frith, 1983), the embedded figures task of the Wechsler intelligence test (Jolliffe & Baron-Cohen, 1997; Mitchell & Ropar, 2004; Shah & Frith, 1983), perceptual learning tasks (Plaisted, O'Riordan, & Baron-Cohen, 1998), and global precedence tasks (Plaisted, Swettenham, & Rees, 1999). Individuals with autism appear to employ a cognitive strategy for such tasks which relies more heavily on low-level processes implemented in relatively local circuits (Koshino et al., 2005; Ring et al., 1999). In the embedded figures task — a task requiring detection and discrimination of simple stimuli, and analysis and memory of perceptual detail — *f*MRI results show less extensive activation overall in individuals with autism compared to normal controls, no activation of prefrontal areas normally related to memory, and more activation in visual cortex (Ring et al., 1999). Visual cortex, in fact, appears to play a greater role than normal in satisfying the memory requirements of such tasks (Koshino et al., 2005). In an n-back task, individuals with autism were found to activate visual cortex to a greater extent than normal controls (Koshino et al.,

2005). And, measures of functional connectivity from *f*MRI indicate that this altered pattern of activation involves relatively small-scale networks (Castelli, Frith, Happe, & Frith, 2002; Just, Cherkassky, Keller, & Minshew, 2004; Koshino et al., 2005; Ring et al., 1999). For tasks in which high-level processing normally interferes with low-level processing — *e.g.*, the global precedence task, the embedded figures task, and the block design task — the reduced influence of high-level processing on low-level processing should logically result in superior performance. And in the block design task, for instance, children with autism show superior performance only when the designs are presented whole, but not when the designs are presented as segmented pieces (Shah & Frith, 1993). The Gestalt design appears to have less impact on children with autism than on typically developing children. This has been taken as support for the theory of weak central coherence (Shah & Frith, 1993); the hypothesis presented here can be seen, for these cases, as providing a mechanism which explains why children with autism exhibit weak central coherence.

This mechanism, and the modeling results presented above, also provide an explanation for the heterogeneity in autism. The developmental performance measures for the networks grown at the rate of children with autism showed considerable between-subject variability in both the degree to which their performance was reduced relative to the networks grown at the rate of typically developing children, and the time at which the greatest reduction occurred. There was also considerable variability between training sets. The individual variation suggests that the precise impact of the brain growth trajectory on functional connectivity, behavior, and physical connectivity, is likely to depend on potentially small differences in brain

structure. The variation for different training sets indicates that this relationship is also likely to be modulated by differences in the environment. And these sources of variability can affect the networks subserving different functions relatively independently. Thus the same growth trajectory can impact different subsets of behaviors differentially in different individuals. Additionally, variability in brain size prenatally, and early in postnatal development, should lead to differences in the degree of commitment to widely distributed networks, and therefore in the amount of functional disruption that later rapid brain growth would produce. Variability in the amount of brain development that occurs before the period of accelerated brain growth should have a similar impact, and will also interact with developmental changes in neuroplasticity. And more rapid brain growth is more likely to be disruptive, as are differences in maximum brain size achieved.

Core aspects of the behavioral phenotype in autism spectrum disorders, as well as many of the ostensibly peripheral aspects, may thus be related to the effect that abnormalities in the growth trajectory have on conduction delay and, in turn, functional and physical connectivity, and performance. The modeling results presented here take this beyond pure speculation; they provide an in principle demonstration. The different outcomes for the two growth patterns reflect differences solely in inter-hemispheric conduction delay. But these models, and the input-output pairs they were trained on, are obviously very far from reality. The results are thus simply suggestive with respect to autism; and the above speculations are merely an initial exploration of the aspects of autism that might, via this mechanism, be related to the early brain overgrowth. But the relations between the trajectory of brain growth

and functional connectivity, the behavioral phenotype, and physical connectivity, are almost unknown; and the empirical research that tests the hypothesis outlined here, for the most part, remains to be done.

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Chapter V

The Relation Between Connection Length and Degree of Connectivity in Autism: A DTI Analysis of the Impact of Early Brain Overgrowth on Connectivity

V.A Abstract

Children with autism are known to have enlarged brains during the first years of life. The increased conduction delays and cellular costs presumably associated with the longer long-distance connections of these larger brains have been hypothesized to lead to decreased long-distance connectivity. This prediction was tested by comparing the relation between connection length and degree of connectivity — the ratio of between-area connections to total cortico-cortical projection neurons in the areas connected — in young adult males with autism and in typical young adult males. The prediction was verified. Using diffusion tensor imaging and tractography to detail the patterns of inter-hemispheric connectivity in each of five divisions of the corpus callosum, and to determine the length of the connections, and histology-based formulae to estimate degree of connectivity from volumetric measures, we show that the relation between connection length and degree of connectivity in autism shows the typical negative relationship in all five sub-regions, but a reduced degree of connectivity in anterior regions — which is the locus of development during the period of maximal brain overgrowth, and where the interhemispheric connections have the smallest diameters, and so where differences in brain size will have the greatest impact on conduction delay.

V.B Introduction

Across species, and across individuals, long-distance connectivity — at least that between the two hemispheres, *i.e.*, the corpus callosum — does not scale with brain size (Lewis, Theilmann, Sereno, & Townsend, 2008; Rilling & Insel, 1999). This has been hypothesized to be due to the increased conduction delays and cellular costs associated with the longer long-distance connections of larger brains (Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994); and it has been suggested that this is a consequence of developmental mechanisms (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008). Conduction delay is primarily a function of axon diameter and length (Waxman, 1977), and for the vast majority of the inter-hemispheric connections, axon diameter does not scale sufficiently with brain size to compensate for the increased length (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Jerison, 1991; Olivares, Montiel, & Aboitiz, 2001; Schüz & Preissl, 1996); and the cellular costs for these longer connections will be greater, regardless (Karbowski, 2007). Mature patterns of cortical connectivity appear to be arrived at through prenatal exuberance followed by postnatal pruning (LaMantia & Rakic, 1990; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986), the latter of which is thought to be moderated by an activity dependent competition for neurotrophins (Barres & Raff, 1993; Callaway, Soha, & Van Essen, 1987; Lewin & Barde, 1996; Van Ooyen & Willshaw, 1999). Brain-size differences during development should impact this competition, and so the growth and retention of connections (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008). Supporting this

hypothesis are findings that show that the relative decrease in long-distance connectivity develops: In typical adult males there is a negative relation between connection length and degree of interhemispheric connectivity — the number of axons that interconnect areas in either hemisphere relative to the number of projection neurons in the areas connected (Lewis, Theilmann, Sereno, & Townsend, 2008); but this relationship is not present during late childhood in typically developing boys (Lewis, Theilmann, Travis, Onishi, & Townsend, 2008).

Children with autism spectrum disorder have abnormally large brains after about the second year of life (Aylward, Minshew, Field, Sparks, & Singh, 2002; Bailey et al., 1993; Bailey et al., 1998; Bauman & Kemper, 1985; Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; M. Davidovitch, Patterson, & Gartside, 1996; Dementieva et al., 2005; E. Fombonne, Roge, Claverie, County, & Fremolle, 1999; Hazlett et al., 2005; Kemper & Bauman, 1998; J.E. Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000; Piven et al., 1995; Sparks et al., 2002; Woodhouse et al., 1996), and for several years thereafter this size difference can be multiple standard deviations above the norm (Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Dementieva et al., 2005; Hazlett et al., 2005; Redcay & Courchesne, 2005; Sparks et al., 2002). The prediction of the developmental hypothesis outlined above is that this early brain overgrowth should lead to a lesser degree of long-distance connectivity (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008). Brain development, however, is not spatio-temporally homogenous (J.N. Giedd et al., 1999; Thompson et al., 2000), and so the impact of this early brain overgrowth should not be

expected to be uniform. A rostral-caudal wave of growth has been shown in the callosum in typically developing children (Thompson *et al.*, 2000), with peak growth concentrated in the anterior during early childhood. Additionally, average fiber diameter increases from the anterior to the posterior of the callosum (Aboitiz, Scheibel, Fisher, & Zaidel, 1992), so differences in connection length will have the greatest impact in the anterior. Thus, individuals with autism should show a lesser degree of long-distance connectivity between anterior regions of the brain. Using diffusion tensor imaging and tractography to detail the patterns of inter-hemispheric connectivity and to determine the length of the connections, and histology-based formulae to estimate degree of connectivity from volumetric measures, we contrast the results for young adult males with autism with those reported by Lewis *et al* (2008) in typical young adult males, and show that this prediction holds.

V.C Methods

V.C.1 Subjects

A total of 15 young adult males with autism ranging between 19 and 45 years of age (mean 32.25; stddev 9.98) participated in the study. All subjects met diagnostic criteria for autism spectrum disorder on the DSM-III-R or the DSM-IV. Based on early language delay, twelve of the fifteen subjects also met diagnostic criteria for autism spectrum disorder on the Autism Diagnostic Interview-R (ADI-R). The ADI-R was not available for the remaining three. Twelve subjects met criteria for autism and three for Asperger's. Individuals with a history of significant medical or neurological disorders including seizures or with Fragile X syndrome were excluded from the

sample. General intellectual ability was evaluated by the Wechsler Adult Intelligence Scale-Revised (WAIS-R) or the Wechsler Abbreviated Scale of Intelligence (WASI). Mean scores were: Verbal IQ, 88.00 ± 23.7 ; Non-verbal IQ, 101.58 ± 18.0. Those subjects who were capable gave informed consent; a parent gave informed consent for the others. The study was approved by the Human Research Protections Program at the University of California, San Diego.

V.C.2 Imaging

All subjects were scanned at the UCSD Center for fMRI on a GE Signa EXCITE 3.0T short bore scanner with an eight-channel array head coil. The scan protocols were identical to those used by Lewis *et al* (2008), *i.e.*, four types of images were acquired from each subject: (i) one set of 3D T_1-weighted images (Fast Gradient Echo, Spoiled Gradient Recalled; Echo Time [TE] = 3.1 ms; flip angle = 12°; Number of Excitations [NEX] = 1; Field Of View [FOV] = 25 cm; matrix = 256 x 256); (ii) two sets of T_2-weighted images (dual spin-echo, Echo Planar Imaging [EPI]; Time to Repetition [TR] = 15 s; TE = 89 ms; 45 axial slices; NEX = 2; FOV = 24 cm; matrix = 128 x 128; resolution = 1.875 x 1.875 x 3 mm; 3 mm interleaved contiguous slices); (iii) two sets of diffusion weighted images isotropically distributed along 15 directions (dual spin-echo, EPI; TR = 15 s; TE = 89 ms; 45 axial slices; NEX = 2; FOV = 24 cm; matrix = 128 x 128; resolution = 1.875 x 1.875 x 3 mm; 3 mm interleaved contiguous slices; b value = 1,400 s/mm^2); and (iv) fieldmaps matched to the diffusion-weighted images.

The T_2-weighted images were acquired together with the diffusion weighted images, both with a NEX of 2 — so each image was acquired four times. Fieldmaps were acquired before the first set of diffusion images, and after the second set. And, where within-scan motion made the use of a scan questionable, the scan was aborted and reinitiated.

V.C.3 Image Processing

The data were processed as per Lewis *et al* (2008). The steps are as follows. The T_1-weighted images were AC (anterior commissure) – PC (posterior commissure) aligned using AFNI, an open source environment for processing and displaying MRI data (Cox, 1996). The semi-automated procedure described in Lewis *et al* (2008) was then used to identify the boundary and divisions of the corpus callosum. That procedure uses an implementation of the active contour algorithm to locate a smoothed boundary at the center of the gradient at the edge of the callosum. The divisions of the callosum are then determined using the method described by Clarke *et al.* (1989), *i.e.*, the midline of the callosum is located and divided into five equal length segments, and the shortest length lines that cut the callosum at these dividing points are determined; these are the regional boundaries. Figure V-1 shows the subregions of the callosum arrived at via this procedure.

The two sets of diffusion-weighted images were corrected for distortions caused by inhomogeneities in the magnetic field, using the corresponding fieldmaps, as well as for within-scan motion. This was done using software developed by the

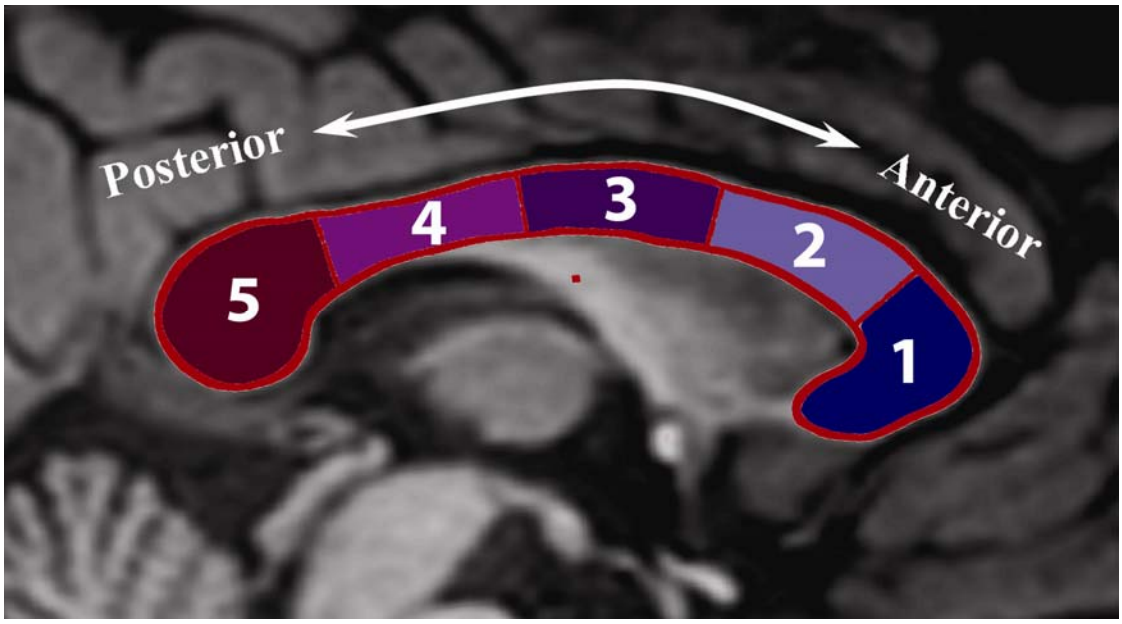

Figure V-1. The divisions of the corpus callosum.

UCSD Center for fMRI. Between-scan motion was corrected for by converting the resultant volumes to diffusion-tensor volumes, and coregistering them using non-linear tensor-to-tensor registration (Park et al., 2003). This was done using the 3D Slicer DTMRI module (an Open Source development project begun at the Massachusetts Institute of Technology Artificial Intelligence Laboratory and the Surgical Planning Laboratory at Brigham and Women's Hospital). The resultant tensor volumes were then averaged.

The non-linear transformation used to align the two diffusion-tensor volumes was also used to align the associated T_2-weighted volumes. These T_2-weighted volumes were then averaged, and the T_1- and T_2-weighted volumes were processed with *freesurfer* (BioMedical Imaging, Charleston, Mass., and Cortech Labs, La Jolla,

Calif.) to obtain a segmentation and the cortical gray-matter measures used in the analyses. The segmentation provided the basis for the creation of a seed region for fiber-tract generation. The seed region comprised the white-matter voxels adjacent to the cortex.

The average diffusion-tensor volume was then coregistered with the T_1-weighted volume, and tracts were generated from all voxels in the seed region. The coregistration was accomplished by generating a fractional anisotropy volume from the tensors, coregistering the fractional anisotropy volume to the T_1-weighted volume, and applying that transform to the tensor volume. Tractography was done using a modified version of *3D Slicer*, which allowed tracts to be terminated at the mid-sagittal point of the corpus callosum, and to be filtered out if they terminated elsewhere. Tracts were further constrained by a radius of curvature limit of 1mm, and a fractional anisotropy threshold of 0.15. The surviving tracts were then grouped by sub-region using the volume in which the sub-regions of the callosum had been labeled. Figure V-2 shows the set of fiber tracts produced by this method. The tracts are colored in five shades ranging from blue in sub-region 1 to red in sub-region 5.

As discussed in Lewis *et al* (2008), temporal cortex poses particular difficulties for tractography, and so, as in Lewis *et al* (2008), it is excluded from the analysis. Callosal fibers that originate or terminate in temporal cortex must cross through thalamo-cortical connections, and those that project to or from anterior regions, must intermingle with non-callosal fibers in the inferior longitudinal fasciculus. Both situations may lead to a failure of tractography: the early termination,

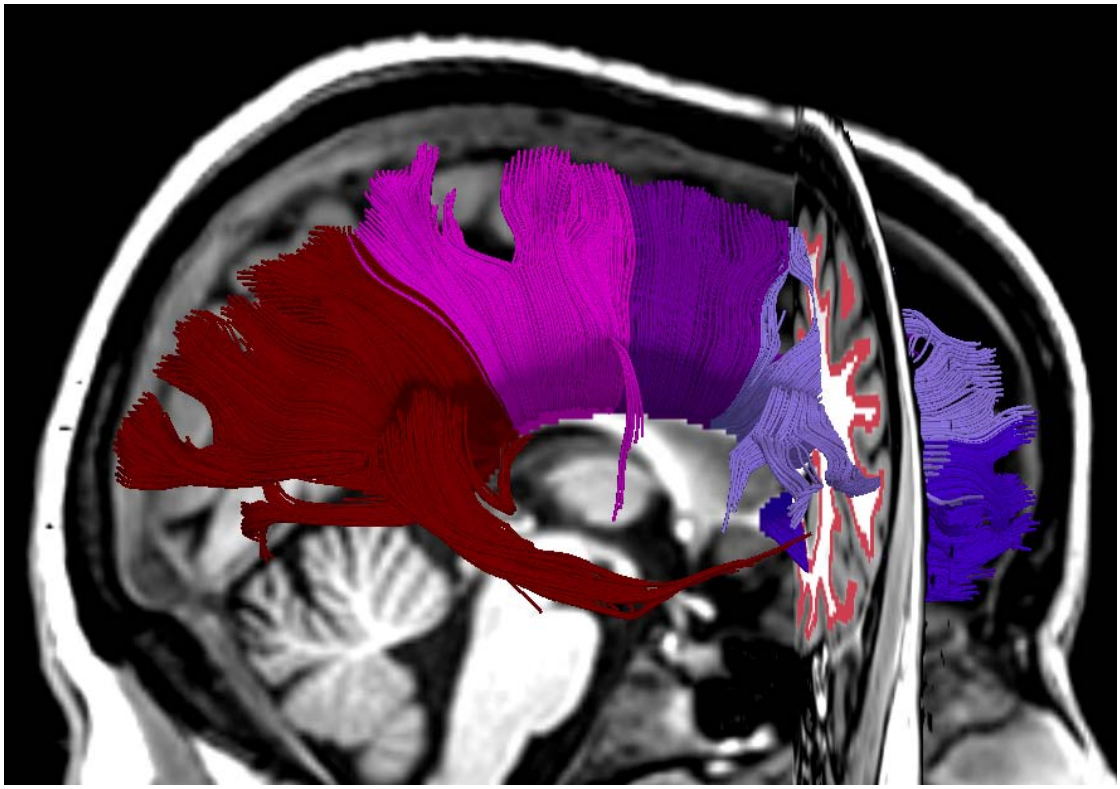

Figure V-2. The set of tracts that pass through the five sub-regions of the corpus callosum. The seed region for the tracts is visible in the coronal plane.

and so loss, of tracts, in the case of crossing fibers; false tracts, where callosal and non-callosal fibers intermingle. The tracts that originate in temporal cortex pass exclusively through the splenium, and so the exclusion of temporal cortex from the analysis requires an adjustment to only sub-region 5 of the callosum; the analyses takes that part of sub-region 5 to which tracts project that originate outside of the temporal lobe.

In order to estimate the degree of connectivity for each sub-region of the callosum, the cortex was divided into areas corresponding to the callosal sub-regions. The *freesurfer* cortical labels resulting from the automatic parcellation were assigned

to callosal sub-regions with weights that reflected their contribution. Their contribution to a given sub-region was defined in terms of the fraction of inter-hemispheric connections that originated in the labeled area, and the fraction of such connections that passed through the sub-region. The cortical divisions were taken from Lewis *et al* (2008), and are depicted in Figure V-3 — with colors corresponding to those in Figure V-2 — and detailed in Table V-2.

V.C.4 Data Analysis

The data were analyzed exactly as in Lewis *et al* (2008). The degree of connectivity was calculated as the ratio of an estimate of the number of interhemispheric connections in each sub-region of the callosum to an estimate of total cortico-cortical projection neurons in the cortical areas connected by the sub-region. Connection length was estimated as the average length of the longest fibers passing through each sub-region.

The estimate of the number of fibers passing through each region of the callosum is based on the work of Tomasch (1954) showing that the callosum consists of approximately 190 million fibers, and studies of axon diameter in the corpus callosum showing that, except for the largest approximately 0.1% of the fibers, the distribution of fibers does not vary with brain size (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Jerison, 1991; Olivares, Montiel, & Aboitiz, 2001; Schüz & Preissl, 1996). Thus, the number of interhemispheric connections in each region can be estimated to be approximately 190 million times the ratio of the area of that region

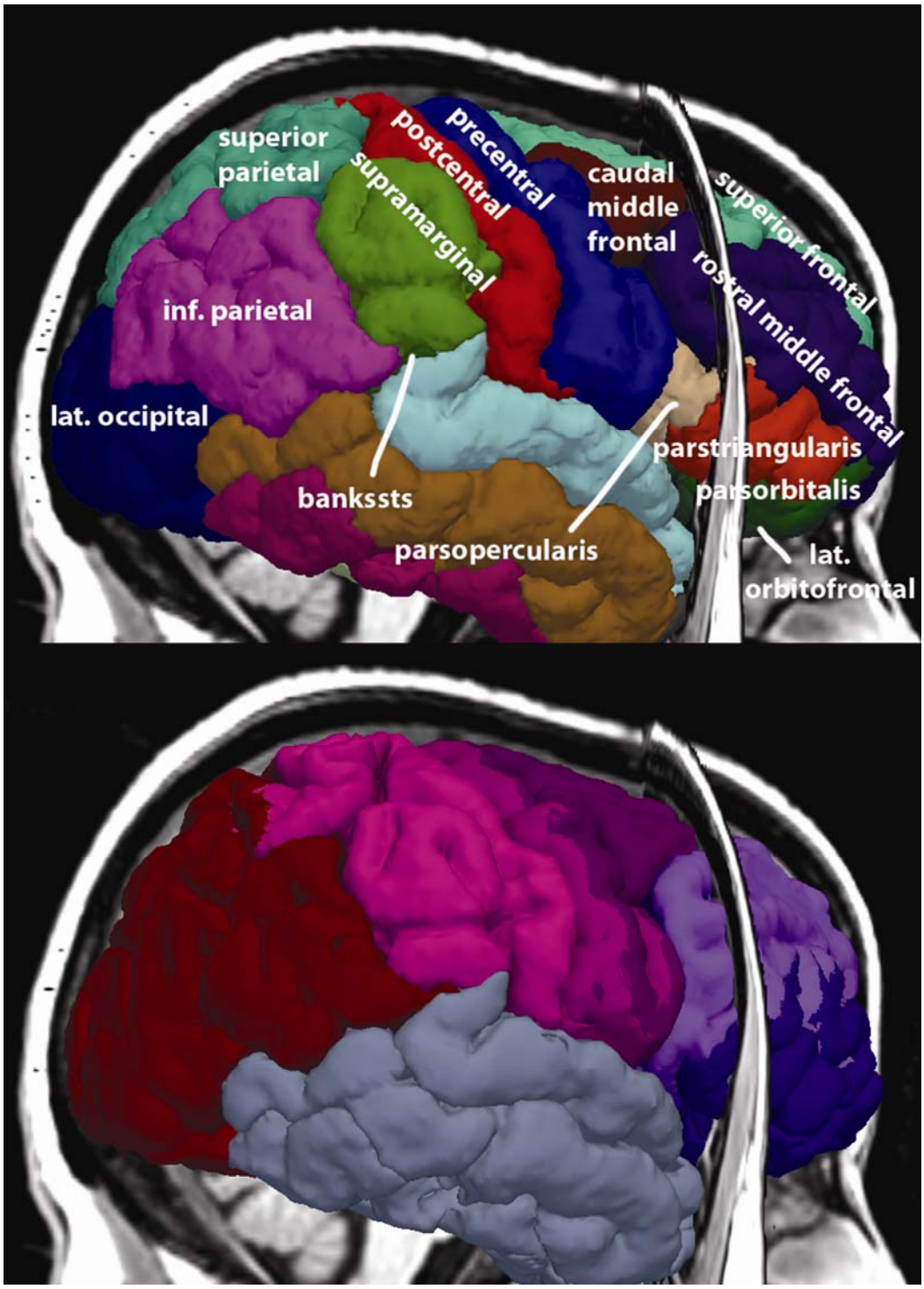

Figure V-3. The cortical divisions corresponding to the five regions of the corpus callosum. The cortical parcellation provided by *freesurfer* is shown in the top figure; the assignment of these labels to cortical regions is illustrated in the bottom figure — with colors corresponding to those in Figure V-2.

Table V-1. The cortical divisions. Cortical labels that were assigned to more than one callosal region are shown centered between those regions; the surface area and volume associated with the cortical label were divided equally between the associated callosal regions. A fraction prefixed to a cortical label indicates that only that much of the surface area and volume will be used**.**

CC1	CC2	CC3	CC4	CC5
frontal pole			¾ postcentral	cuneus
½ lat. orbitofrontal		paracentral		lingual
¼ parstriangularis	caudal middle frontal		precuneus	
¼ parsorbitalis	¾ precentral		superior parietal	
¼ parsopercularis			½ inf. parietal	
rostral middle frontal			¼ supramarginal	½ lat. occipital
superior frontal				¼ bankssts
				pericalcarine

to the typical average total area of the callosum. The typical average total area of the callosum was the across-subject average in the data of Lewis *et al* (2008). The callosum continues to grow during this period (Pujol, Vendrell, Junqué, Martí-Vilalta, & Capdevila, 1993), so the area measures of each sub-region were adjusted for age effects, and the adjusted measures were used in the estimate of the number of axons that pass through that sub-region.

The estimate of the number of projections neurons in each area of cortex was based on the histological work of Pakkenberg and Gundersen (1997) and van Kooten *et al* (2008). Sampling from the brains of 62 males between 19 and 87 years of age and 32 females between 18 and 93 years of age, Pakkenberg and Gundersen (1997) derived a formula by which neocortical neuron number can be predicted with a 95% tolerance limit of ±24% based on gender, age, gray matter volume, and cortical surface area. The formula is as follows:

$$N_{neurons} = 10^9 * \exp[-3.406\ (+\ 0.031 \text{ if male}) + (0.00018 * \text{age}) + (0.579 * \ln[Vol_{cortex}]) + (0.379 * \ln[Surf_{cortex}])].$$

The results from van Kooten *et al* (2008), comparing individuals with autism to controls, show no significant differences in neuron density or total neuron number. Thus, as in Lewis *et al* (2008), this formula was used to estimate the number of projection neurons associated with each of the divisions of cortex, as defined above, assuming that projection neurons scale with the total number of neurons. The measures of cortical gray-matter volume and cortical surface area for each cortical area were provided by *freesurfer*.

The length of the interhemispheric connections passing through each sub-region of the callosum was estimated from the tracts terminating in that sub-region. The measure of length was an average of the lengths associated with each voxel of that sub-region on the midsagittal slice; the length associated with each voxel was calculated as the average of the longest 10% of the tracts terminating at that voxel.

V.D Results

Regressing the degree of connectivity for subregion *i* of the callosum against the average length of the connections passing through subregion *i* yielded relationships similar to those reported for typical adult males (Lewis, Theilmann, Sereno, & Townsend, 2008). The slopes of the regressions did not significantly differ from those reported for typical adult males, in any subregion (Lewis, Theilmann, Sereno, & Townsend, 2008). In the two anterior-most subregions, however, degree of connectivity was significantly reduced. The group differences from an ANOVA with connection length as a covariate were significant at ($F(1,34) = 4.578$, $p < 0.040$) and ($F(1,34) = 6.526$, $p < 0.015$) for subregions 1 and 2, respectively. The midbody — subregion 3 — showed a marginal reduction. These results are shown in Figure V-4 and Figure V-5. The significance and r^2 values for the regressions are given in Table V-2.

V.E Discussion

The results here show that individuals with autism exhibit the typical negative relation between connection length and degree of connectivity in the callosum, but a reduced degree of connectivity in anterior subregions. Both of these things suggest the normal influence of brain size on the organization of white-matter — *i.e.*, the influence hypothesized to underlie the development of this negative relation in typically developing children (Lewis, Theilmann, Travis, Onishi, & Townsend, 2008). That regressing degree of connectivity on connection length yields relations with similar slopes to those in typical adult males indicates that differences in connection

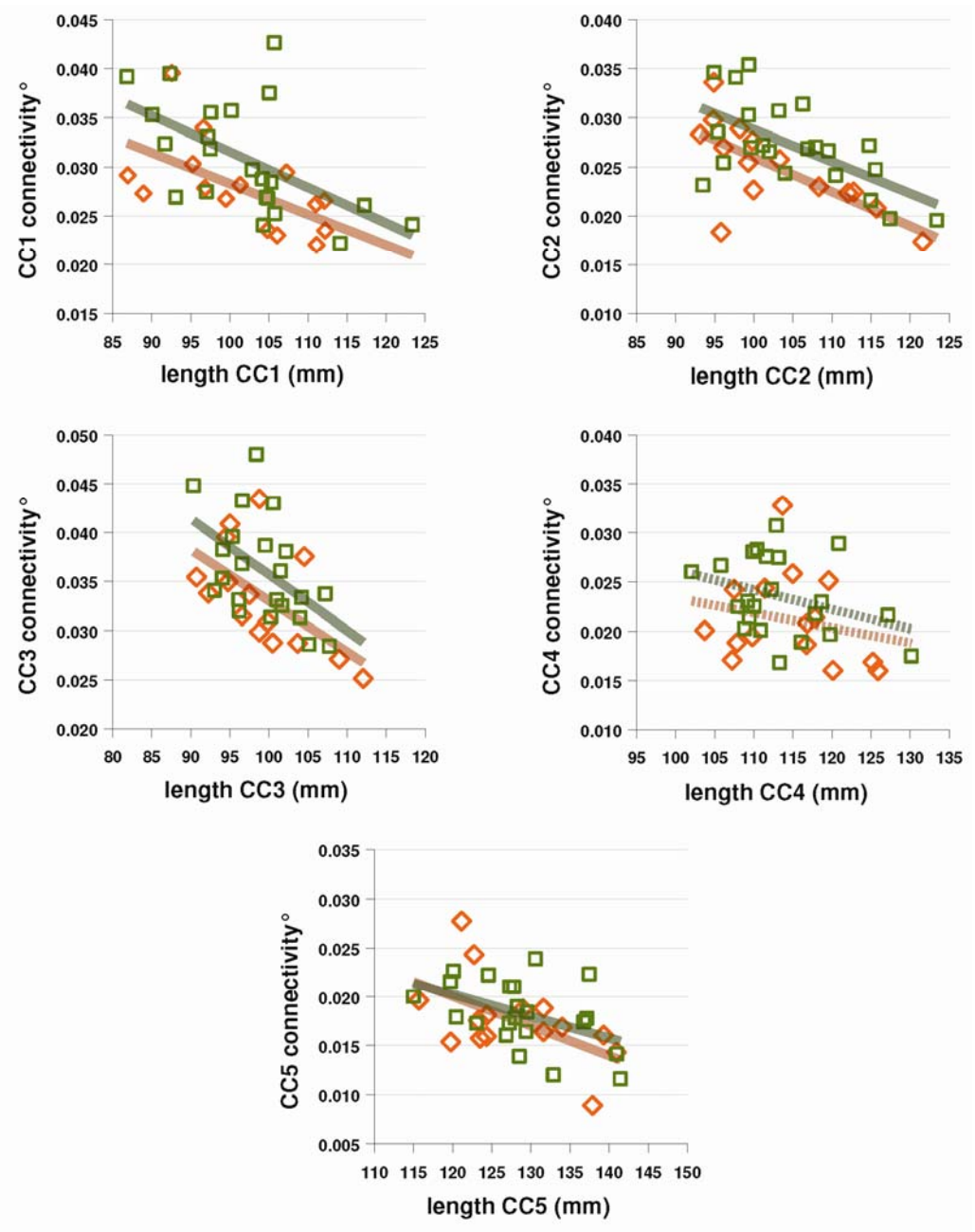

Figure V-4. The relation between degree of connectivity for subregion *i* of the callosum — indicated as CC_i *connectivity*° — and the average length of the connections passing through subregion *i*, for individuals with autism and for controls. Data points for individuals with autism are indicated with orange diamonds; data points for controls are indicated with green squares. Significant regressions are indicated with solid lines; the dashed lines in subregion 4 indicate that the regressions were non-significant. The significance and r^2 values for the regressions are presented in Table V-2.

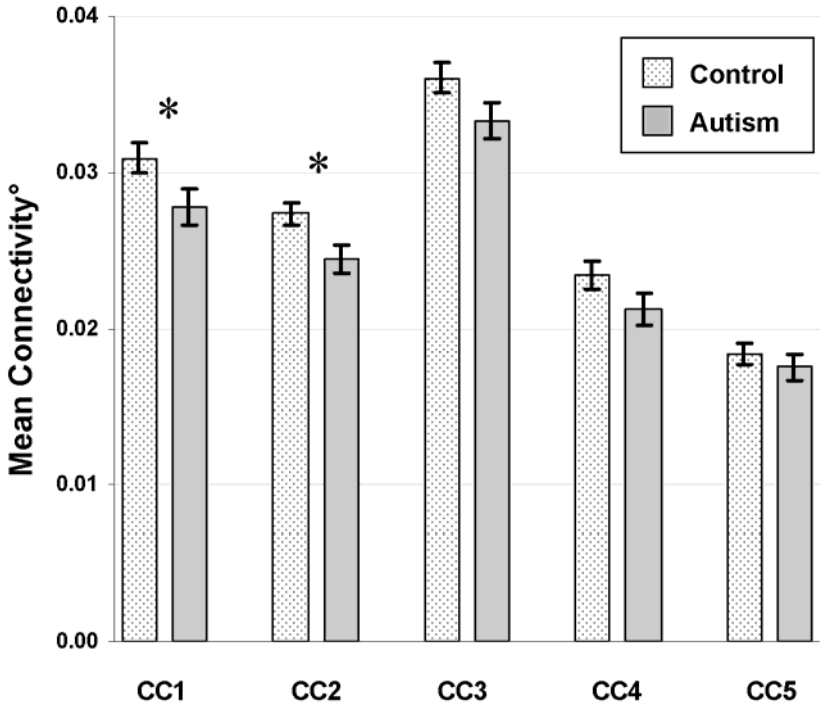

Figure V-5. The group differences for individuals with autism and controls. The differences are significant in subregions 1 and 2 with significance values of 0.040 and 0.015, respectively. The difference is marginal in subregion 3 with a significance value of 0.079.

Table V-2. The significance and r^2 values for regressions of the degree of connectivity for sub-region *i* against the average length of the connections in sub-region *i*. These values correspond to the regression plots in Figure V-4..

	CC_1		CC_2		CC_3		CC_4		CC_5	
	Sig.	**r^2**	**Sig.**	**r^2**	**Sig.**	**r^2**	Sig.	r^2	**Sig.**	**r^2**
autism	**.020**	**.351**	**.004**	**.479**	**.022**	**.342**	.435	.048	**.039**	**.289**
control	**.008**	**.299**	**.002**	**.391**	**.015**	**.263**	.125	.113	**.038**	**.198**

length across individuals with autism influence the growth and retention of connections to approximately the same extent as in typically developing individuals. And, that it is the anterior of the callosum that shows a significantly reduced degree of connectivity fits with the pattern of development of the callosum, and with the hypothesized influence of the longer long-distance connections associated with the early brain overgrowth on the growth and retention of these connections (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008; Lewis, Elman, & Courchesne, 2005).

Developmental changes are most rapid in the anterior of the callosum during early childhood (Thompson *et al.*, 2000), and this is the period of maximal brain overgrowth in autism (Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Dementieva et al., 2005; Hazlett et al., 2005; Redcay & Courchesne, 2005; Sparks et al., 2002; Thompson et al., 2000), as well as the region of the callosum with the smallest diameter fibers (Aboitiz, Scheibel, Fisher, & Zaidel, 1992), and so the region in which differences in connection length will have the greatest impact on conduction delay. The results thus suggests that findings of reduced large-scale functional and anatomical connectivity in individuals with autism spectrum disorder (Castelli, Frith, Happe, & Frith, 2002; Egaas, Courchesne, & Saitoh, 1995; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; H. Koshino et al., 2005; Manes et al., 1999; Murias, Webb, Greenson, & Dawson, 2007; Piven, Bailey, Ranson, & Arndt, 1997; Ring et al., 1999; Vidal et al., 2006; Waiter et al., 2005) may, in fact, be attributable to the early brain overgrowth.

That the reductions in degree of connectivity are most pronounced in frontal subregions fits also with findings of increased cortical folding in frontal regions in autism (Hardan, Jou, Keshavan, Varma, & Minshew, 2004; Nordahl et al., 2007). Across species, and across at least human individuals, brain size is positively correlated with gyrification (Im et al., 2008; Toro et al., 2008). Van Essen (1997) has proposed that this is a result of the mechanical tension of cortical connections. According to that theory, decreased long-distance connectivity should correlate with increased cortical folding. Thus the reduced degree of connectivity found here in anterior regions in individuals with autism fits with the findings of increased cortical folding in frontal regions (Hardan, Jou, Keshavan, Varma, & Minshew, 2004; Nordahl et al., 2007).

That the reductions are most pronounced in frontal regions, and that this is a result of the brain overgrowth, also fits with the finding that white-matter volume is particularly enlarged in the outer radiate portion of the frontal lobes in autism during late childhood (Herbert et al., 2004). This reflects an increase in short-distance connectivity — *i.e.*, the U-fibers — and suggests that the increased frontal volume observed in younger children with autism (Carper & Courchesne, 2005) is sustained throughout childhood, resulting in a decrease in long-distance connectivity and an increase in short-distance connectivity.

The reductions in degree of connectivity, however, are presumably not limited to the interhemispheric connections between the frontal lobes, but rather include long-distance connections that have cell bodies or terminal buttons in the frontal lobe. The factors which make for the more rapid changes in frontal cortex during early

development (Thompson *et al.*, 2000) act via neurotrophins supplied to the terminal buttons (Cao et al., 2007; Lewin & Barde, 1996; Van Ooyen & Willshaw, 1999). Assuming that the increased size of frontal cortex translates into longer connections for those that traverse it to more posterior regions, as well as those that form the callosum, the hypothesized relation between connection length and degree of connectivity should apply to the former as well as the latter. These connections are more difficult to measure, and the relation between connection length and degree of connectivity remains to be directly assessed; but there is evidence of reduced connectivity between frontal and parietal, occipital, and temporal lobes in individuals with autism. Individuals with autism show significantly fewer large positive correlations in regional cerebral metabolic rates for glucose between frontal and parietal regions (Horwitz, Rumsey, Grady, & Rapoport, 1988). Functional connectivity — *i.e.*, the degree of synchronization — between the frontal and parietal areas of activation is lower for autistic than for control participants, during an executive function task, and the size of the genu of the corpus callosum is correlated with frontal–parietal functional connectivity (Just, Cherkassky, Keller, Kana, & Minshew, 2007). And functional connectivity is also lower for autistic than for control participants between Broca's area in the frontal lobe and Wernicke's area in the superior temporal gyrus, during sentence comprehension (Just, Cherkassky, Keller, & Minshew, 2004). Also, there is evidence that the mirror-neuron system (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996) — which spans from

visual cortex to the inferior frontal gyrus — is dysfunctional in autism (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006; Oberman et al., in press).

Previous research is in general agreement that there is reduced long-distance anatomical connectivity in autism (Alexander et al., 2007; Boger-Megiddo et al., 2006; Castelli, Frith, Happe, & Frith, 2002; Egaas, Courchesne, & Saitoh, 1995; Hardan, Minshew, & Keshavan, 2000; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; Kilian et al., 2008; H. Koshino et al., 2005; Manes et al., 1999; Piven, Bailey, Ranson, & Arndt, 1997; Ring et al., 1999; Vidal et al., 2006; Waiter et al., 2005), but not that the reduction is predominantly frontal. Some studies have reported reductions in the anterior of the callosum (Hardan, Minshew, & Keshavan, 2000; Manes et al., 1999; Vidal et al., 2006), but others have reported reductions more broadly (Alexander *et al.*, 2007; Boger-Megiddo *et al.*, 2006; Vidal *et al.*, 2006), or specifically in more posterior regions (Egaas, Courchesne, & Saitoh, 1995; Piven, Bailey, Ranson, & Arndt, 1997; Waiter et al., 2005). These discrepancies, we suggest, are attributable to differences in the subject populations, and to the ways in which differences between the autism and control groups are controlled for.

Since brain development is not spatio-temporally homogenous (Jay N. Giedd et al., 1999; J.N. Giedd et al., 1999; Giedd et al., 1996; Keshavan et al., 2002; Thompson et al., 2000) and the callosum continues to grow up through the third decade of life (Pujol, Vendrell, Junqué, Martí-Vilalta, & Capdevila, 1993), age differences, both within and across studies, will potentially have a profound effect on the results. A rostral-caudal wave of growth has been shown in the callosum in

typically developing children (Thompson *et al.*, 2000), and there are substantial changes during late childhood and adolescence in posterior regions (Jay N. Giedd et al., 1999; Giedd et al., 1996; Keshavan et al., 2002; Thompson et al., 2000). Findings from studies of the callosum based on child or adolescent subjects of different ages are, therefore, at least with respect to the posterior of the callosum, not directly comparable, other than as developmental data. Reductions in the size of posterior regions of the callosum in children and adolescents with autism might reflect differences in the rate of growth of the callosum in these individuals. All previous studies included children or adolescents: subjects ranged between a mean of approximately 4 years of age (Boger-Megiddo *et al.*, 2006) and a mean of just over 22 years of age (Hardan, Minshew, & Keshavan, 2000), and the standard deviation of age for the study at the adult end of the spectrum was 10.1 years. Many of these previous studies, however, also show anterior reductions (Alexander et al., 2007; Boger-Megiddo et al., 2006; Hardan, Minshew, & Keshavan, 2000; Kilian et al., 2008; Manes et al., 1999; Vidal et al., 2006), which may be more meaningful, given the rostral-caudal growth pattern of the callosum (Thompson *et al.*, 2000).

Controlling for age effects in samples which include children and adolescents is critical, and is complicated by the non-uniform pattern of brain overgrowth in autism (Carper & Courchesne, 2005; Hazlett et al., 2005; Piven, Arndt, J., & Andreasen, 1996), because it is also critical to control for brain size — or preferably, the length of the interhemispheric connections (Lewis, Theilmann, Sereno, & Townsend, 2008). Brain overgrowth in individuals with autism has been found to be generalized in toddlers (Hazlett *et al.*, 2005), primarily frontal in early childhood

(Carper & Courchesne, 2005), and in parietal and occipital lobes, but not frontal lobes, by adulthood (Piven, Arndt, J., & Andreasen, 1996). Adjustments for age differences must thus be done to subregions of both the callosum and the cortex, not to the total callosal area and total brain volume. And corrections for brain size must be done to subregions of the callosum using the corresponding subregions of brain. All of the previous results were based on data from children and/or adolescents, but none utilized regionalized corrections for age or brain size.

Differences in the timing and severity of brain overgrowth may also underlie the discrepancies in the findings of this previous research. There is evidence of a positive correlation between rate of growth in head circumference and severity of outcome within the autism spectrum (Akshoomoff et al., 2004; Courchesne, Carper, & Akshoomoff, 2003; C. Deutsch & R. M. Joseph, 2003; c.f. Sparks et al., 2002; Tager-Flusberg & Joseph, 2003). Thus, low functioning autistic individuals exhibit brain overgrowth earlier in development, and so the impact of connection length on degree of connectivity should have a greater effect in the anterior of the callosum, where developmental changes are occurring most rapidly during the first years of life (Thompson *et al.*, 2000). Thus, the anterior reductions in callosal area reported by Manes *et al.* (1999), for example, may also reflect, in part, the comparison of low functioning, rather than high functioning, individuals with autism to controls.

Finally, differences among these findings may stem from the handling of individual differences in brain size. Multiple studies of the corpus callosum in autism have now shown that controlling for brain size impacts the results (Manes et al., 1999;

Piven, Bailey, Ranson, & Arndt, 1997; Vidal et al., 2006). Not all of these previous studies controlled for brain size.

The current research differs in important ways from any of these previous works. First, there is a fundamental distinction between controlling for size and using measures of relative size like degree of connectivity (Smith, 2005). Second, the current research uses connection length rather than brain volume as a covariate in the analysis; though brain size correlates with the length of the interhemispheric connections (Braitenberg, 2001), the latter accounts for more of the variability in callosum size than does the former (Lewis, Theilmann, Sereno, & Townsend, 2008). Third, both the relative size measures and the measures of connection length are regionally specific, and thus the non-uniformity of the brain size differences does not skew the results. And finally, the current results are based on young adults, and thus presumably the observed reductions in degree of connectivity in the anterior of the callosum represent true reductions, not merely developmental timing differences.

But a few caveats should be noted. First, the results here rely on the histology showing no differences in neuron density or total neuron number in individuals with autism and in controls (van Kooten *et al.*, 2008). That finding, however, is based on a small mixed-gender sample that primarily consists of brains from children and adolescents. Second, as with Lewis *et al* (Lewis, Theilmann, Sereno, & Townsend, 2008), our results rely on the assumption that the number of cortico-cortical projection neurons scales with the total number of neurons in cortex. The current results, however, additionally assume that the scaling factor in autism is the same as in typical adults. Third, our results assume that tractography will provide equally accurate

measures of connection length in autistic brains and control brains. Reduced fractional anisotropy values in individuals with autism (Barnea-Goraly et al., 2004), however, may result in the failure of tractography for some of the callosal tracts, and so in inaccuracies in the measures of connection length. Fourth, the estimates of the number of fibers that comprise the callosum are also based on histology from typical adults. These estimates, most likely, are inaccurate in individuals with autism: the lower fractional anisotropy values in autism (Barnea-Goraly et al., 2004) suggest decreased fiber density. Thus estimates based on normal adult data are likely underestimates, and so the reductions are likely even greater.

But, the results here fit with a considerable body of evidence of under-connectivity in autism (Alexander et al., 2007; Cherkassky, Kana, Keller, & Just, 2006; Egaas, Courchesne, & Saitoh, 1995; Hardan, Jou, Keshavan, Varma, & Minshew, 2004; Hardan, Minshew, & Keshavan, 2000; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; Kana, Keller, Minshew, & Just, 2007; Hideya Koshino et al., 2008; Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis, Elman, & Courchesne, 2005; Manes et al., 1999; Mason, Williams, Kana, Minshew, & Just, 2008; McAlonan et al., 2005; Murias, Webb, Greenson, & Dawson, 2007; Piven, Bailey, Ranson, & Arndt, 1997; Vidal et al., 2006; Villalobos, Mizuno, Dahl, Kemmotsu, & Müller, 2005), and with the developmental hypothesis as to the origins of that under-connectivity (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008; Lewis, Elman, & Courchesne, 2005). Lewis and

Elman (2008) tested the hypothesized impact of the early brain overgrowth in autism using neural networks which modeled interhemispheric interaction. The networks were grown at the rate of either typically developing children or children with autism. The influence of the length of the interhemispheric connections was analyzed at multiple developmental time points, and by 2 years of simulated age, the networks that modeled autistic growth showed a reduced reliance on long-distance connections; and direct analysis of the connection weights showed a parallel reduction in connectivity. The results here are consistent with those modeling results.

Under-connectivity has been associated with many aspects of the behavioral phenotype. Reduced functional connectivity has been found in individuals with autism, for example, on language tasks (Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006). Language abilities rely on the rapid integration of syntactic and prosodic information in the acoustic signal, as well as the information available in facial dynamics and gesture. These networks span the brain. Executive function deficits in individuals with autism have also been associated with reduced functional connectivity (Just, Cherkassky, Keller, Kana, & Minshew, 2007), as have deficits in working memory for faces (Hideya Koshino et al., 2008), and in Theory of Mind (Mason, Williams, Kana, Minshew, & Just, 2008). Functional under-connectivity has also been found between visual cortex and the inferior frontal cortex (Villalobos, Mizuno, Dahl, Kemmotsu, & Müller, 2005) — corresponding to the mirror neuron system (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996) which has been hypothesized to play a critical role in the ability to understand other individuals' movements, and the ability

to understand social interactions (Rizzolatti & Craighero, 2004; Williams, Whiten, & Singh, 2004).

Further, assuming that the abnormal early brain overgrowth in autism leads to this later-observed under-connectivity (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008; Lewis, Elman, & Courchesne, 2005), there will be a substantial reorganization of white-matter during early childhood. This reorganization is plausibly extremely functionally disruptive, and may explain the timing of the onset of the behavioral symptoms, and the frequent occurrence of developmental regression — *i.e.*, the loss of skills that have already been acquired (Michael Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Eric Fombonne & Chakrabarti, 2001; Goldberg et al., 2003; Kurita, 1985; Janet E. Lainhart et al., 2002; Lord, Shulman, & DiLavore, 2004; Luyster et al., 2005; Rapin & Katzman, 1998; Rogers, 2004; Rutter & Lord, 1987; Shinnar et al., 2001; Simons & Oishi, 1987; Wilson, Djukic, Shinnar, Dharmani, & Rapin, 2003). In support of this, there is some evidence that the degree of abnormality in the rate of brain growth is related to the severity of the outcome (Akshoomoff et al., 2004; Courchesne, Carper, & Akshoomoff, 2003; C. K. Deutsch & R. M. Joseph, 2003; c.f. Sparks et al., 2002; Tager-Flusberg & Joseph, 2003).

The hypothesis that the early brain overgrowth in autism causes the loss of a greater number of long-distance connections (Lewis & Courchesne, 2004; Lewis, Courchesne, & Elman, 2003; Lewis, Courchesne, & Elman., 2004; Lewis & Elman, 2008; Lewis, Elman, & Courchesne, 2005) thus adds to the under-connectivity theory

of autism, and provides a parsimonious explanation for the etiology of under-connectivity. The results here are consistent with that hypothesis.

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Chapter VI
Summary and Concluding Remarks

VI.A Summary

The research presented in the preceding chapters builds on the work that has grown from Ramón y Cajal's hypothesis that neural circuit design is under pressure to minimize cellular costs and conduction delays (Ramón y Cajal, 1995). These design principles have been related to a variety of cross-species scaling facts — most notable from the current perspective, the hyposcaling of the corpus callosum (Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994); but also the rate at which white-matter scales with gray-matter (Zhang & Sejnowski, 2000); the increase in modularity with increases in brain size (Kaas, 2000); the placement of cortical areas (Cherniak, 1994, 1995); and the increase in gyrification with increasing brain size (Van Essen, 1997). This dissertation has extended these ideas to individual variation in brain size within humans, and tied the hypothesized forces to developmental mechanisms.

The research has taken two approaches: structural neuroimaging studies were done in order to assess how the organization of white-matter changes with individual differences in the length of the interhemispheric connections; and computational modeling was used to explore the causal aspect of the hypothesis, *i.e.*, that the longer conduction delays presumably associated with larger brains lead to reduced functional and physical connectivity during development. Autism was used as a test case, since children with autism have unusually large brains throughout childhood (Aylward,

Minshew, Field, Sparks, & Singh, 2002; Bailey et al., 1993; Bailey et al., 1998; Bauman & Kemper, 1985; Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Davidovitch, Patterson, & Gartside, 1996; Dementieva et al., 2005; Fombonne, Roge, Claverie, County, & Fremolle, 1999; Hazlett et al., 2005; Kemper & Bauman, 1998; Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000; Piven et al., 1995; Sparks et al., 2002; Woodhouse et al., 1996).

Previous neuroimaging research related to this topic has been limited to morphometric measures, and has assessed the relation between measures such as forebrain volume or cortical surface area and the cross-sectional area of the corpus callosum (Jäncke, Preis, & Steinmetz, 1999; Jäncke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Jäncke & Steinmetz, 1998; Rauch & Jinkins, 1994; Rilling & Insel, 1999). But these are proxies for the measures that are hypothesized to be of importance — *i.e.*, connection length and relative connectivity. The advent of diffusion tensor imaging allowed the dissertation research to more directly assess the relation of interest. The research here used diffusion tensor imaging and tractography to detail the patterns of interhemispheric connectivity and to determine the average length of the longest interhemispheric connections; and formulae based on histological results allowed estimates of degree of connectivity — the ratio of an estimate of the number of interhemispheric connections to an estimate of total cortico-cortical projection neurons in the cortical areas connected.

Using this methodology, in Chapter II it was shown that connection length is negatively correlated with degree of connectivity in the normal adult brain. The degree of interhemispheric connectivity was estimated for each of five sub-regions of

the corpus callosum in 22 normal males between 20 and 45 years of age (mean 31.68; stddev 8.75), and the average length of the longest tracts passing through each point of each subregion was calculated. Connection length was negatively correlated with degree of connectivity in all five subregions, and the relation was significant in four of the five — the exception being the isthmus — with an average r^2 of 0.255. Thus, the hyposcaling of the callosum hypothesized and observed with respect to cross-species comparisons (Hopkins & Rilling, 2000; Rilling & Insel, 1999; Ringo, Doty, Demeter, & Simard, 1994) was shown to also apply to individual variation in humans.

Using the same methodology, in Chapter III it was shown that this relation is not yet developed by late childhood. The degree of interhemispheric connectivity and the average length of the longest tracts in each of the five subregions of the callosum were estimated in 19 typically developing boys between 7 and 11 years of age. A significant relation between connection length and degree of connectivity was found only in the posterior-most subregion. The anterior four subregions showed essentially no relation: averaging over the anterior 4 subregions, connection length accounted for less than 7 percent of the variance in degree of connectivity, and one subregion contributed to this via a positive rather than negative relation. In the adults, connection length accounted for almost 27 percent of the variance in the anterior four subregions. These results, taken together, indicate that the relation between connection length and degree of connectivity develops during childhood and adolescence.

That the negative relation between connection length and degree of connectivity develops is compatible with the hypothesis that longer connections lead

to fewer of them being retained during development, but does not show that causality runs in this direction. The computational modeling study presented in Chapter IV provided a proof of concept. Neural networks which modeled interhemispheric interaction were grown at the rate of either typically developing children or children with autism, and trained with either short or long response times. The influence of the length of the interhemispheric connections was analyzed at 0, 12, 24, 36, and 48 months of simulated age. After 12 months of simulated age, the networks that modeled autistic growth were less affected by removal of the interhemispheric connections than those that modeled normal growth — indicating reduced functional connectivity — for short response times, and this difference increased substantially at approximately 24 simulated months of age. The performance of the networks showed a corresponding decline. And direct analysis of the connection weights showed a parallel reduction in connectivity. Since, aside from the longer conduction delays associated with the pattern of brain overgrowth in autism, the models were identical, these results show that longer long-distance connections may lead to reduced functional and structural connectivity.

The prediction of reduced long-distance connectivity in autism was pursued in chapter V with neuroimaging, using the same methodology as with the adults and children. The relation between connection length and degree of connectivity in young adult males with autism was examined and compared to the results of the typically developing young adult males. The prediction was verified. Connection length and degree of connectivity showed the typical negative relation in all five subregions of the callosum, but with a reduced degree of connectivity in anterior subregions. Thus

differences in connection length across individuals with autism appear to influence the growth and retention of connections to approximately the same extent as in typically developing individuals. But, during the period of maximal brain overgrowth (Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Dementieva et al., 2005; Hazlett et al., 2005; Redcay & Courchesne, 2005; Sparks et al., 2002) the anterior of the callosum, which contains smaller diameter fibers than more posterior regions (Aboitiz, Scheibel, Fisher, & Zaidel, 1992), and so will show greater increases in conduction delay with increasing length, is undergoing rapid change (Thompson et al., 2000). Thus, the larger conduction delays and cellular costs presumably associated with the longer long-distance connections in the larger brains of children with autism have a particularly large impact on the growth and retention of connections in anterior regions.

In sum, this dissertation investigated the hypothesis that the length of the long-distance connections influences the way in which the brain organizes itself during development, and showed that (i) there is a negative relation between connection length and degree of connectivity in adults; (ii) that that relation develops; (iii) that abnormal differences in brain size during development can lead to these diffeences in connectivity; and (iv) that abnormal differences in brain size during development, in fact, are associated with the predicted differences in connectivity.

VI.B Concluding Remarks

Central to this research has been the hypothesis that normal developmental mechanisms optimally wire the brain, and thus that differences in brain size during

development will result in differences in structural and functional organization. The results presented here have provided reason to believe this may be correct. But this research is far from complete. Much is assumed; much is speculative; there are many limitations; and many questions remain.

Most crtically, the hypothesized causal mechanism has not been shown to be the source of the relation. The research presented here has shown that the relation between connection length and degree of connectivity develops, and that the increased conduction delays presumably associated with longer long-distance connections may underlie this; but not that this is in fact the case. It might also be that there is an increase in the growth and retention of short-distance connectivity, and so an increase in brain volume and surface area, and so a decrease in relative connectivity. The negative relation between connection length and the area of the subregions of the callosum argues for the former interpretation, but longitudinal data over development would better address this issue. Longitudinal data should reveal whether changes in degree of connectivity during development are primarily the result of increases in cortical volume and surface area, or of reductions in the callosum. This is, in fact, work that is currently in progress; the data presented in chapter III, are from a longitudinal study of development in which structural data were collected twice, with one year between scans.

That increased conduction delays and cellular costs are associated with decreases in degree of connectivity, in fact, remains an unsupported inference. Variation in connection length has been assumed to be insufficiently compensated for by increases in axon diameter or myelination. This is supported in comparative

neuroanatomy research (Olivares, Montiel, & Aboitiz, 2001; Wang et al., 2008), but is an extrapolation with respect to individual differences in length within species, and is unsupported in development. Differences in rate of brain growth may be accompanied by parallel differences in rate of myelination and increases in axon diameter. Histological data over development are required to support this inference.

Conduction delays can be assessed somewhat more directly. In non-humans, interhemispheric transmission time has been studied using intracellular antidromic stimulation — *i.e.*, stimulation of the peripheral part of the axon, and intra- or extra-cellular recording at the soma. This provides a reasonably accurate measure of conduction delay for an individual axon; and so can be used to determine the distribution of conduction delays. The studies to date, however, have not looked at the effect of within-species differences in brain size on interhemispheric conduction delay, nor at developmental changes in interhemispheric conduction delay. And the cross-species comparisons have concentrated on sets of callosal connections which show unusual, possibly ecology-driven, variation in diameter across species, *e.g.*, those at the border of areas 17/18 (Innocenti, Aggoun-Zouaoui, & Lehmann, 1995; Olivares, Montiel, & Aboitiz, 2001; Simmons & Pearlman, 1983; Swadlow, 1974).

But a similar approach can be used to measure interhemispheric transfer time in humans. Transcranial magnetic stimulation can be used to generate activity, and electroencephalography can be used to record the spread of that activity (Ilmoniemi, Ruohonen, & Karhu, 1999). Transcranial magnetic stimulation introduces a number of complexities, however: it is extremely non-focal; sub-threshold stimulation affects the spread of activation in complicated ways; and the magnetic field decays quickly,

and so differences in the distance from the stimulating coil to cortex make a large difference in terms of the strength of stimulation and the size of the surrounding area of sub-threshold stimulation. It has, nonetheless, been used to estimate callosal conduction times (Hanajima et al., 2001). These measures are, however, most likely measures of the shortest interhemispheric transfer time, which are not representative of the average conduction delay.

A somewhat less complicated approach is to use latency differences between evoked potentials recorded from homologous sites over either hemisphere in response to unilateral input. This has been done using visual stimuli (Alexa Ledlow, 1978; Andreassi, Okamura, & Stern, 1975; Nalcaci, Basar-Eroglu, & Stadler, 1999; Saron & Davidson, 1989), as well as somatosensory stimuli (Gott, Hughes, & Binggeli, 1985; Gulmann, Wildschiodtz, & Orbaek, 1982; Salamy, 1978), and auditory stimuli (Mononen & Seitz, 1977). Again, these measures most likely represent the shortest conduction delays. But the evoked potentials are thought to be an aggregate of signals from separate pools of neurons oscillating at different frequencies; and different interhemispheric conduction delays have been associated with different frequency bands (Nalcaci, Basar-Eroglu, & Stadler, 1999). This may provide a way to assess the conduction delay associated with average diameter fibers.

Such an approach might also be used to assess the cellular costs associated with interhemispheric connections. Metabolic changes associated with neuronal activation can now be measured by functional magnetic resonance spectroscopy. Changes in measures of various metabolites from presentations of unilateral input could provide an estimate of the metabolic cost of interhemispheric signaling. This is,

of course, complicated by issues of connection density; but before the relation between connection length and degree of connectivity develops, such measures could provide an estimate of the relation between connection length and the associated metabolic costs.

At the level of mechanism, the greater conduction delays assumed to be associated with longer long-distance connections were predicted to lead, over development, to decreased functional connectivity, which would subsequently lead to decreased structural connectivity. The dissertation research focused on the structural aspect of this compound prediction; functional connectivity was only considered in the computational modeling study, and there the temporal resolution was too course to determine the direction of causality. But data have been collected to test this prediction. As mentioned above, the data presented in chapter III, are from a longitudinal study with structural data collected one year earlier than the data presented here. Together with the MRI data, EEG data were also collected; the study was designed to test exactly this prediction. But these data remain to be analyzed.

To properly investigate the developmental hypothesis of this dissertation, however, a substantially larger set of longitudinal data will be required. The sample sizes here are small, and even when the longitudinal data are included, there is far too little developmental data. The results of chapters II and III show that the relation between connection length and degree of connectivity develops during and after childhood. The data here provide only a snapshot during late childhood. Functional and structural longitudinal data throughout childhood and adolescence are necessary to adequately assess the developmental role of connection length in determining the

organization of cortex. And this should be done for typical development, for autism, and for other developmental disorders that show abnormalities in brain size.

Thus, issues remain, but there is a way forward; and the results presented here have provided reason to believe that it is worth moving forward.

VI.C References

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