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# 3

## A Theory of Autism Based on Frontal-Posterior Underconnectivity

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**A**lthough autism was first formally described many decades ago by Kanner (1943) and Asperger (1944), research on the disorder in the U.S. remained scarce until the 1990s. At that time, researchers developed new neuroscientific methods that could be applied to investigations of the psychological and biological underpinnings of autism, including genomics, eye-movement tracking, and electrophysiology. As a result, researchers and practitioners are gaining greater understanding of the disorder. The complexity and enigma of autism still remain, particularly its alterations of a wide and seemingly unrelated group of behavioral symptoms that have no obvious correspondence to a single biological function. In addition, the disorder occasionally includes perceptual advantages. To address the three elements of the enigma, we suggest that the diversity of symptoms can be understood as a consequence of a widespread neural systems disorder; the link to a biological substrate is illuminated by brain imaging; and a perturbation of the cortical system can have both negative and positive impacts on functioning.

Our focus here is on a theory of autism based on neuroimaging findings regarding cortical underconnectivity. The theory of underconnectivity proposes that the behavioral symptoms of autism result from abnormalities in the coordination of function among collaborating brain regions. This theoretical view first emerged from functional magnetic resonance imaging (fMRI) measurements of cortical activation demonstrating that the degree of synchronization (*or functional connectivity*) between frontal and posterior brain regions was lower in autism. The observation was first made in a language comprehension task (Just, Cherkassky, Keller, & Minshew, 2004), and many studies have replicated these findings in tasks that require synchronization between frontal and posterior regions of the brain (Damarla et al., 2010; Just et al., 2004; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Kana, Keller, Cherkassky, Minshew, & Just, 2006, 2009; Kana, Keller, Minshew, & Just, 2007; Koshino et al., 2005, 2008; Mason, Williams, Kana, Minshew, & Just, 2008; Mizuno et al., 2011; see Schipul, Keller, & Just, 2011 for a recent review). We propose that the lower synchronization arises due to a reduction of the maximal rate of data transfer (*or bandwidth*) (Shannon, 1949) between frontal and posterior cortical areas in autism. Decreased bandwidth impacts performance of the brain system when the inter-regional communication needs are high.

To describe the implications of the theory of underconnectivity, this chapter is organized into several sections: a summary of previous findings, a description of underconnectivity theory and of its implementation as a computational model, and a discussion of its relation to other theories.

## WHITE MATTER ABNORMALITIES IN AUTISM

White matter is the unsung hero of the human brain. It constitutes about 45% of the brain. Like any element of infrastructure, it allows the main work of the brain to proceed without explicitly attending to the white matter communication pathways that link various gray matter areas to each other. The main work of the brain is the thinking that gets us all through our lives. That thinking requires the collaborative activity of many gray matter brain areas whose intercommunication vitally depends on the white matter pathways. Every act of thinking requires the collaborative activity of about 20 gray matter computational centers. Human thought is a network activity. For example, reading a sentence requires at least the collaborative work of Wernicke's area in the left temporal lobe, Broca's area in the left frontal, left angular gyrus in the parietal lobe, primary and secondary visual areas in the occipital lobe, as well as the right hemisphere homologs of some of these areas.

Alterations in white matter can impair thought processes. White matter properties are key determinants of the conduction velocity and hence the bandwidth of the communication channels in the brain (Waxman, 1980), thereby impacting cortical connectivity. One such property is the degree of myelination of axons, or the formation of insulating white matter around axons.

The myelin sheath can increase the transmission speed and bandwidth of an axon by a factor of 10 or more (Hartline & Colman, 2007), so myelination and its distribution have a clear relation to cortical communication capacities, including synchronization.

In addition, several studies have reported white matter volumetric abnormalities in autism, with increased volume in some areas and decreased volume in other areas. The increased brain size observed in children with autism is largely due to volume differences in white matter, particularly in the frontal lobes (Carper, Moses, Tigue, & Courchesne, 2002, Herbert et al., 2004). One study reported overall greater white matter volume in 7- to 11-year-old children with autism (Herbert et al., 2003), and the authors found in a later study that this deviation was greatest in the radiate white matter in the frontal lobe (Herbert et al., 2004). Later in life, adolescents and adults with autism actually exhibit reduced white matter volume (Courchesne et al., 2001, Courchesne, Redcay, & Kennedy, 2004; Waiter et al., 2005), although typically developing individuals show a linear increase in white matter volume between the ages of four and 22 years (Giedd et al., 1999).

The most prominent white matter tract in the cortex, the corpus callosum, also shows abnormalities in autism. The corpus callosum enables communication among functional systems in the two hemispheres. It is usually slightly *smaller* in individuals with autism (Chung, Dalton, Alexander, & Davidson, 2004; Hardan, Minshew, & Keshavan, 2000; Manes et al., 1999; Piven, Bailey, Ranson, & Arndt, 1997; Vidal et al., 2006). As noted above, total brain size is abnormal in autism, and *larger* brain volume is correlated with *smaller* corpus callosum size (Jancke, Preis, & Steinmetz, 1999; Jancke, Staiger, Schlaug, Huang, & Steinmetz, 1997), suggesting multiple loci of disruption in connectivity (Ringo, 1991). The abnormalities in white matter in autism, including myelination and corpus callosum size, form a plausible neural basis for disrupted systems-level connectivity in autism.

## BIOLOGICAL MECHANISMS AFFECTING CONNECTIVITY

Irregularities in a number of early neurodevelopmental processes could individually or in combination result in abnormalities in the brain's development of white matter connectivity (Bailey et al., 1998; Geschwind & Levitt, 2007). For instance, specialized glial cells, oligodendrocytes, are responsible for the production of myelin, which enhances neural transmission. Other glial cells manage waste and clean up neurotransmitters, which helps to organize the structure of the neuronal network. Postmortem samples of gray and white matter taken from individuals with autism show evidence of astroglial and microglial activation and neuroinflammation (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005).

Neuronal migration abnormalities in autism can lead to fractionated and incompletely or aberrantly formed minicolumn vertical circuitry. Abnormal

minicolumn organization can result in an imbalance between excitation and inhibition within and between minicolumns (Courchesne, Redcay, Morgan, & Kennedy, 2005), or an abundance of short connective fibers relative to long ones, which may lead to a deficiency in inter-regional connectivity. More numerous and abnormally narrow minicolumns in frontal and temporal cortex have been reported in autism (Casanova et al., 2006). A recent postmortem study by Courchesne and colleagues (2011) found significantly increased numbers of neurons in the prefrontal cortex of individuals with autism relative to typically developing individuals.

Yet another possibility is that anomalies in neurochemistry could affect brain development and connectivity. Reductions in N-acetylaspartate (NAA), an amino acid that supports axon myelination (Baslow, 2003), have been demonstrated in several brain regions in autism, including cingulate gyrus, temporal gray matter, frontal and parietal white matter, hippocampal-amygdaloid complex, and cerebellum (Friedman et al., 2003; Hisaoka, Harada, Nishitani, & Mori, 2001; Levitt et al., 2003; Otsuka, Harada, Mori, Hisaoka, & Nishitani, 1999). Another amino acid, glutamate, affects neuronal migration, differentiation, axon genesis, and plasticity (Coyle, Leski, & Morrison, 2002), and several authors have proposed that autism is related to glutamatergic dysfunction (Carlsson, 1998; Polleux & Lauder, 2004; Rubenstein & Merzenich, 2003). Irregularities in these two amino acids, and potentially others, could be a factor in the abnormal development of connections and functioning in people with autism.

In summary, the disruption of cortical connectivity described in the theory of underconnectivity could plausibly stem from one or more of the biological mechanisms described above.

## BRAIN-IMAGING EVIDENCE OF DISRUPTED CONNECTIVITY IN AUTISM

The lower-level biological mechanisms cited above could underpin cortical connectivity disruption. Four recent brain-imaging findings converge to more directly implicate aberrant cortical connectivity in autism.

First, the synchronization of brain activation between frontal and posterior regions of the cortex is lower in autism than in control groups across a number of different domains of thought. Poor synchronization of activation has been demonstrated in tasks such as language comprehension (Just et al., 2004; Kana et al., 2006; Mason et al., 2008; Mizuno et al., 2011), executive function (Just et al., 2007), social processing (Kana et al., 2009; Koshino et al., 2008; Schipul, Williams, Keller, Minshew, & Just, 2012), working memory (Koshino et al., 2005, 2008), high-level inhibition (Kana et al., 2007; Solomon et al., 2009), and visuospatial processing (Damarla et al., 2010). The lower synchronization, or functional connectivity, in autism measured during task performance reflects the lower degree of coordination between the two regions.

In addition to task-related functional connectivity, a number of studies have investigated task-free (or "intrinsic") functional connectivity in autism. By partialling out task-driven effects, such studies have shown evidence of both reduced (Jones et al., 2010; Villalobos, Mizuno, Dahl, Kemmotsu, & Muller, 2005) and increased (Mizuno, Villalobos, Davies, Dahl, & Muller, 2006; Noonan, Haist, & Muller, 2009; Turner, Frost, Linsenbardt, McIlroy, & Muller, 2006; Shih et al., 2010) task-free functional connectivity in autism relative to controls. Although the significance of these results remains unclear, both increases and decreases in task-free functional connectivity could plausibly reduce the available bandwidth of communication for task-relevant processing (see Schipul et al., 2011, for a discussion).

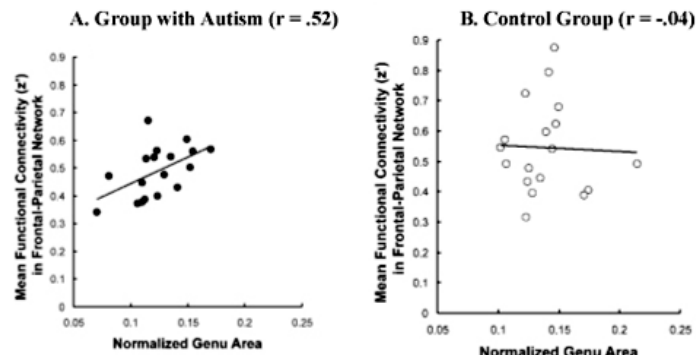
Similarly, underconnectivity is evident during a resting state in which the "task" consists of relaxed, internally generated thought. The functional connectivity between frontal and posterior areas of the default network (regions more active during rest than they are during an externally imposed task) is lower in autism than in controls (Cherkassky, Kana, Keller, & Just, 2006). This reduction in functional connectivity persists even when high-frequency fluctuations in activation are filtered out (in an effort to limit measurement to spontaneous physiological changes rather than cognitively driven modulations of activation) (Assaf et al., 2010; Kennedy & Courchesne, 2008; Monk et al., 2009; Weng et al., 2010). This finding has been replicated with EEG methods, measuring activity across cortical areas within the alpha range (8-10 Hz) (Coben, Clarke, Hudspeth, & Barry, 2008; Murias, Webb, Greenson, & Dawson, 2007). Coben et al. (2008) interpreted their EEG results as indicating "...dysfunctional integration of frontal and posterior brain regions in autistics along with a pattern of neural underconnectivity."

In sum, fMRI studies of task-relevant and task-free functional connectivity find reduced frontal-posterior synchronization of activation across many different types of thinking, but particularly in more complex tasks that involve frontal participation.

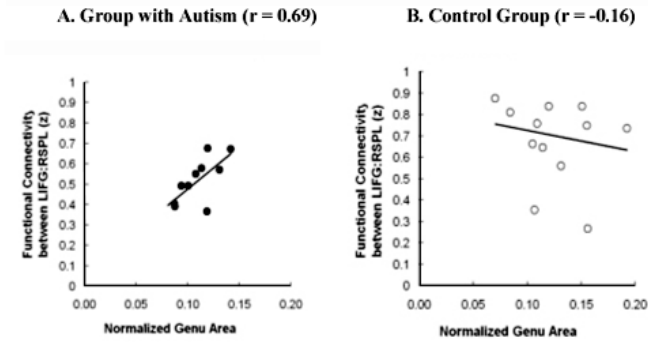
A second brain-imaging finding supporting the theory of underconnectivity is that, as described above, there are white matter volumetric abnormalities in autism that lead to cortico-cortical connection abnormalities (e.g., Carper et al., 2002; Courchesne et al., 2001; Herbert et al., 2004). These studies indicate that, for individuals with autism, there is a tendency towards excess white matter volume in some regions (such as the frontal radiate white matter) and diminished volume in other regions (such as the corpus callosum).

The third finding deals specifically with the size of the corpus callosum and how it relates to frontal-posterior connectivity. Among individuals with autism, the reduced size of their corpus callosum is correlated with the degree of impairment in functional connectivity during thinking tasks and in resting state (Cherkassky et al., 2006; Just et al., 2007; Kana et al., 2006, 2009; Schipul et al., 2011). More specifically, across a diverse set of studies, the extent of functional connectivity between frontal and posterior regions is correlated with the

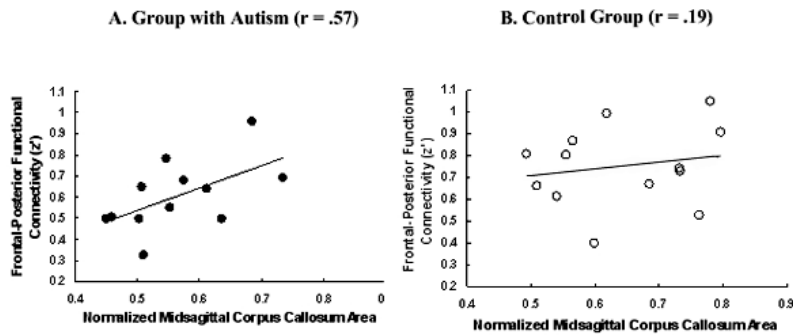
## Tower Of London Task



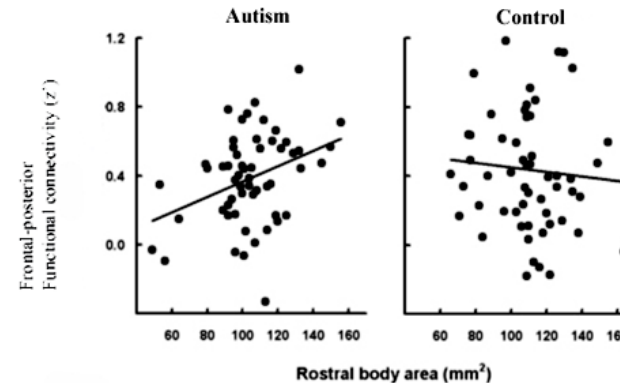
## Sentence Imagery Task



## Embedded Figures Task



## Resting State Activity



(A)

Figure 3.1 Correlation in four studies between the relevant portion of the corpus callosum and the mean functional connectivity between frontal and posterior areas for the Autism group (A) and a lack of correlation for the Control group (B).

size of the segment of the corpus callosum that connects these cortical regions, as shown in Figure 3.1. The corpus callosum size deficit is interpreted as a more general index of white matter disruption in autism that constrains the communication bandwidth between frontal and posterior brain regions and limits their synchronization. (For neurotypical participants, there is no correlation between the size of the corpus callosum or its segments with frontal-posterior functional connectivity, presumably because the white matter does not impose a constraint on bandwidth or synchronization.)

(B)

Figure 3.1 Continued

Fourth, several recent diffusion tensor imaging (DTI) studies of white matter in autism have found abnormalities in the connective tracts, particularly in fractional anisotropy, a measure of coherence of directionality of white matter fibers. At very young ages (two or three years), there is evidence of *increased* fractional anisotropy in autism, particularly in the frontal lobe and corpus callosum (Ben Bashat et al., 2007), consistent with early overgrowth of white matter, discussed above. By five years of age, however, fractional anisotropy is reduced for tracts that connect regions within the frontal lobes (Sundaram et al., 2008). In older children and adolescents (10- to 18-year-olds), there is reduced fractional anisotropy in specific frontal-posterior tracts in autism (Sahyoun, Belliveau, Soulieres, Schwartz, & Mody, 2010), as well as

autism-related differences in hemispheric lateralization of fractional anisotropy in the arcuate fasciculus connecting frontal, parietal, and temporal cortices (Fletcher et al., 2010; Knaus et al., 2010). One study of children and adolescents with autism found reduced fractional anisotropy in white matter adjacent to the ventromedial prefrontal cortices, anterior cingulate gyri, temporoparietal junction, and in the corpus callosum (Barnea-Goraly et al., 2004). Reduced fractional anisotropy persists into adulthood in the corpus callosum and in tracts in the frontal and temporal lobes (Alexander et al., 2007; Keller, Kana, & Just, 2007; Lee et al., 2007). Cumulatively, these studies provide clear evidence of a relationship between autism and disruption of the white matter that provides the anatomical connectivity among frontal and posterior brain regions, a disruption that is exacerbated with development. The DTI finding most relevant to the theory proposed in this chapter is reduced fractional anisotropy in an area of the left anterior corona radiata, consistent with either the left uncinate fasciculus (connecting the frontal and temporal lobes) or the left inferior frontal-occipital fasciculus, observed in a sample of 52 adults and adolescents with autism compared to age- and IQ-matched controls (Keller and Just, 2009a).

These converging findings suggest that reductions in communication and connectivity among cortical regions may be part of the pervasive core processing deficits in autism (Belmonte et al., 2004; Courchesne & Pierce, 2005a, 2005b; Herbert et al., 2004; Just et al., 2004; Keller et al., 2007; Rippon, Brock, Brown, & Boucher, 2007). Below, we describe a theory of autism based on disruption of cortical connectivity.

## UNDERCONNECTIVITY THEORY

The cortical underconnectivity theory (Just et al., 2004, 2007) posits that interregional (systems-level) connective circuitry in the brain is disrupted in autism. In particular, the communication bandwidth between frontal areas and posterior cortical areas is proposed to be lower in autism than in control participants. The theory proposes a causal relationship between the anatomical, physiological (brain activity), and psychological phenomena. Thus, any psychological process which requires extensive coordination between frontal and posterior brain regions is susceptible to disruption, particularly when the task is complex and requires integration of different types of cortical computations. Underconnectivity is proposed as a unifying theory for explaining a range of deficits at the levels of psychological function, cortical function, and cortical anatomy, and the heterogeneity of possible connective disturbances could underlie the considerable heterogeneity of behavioral symptoms of autism. This is an initial attempt at an exhaustive theory, in the sense that no other independent factors that do not stem from or underlie connectivity aberrations are presumed to underlie autism.

### *Bandwidth Limitations in Autism*

The bandwidth of a communication channel is the amount of information that can be transmitted per unit time, and this property is crucial for the functioning of a network of interconnected nodes whose mainstay is collaborative interaction. Human thought relies on co-activation of a network of cortical areas linked by white matter tracts providing anatomical connectivity. As discussed above, fMRI studies have demonstrated that synchronization between frontal and posterior areas is lower in autism (Just et al., 2004, 2007; Kana et al., 2006, 2007; Koshino et al., 2005; Villalobos et al., 2005). Figure 3.2A (see plate section) illustrates this deficit in connectivity when participants complete a Tower of London (TOL) problem-solving task, which entails activation of both frontal and parietal areas. We attribute the lower synchronization demonstrated in this and other tasks to a lower communication bandwidth between frontal and posterior areas in autism relative to controls, depicted schematically in Figures 3.2B and 3.2C. The model presented below demonstrates that a bandwidth constraint, coupled with increased autonomy of the parietal lobe, results in a reduction of frontal-parietal synchronization. The model also explains the behavioral differences in task performance seen between groups as a function of a frontal-parietal bandwidth constraint in autism.

The functional connectivities plotted in Figure 3.2A are means of correlations of activation times-series data, averaged over 18 participants in each group and over multiple pairs of activated frontal-parietal pairs of regions of interest. The correlations measure the degree to which the activation levels in two regions rise and fall together. Figure 3.3 illustrates the coordination of two regions for one participant with autism (top panel) and one control participant (bottom panel): a frontal region (left DLPFC) and a parietal region (left parietal). Visual inspection and the correlation coefficients indicate that the two curves are less correlated for the participant with autism compared to the control participant (and Figure 3.2A shows the mean frontal-parietal correlation for each group across all frontal-parietal pairs of regions). These figures illustrate functional underconnectivity in autism compared to controls in TOL problem-solving, and this pattern is replicated in many other tasks requiring synchronization of frontal and posterior areas.

Such functional underconnectivity of a very similar form has also been observed in autism in a number of diverse domains. One of these was a social task involving face perception and working memory, exhibiting reduced synchronization between the fusiform face area and a frontal area (Koshino et al., 2008). Another was a Theory of Mind task in which the intentions of animated geometric objects were being inferred from their motions, exhibiting reduced functional connectivity between the medial frontal area and the right posterior superior temporal area (both associated with Theory of Mind processing) (Kana et al., 2009). Another study was a sentence comprehension task in which participants had to construct a visual image in order to evaluate

whether the sentence was true or false, requiring coordination between a frontal language area and a parietal spatial processing area (Kana et al., 2006). Yet another was a task requiring complex inhibition, displaying reduced frontal-parietal connectivity (Kana et al., 2007). Finally, even in a resting state when participants were not performing any assigned task, the functional underconnectivity in autism between frontal and posterior regions continued to be manifested (Cherkassky et al., 2006). The diversity of these tasks speaks to the generality of the functional underconnectivity phenomenon.

Figures 3.2A and 3.3 depict the main phenomenon for which the computational modeling, described below, attempts to provide a postulated mechanism—that is, a lowered communication bandwidth. A key assumption is that

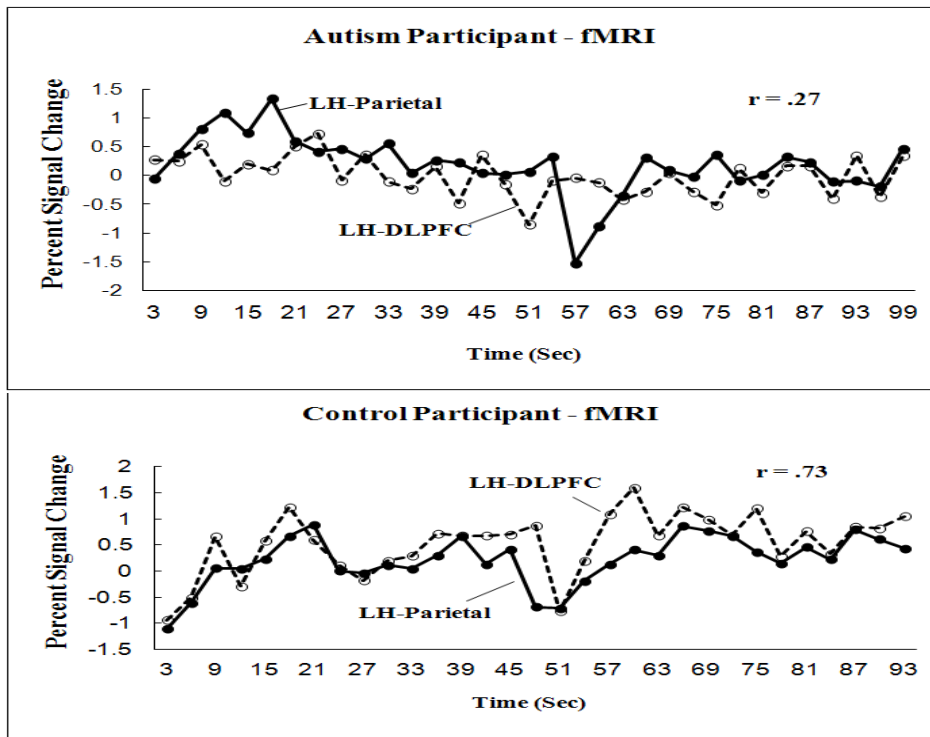


Figure 3.3 Higher frontal-parietal functional connectivity between the two activation time series in a control participant (correlation  $r = .73$ ) (bottom panel) in the Tower of London task than in an autism participant ( $r = .27$ ) (top panel) (data from Just et al., 2007).

lowering the bandwidth will produce an adaptation in the system. Adaptation in a computer network illustrates that agents in a collaborative environment can become more autonomous when inter-agent communication is impaired (Stone & Veloso, 1999), and communication networks can switch to an asynchronous mode when bandwidth decreases (Fall, 2003). Analogously, the underconnectivity theory of autism predicts that decreased cortical bandwidth could result in concomitant adaptations in cortical functioning, most probably increased posterior (in this case, parietal) autonomy from frontal influences. Moreover, it is also plausible that decreased bandwidth could give rise to increased functional connectivity among posterior regions.

## COMPUTATIONAL MODELING OF BRAIN FUNCTION AND COGNITION

Here we briefly describe a recent computational account (Just et al., 2012) of the lower frontal-posterior functional connectivity and longer response times in autism in a high-level visual problem-solving task, the Tower of London. The model is expressed within the 4CAPS cognitive neuroarchitecture, which accounts for cortical function in terms of a set of collaborating computational centers intended to correspond to cortical centers (Just & Varma, 2007). The autism model of the Tower of London task is an adaptation of a previous TOL model developed to account for the brain activation and performance of typically developing individuals (Newman, Carpenter, Varma, & Just, 2003). (The task required re-arranging the positions of three distinctive balls in three suspended pool pockets until they matched a specified goal [or ending] configuration, as shown in Figure 3.4.) The model contained two frontal centers and two parietal centers. The autism model contained two adaptations. One was a lowering of the communication bandwidth between the frontal and parietal centers, which slowed performance when a center had to wait longer for critical input from another center. The second adaptation was an increased autonomy accorded to the parietal centers, such that they were enabled to proceed

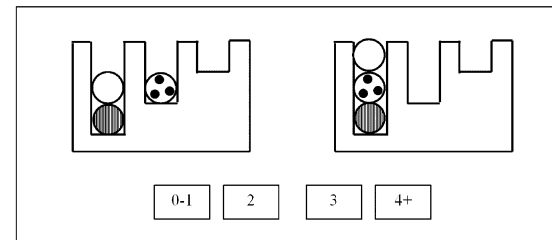


Figure 3.4 A sample Tower of London problem. This display shows a three-move problem and a schematic diagram showing the response buttons to indicate the number of moves required.

without frontal input in certain circumstances. (An example of one such circumstance occurs during the last move of a problem: If a parietal center is proposing a move in the puzzle that would be the last move of a successful solution, then in the autism model that parietal center is enabled to make the move without requiring the input from the frontal executive centers that would normally collaborate in selecting this move.)

The autism model shows lower functional connectivity between frontal and parietal centers, compared to the original model. When the correlations of the time series for all possible pairs of frontal and parietal centers are averaged for the control model and the full autism model, the resulting difference in functional connectivity strongly resembles the corresponding group difference found in the fMRI data (shown in Figure 3.2A). The autism model also shows increased response times, and the participants with autism did. In addition, the autism model can predict the frontal-parietal functional connectivity of individual participants with autism by making the frontal-posterior bandwidth proportional to an index of that individual's white matter properties. The model thus provides an integrated explanation of how the postulated mechanisms account for some of the central brain imaging and behavioral findings in autism.

### *Cause, Effect, and Adaptation*

The observed brain functioning in autism likely results from both the brain changes introduced by autism and the brain's natural adaptations to the changes during many years of brain development. In this view, greater parietal autonomy and reliance on posterior brain areas is interpreted not as part of the primary physiological basis of autism, but as a functional consequence. The modeling described above reinforces the notion that an adapted system does not always function as well as an intact system might. When completing the more complex TOL problems that required the frontal areas of the brain to manage deeply embedded goals, the adapted system was less effective than an intact system. Lower performance might also occur in other tasks during which certain frontal processes cannot be performed or compensated for by a posterior center (such as Theory of Mind processing). On the other hand, as described below, the adapted system may be more effective in situations in which the frontal contributions may impede performance (such as searching for embedded figures in a distracting context).

## SUMMARY OF PREVIOUS CONNECTIVITY-RELATED FINDINGS: COMMONALITIES ACROSS DOMAINS OF THOUGHT

The model can be extended to account for brain characteristics seen in autism while participants engage in a variety of tasks and types of thinking. A

summary of the findings from studies of 10 types of tasks indicates a number of commonalities as well as specificities. One robust finding across studies is the frontal-posterior undersynchronization, which to date has been observed in every high-level thinking task that has been examined, including tasks of executive functioning, language, memory, social processing, and high-level perception, as well as in a resting state "task," as shown in the third column of Table 3.1. In many of these tasks, the corpus callosum of the participants with autism was reliably smaller than that seen in control participants (fourth column), and the corpus callosum size was correlated with the degree of frontal-posterior synchronization (fifth column). In addition, areas around the corpus callosum showed lower structural integrity in autism, as measured by fractional anisotropy in diffusion tensor imaging studies. Many of these studies also showed decreased activation in a frontal area and increased activation in a posterior association area, consistent with the model's tenets. Thus there are commonalities across domains of thought in the frontal-posterior undersynchronization, in the relation between undersynchronization and properties of the relevant white matter, and in the distribution of activation in the brain (less frontal and more posterior).

### *Domain-Specific Behavioral Findings in Autism*

The brain characteristics of autism also have behavioral manifestations that are task-specific. For example, in pilot studies of the TOL puzzle, participants with autism had more difficulty with more complex problems than did IQ-matched control participants, necessitating an fMRI study design that excluded the most difficult problems. The right-hand column of Table 3.1 describes several behavioral manifestations of autism that are drawn from large behavioral studies (not necessarily from the corresponding brain-imaging studies). For instance, poorer comprehension of complex syntax in autism was observed in the Detroit Test of Oral Directions (Minschew, Goldstein, & Siegel, 1997), and good performance at word recognition was observed by Newman et al. (2007). In general, the tendency is for the autism group to process tasks in a way that relies less on functions that have a vital frontal component (e.g., executive functioning, complex language, Theory of Mind, or face, and social processing) and more on posterior functions (visual or other perceptual processing). This greater reliance on posterior areas may lead to processing that is more independent of frontal areas, more visual or featural in content, and, in some circumstances, more effective for persons with autism compared to neurotypical individuals.

Because this theory accounts for the neuroimaging and behavioral patterns of results in a wide variety of thinking tasks, it is likely that it can be extended to anticipate characteristics of thinking in autism in new situations. If the brain activity and thought processes in people without autism are understood well enough, then the theory-based model can provide a first-order prediction of what will occur in autism.



Table 1. Summary of domain-general and domain-specific autism findings

DOMAIN	TASK	Domain-General Brain Phenomena in Autism					Domain-Specific Behavioral Phenomena in Autism
		Lower Frontal -Posterior synchronization	Smaller Corpus callosum	Correlation between Corpus Callosum and synchronization	Less frontal activation	More Posterior activation	
Executive	Tower of London puzzle (Just et al., 2007)	Yes	Yes	Yes	MFG	LG	
Executive	Inhibition of high-level response (Kana et al., 2007)	Yes	-	-	R IFG	-	Difficulty with more complex problems
Executive	Inhibition of high-level response (Solomon et al., 2009)	Yes	-	-	MFG, R SFG	-	Impaired high-level inhibition
Language	Visual imagery in sentence comprehension (Kana et al., 2006)	Yes	Yes	Yes	L IFG, L MFG	L IPS, R SPL	Imagery activation even for more abstract sentences ("thinking in pictures")
Language	Sentence comprehension (Just et al., 2004)	Yes	-	-	L IFG, MFG	L STG	Difficulty with complex syntax; good word-reading
Memory	Working memory for alphabetic letters (Koshino et al., 2005)	Yes	-	-	L IFG, L MFG	L IT	Letters are coded relatively more visually than verbally
Social	Theory of Mind: animation (Kana et al., 2009)	Yes	Yes	-	MFG	R TPJ	Theory of mind difficulties
Social	Face memory (Koshino et al., 2008)	Yes	-	-	L IFG, MFG	-	Faces are treated as relatively more visual than social objects
Perception	Embedded Figures Test (Damarla et al., 2010)	Yes	Yes	Yes	MFG	R IPS, R SPL	Less interference from higher-order information
Resting State	Fixation (Cherkassky et al., 2006)	Yes	Yes	Yes	-	-	
Resting State	Fixation (Kennedy and Courchesne, 2008)	Yes	Yes	Yes	-	-	
Resting State	Fixation (Monk et al., 2009)	Yes	Yes	Yes	-	-	
Diffusion Tensor Imaging	No Task (Alexander et al., 2007; Bamea-Goraly et al., 2004; Keller et al., 2007)	-	Lower integrity		-	-	

## RELATION TO OTHER THEORIES OF AUTISM

This section compares underconnectivity theory with previous theoretical approaches to autism, such as the theories of weak central coherence (Frith, 1989), impaired complex information processing (Minshew et al., 1997), enhanced perceptual functioning (Mottron, Dawson, Soulières, Hubert, & Burack, 2006), mindblindness (Baron-Cohen, 1995), impaired social processing and motivation (Dawson et al., 2002), and longer-distance cortical communication. Each of these theories captures some fundamental aspect of autism, and all of them are at least partially correct. However, many of these predecessor theories were developed before extensive brain-imaging studies of autism had been performed, focusing instead on behavioral data, so they tend not to be grounded in a biological substrate. We propose that it is this biological substrate that accounts for the diversity of symptoms supporting the diverse theories of autism. The underconnectivity theory provides a basis for comparison with some of the preceding theories described below.

### *Weak Central Coherence (WCC) Theory*

Frith's (1989) theory of weak central coherence (WCC) attempts to explain the tendency in autism to focus on details at the expense of broader integrative information processing. Frith suggested that the flow of normal thought is similar to the flow of a river that imposes coherence among contributing streams or inputs; the theory hypothesizes that, in autism, there is weaker central coherence among the contributing streams of thought. The excellence of this analogy distracts from WCC theory's absence of a plausible underlying biological mechanism, although recently Frith and colleagues have attempted to relate neuroimaging results to WCC. By contrast, underconnectivity theory links together abnormalities in underlying biological structures (i.e., white matter tracts) and cortical communication processes with psychological processes (i.e., inter-regional communication and the sharing of representational elements). As with WCC theory, underconnectivity theory predicts weak coherence among ongoing processes, but specifically when the processes include communication between frontal and posterior areas. Underconnectivity theory interprets weak central coherence as an emergent system property arising from this reduced frontal-posterior communication bandwidth, which does not require the existence of a mechanism that arranges coherence, as WCC implicitly posits. Moreover, the 4CAPS computational model suggests that reduced long-distance bandwidth may result in more autonomous processing centers, resulting in impairments in functions involving a frontal contribution, particularly when a large processing load is being imposed on the system. In sum, WCC theory provides a useful organizing analogy that is applicable to a broad range of phenomena in autism, whereas underconnectivity theory additionally proposes an underlying mechanism that relates the biological and psychological levels.

### *Autism as a Complex Information Processing Disorder*

Minshew and her colleagues (Minshew & Goldstein, 1998; Minshew et al., 1997; Williams, Goldstein, & Minshew, 2006) have observed impairment in autism across many domains when the complexity level of information processing is high. Lower-level processes are spared or even enhanced, but as tasks become more complex, impairment gets more pronounced. In this theory, complexity is not rigorously defined, but it may refer to a higher level of abstraction that the task requires. Underconnectivity theory attributes the complex information processing deficits to a specific biological substrate, frontal-posterior brain connectivity. The difficulties in complex information processing may occur when frontal involvement is mandatory for normal performance (presumably to support the high levels of abstraction), but in autism, the poor frontal-posterior connectivity (abnormally limited bandwidth) undermines the frontal contributions and hence performance is impaired.

Related to the description of autism as a complex information processing disorder is the *executive dysfunction theory of autism* (Hughes, Russell, & Robbins, 1994; Pennington & Ozonoff, 1996), which notes that executive dysfunction in autism tends to be observed in complex tasks. According to under-connectivity theory, executive dysfunction could arise from poor connectivity between the posterior regions and the frontal areas that perform executive functions. For instance, a problem-solving task like TOL requires the coordination between executive (frontal) and spatial (parietal) brain areas. Any limitation of such coordination in autism may manifest itself as a deficit in problem-solving or in executive functioning.

### *Enhanced Perceptual Functioning (EPF)*

Mottron and his colleagues (2006) have hypothesized that autism involves enhancement of certain types of perceptual processing. They argue that, compared to control participants, perceptual processing in autism is locally oriented; includes enhanced low-level discrimination and perception of simple static stimuli; and entails greater use of posterior brain regions in complex visual tasks. Individuals with autism have diminished perception of complex movement, and low-level information processing is autonomous from higher-order operations. This extensive list of the perceptual characteristics in autism bears a good correspondence to the underconnectivity theory position, particularly the theory's postulation of increased autonomy of posterior centers.

Specifically, the bias in autism towards local rather than global processing is attributed by underconnectivity theory to the lower frontal-posterior communication bandwidth, resulting in the degradation of top-down or global influences. Underconnectivity theory also suggests that functional connectivity among posterior areas may actually be *higher* in autism than controls because the decrease in frontal-posterior traffic could lead to increased

posterior autonomy and posterior-posterior bandwidth. In sum, any enhancements in autism in some lower-level perceptual functions may arise secondarily from poorer connectivity between frontal and more posterior (perceptual) areas. Moreover, underconnectivity theory provides a biologically based explanation for some of the perceptual phenomena on which the EPF approach focuses.

### *Mindblindness*

The mindblindness theory (Baron-Cohen, 1995) suggests that the deficits seen in individuals with autism during Theory of Mind (ToM) processing are centrally causal to the disorder. Many behavioral and neuroimaging studies have demonstrated this deficit (e.g., Baron-Cohen, 1989; Happe, 1995; Tager-Flusberg, 1992; Castelli, Frith, Happe, & Frith, 2002; Kana et al., 2009) and its biological substrates in the right posterior superior temporal sulcus and the nearby temporo-parietal junction, and the medial frontal area. Underconnectivity theory posits that, in autism, bandwidth limitations impede the normal communication between these areas, resulting in the observable deficits in ToM.

A recent fMRI study explicitly measured the functional connectivity between the frontal and posterior regions of the ToM cortical network (Kana et al., 2009). The participants viewed an animated interaction between two geometric figures, including trials in which the intentionality of the figures could be inferred (the ToM condition). In the original PET study of ToM using these figures, Castelli et al. (2002) found that the correlation across subjects between the average level of activity in the superior temporal sulcus (an area associated with ToM and the perception of biological motion) and extra-striate cortex was lower across autistic participants than across control participants. Using fMRI, Kana and colleagues (2009) found a reliable reduction in the *synchronization* of the activation (across points in time) between frontal and posterior ToM areas in the group with autism relative to the control group during the ToM task, as the underconnectivity theory predicted.

Underconnectivity theory is a more general approach than ToM or mind-blindness theory, which can be viewed as an instance of reduced frontal-posterior connectivity. The specific roles of the frontal and posterior components of the ToM network are still debated; however, our studies suggest that these cortical areas work together during ToM processing and that this collaboration is disrupted in autism.

### *Impaired Social Processing and Motivation*

Some researchers have attributed a central or causal role to the prominent social interaction deficits seen in individuals with autism (Dawson et al., 2002; Schultz et al., 2003). Contemporary brain-imaging studies of autism have

discovered aberrations in cortical processing of social tasks. For example, one of the key brain areas involved in processing faces (the fusiform face area, or FFA) demonstrates hypoactivation with some displacement of location for people with autism compared to controls (Schultz, 2005; Schultz et al., 2000). However, by expanding the focus to the cortical *network* involved in such tasks, the abnormality can be seen as a result of underconnectivity. In a study using the n-back working memory task with faces as stimuli, Koshino and colleagues (2008) found abnormal FFA activation, but also reported several other network disturbances. First, the autism group had lower functional connectivity between the FFA and frontal areas than did the control group. Second, individuals with autism had less activation in the right posterior ToM areas (posterior middle and superior temporal area), suggesting that social processing was evoked to a lower degree in autism. Because FFA dysfunction is not the only abnormality in neural functioning of social processes, it appears that autism is not just a social processing deficit, but a neural systems disorder, involving abnormal interaction among areas responsible for processing social stimuli, such as faces.

Another proposed explanation for impaired social processing in autism centers around atypical development of the ability to *initiate* joint attention (IJA) (Mundy, Sigman, & Kasari, 1994; Mundy, Sullivan, & Mastergeorge, 2009). This theory suggests that social referencing and learning depends on the initiation of joint attention, which requires close collaboration between temporo-parietal and frontal areas. This proposal is consistent with the under-connectivity theory in that the frontal-posterior communication system is compromised in autism, which would lead to an impairment of IJA as well as a relative preservation of joint attention capabilities that do not involve frontal areas.

Other social processing tasks that are impaired in autism can also be interpreted as connectivity problems. One study investigated the processing of the gaze of an avatar, who looked either towards a visual stimulus in its field of view (an appropriate behavior) or inappropriately away from the stimulus (Pelphrey, Morris, & McCarthy, 2005). For control participants, the posterior superior temporal sulcus (STS) activated differentially to the avatar's appropriate versus inappropriate gaze shifts; however, there was no differential response in STS in participants with autism. The authors suggested that "[i]n individuals with autism, the connection between higher level [frontal] systems and the STS region may be broken, and thus the higher level systems do not engage and maintain activation in the STS region." Again, this pattern is consistent with the theory of frontal-posterior underconnectivity.

Overall, complex social processing involves many brain regions, usually including frontal areas. For proper functioning, these regions require intact connectivity that enables effective communication of information among them. The high informational demands of these tasks are often overlooked, yet the complexity of social thought necessitates a communication infrastructure that

is no less sophisticated than any other type of thought. Perhaps social processing requires an even more finely integrated system, which could explain why social deficits are particularly apparent in autism.

### *Long-Distance Connectivity*

Some researchers have suggested that long-range, but not short-range, brain connectivity may be disrupted in autism (Belmonte et al., 2004; Lewis & Elman, 2008). These theorists suggest that the enlargement of brain size in autism during the early stages of development, described above (Aylward, Minshew, Field, Sparks, & Singh, 2002; Courchesne et al., 2001; Courchesne, Carper, & Akshoomoff, 2003; Piven et al., 1995; Sparks et al., 2002), increases the cortical distance between key processing centers, resulting in disruption of distant inter-regional communication. Specifically, this hypothesis predicts that individuals with autism will have lower fMRI-measured functional connectivity than the control group only for long-distance pairs of areas of activation.

In order to test this hypothesis, we reanalyzed the functional connectivity data in the Just et al. (2007) Tower of London study described above. From 15 functional regions of interest (ROIs), there were 105 pair-wise measures of  $z'$ -transformed functional connectivity. The pairs were categorized as either long- or short-distance using a median split of the Euclidean distances between the centroids of the two ROIs. Contrary to the long-distance hypothesis, there was no interaction between the group difference in functional connectivity with the distance between two ROIs ( $F(1, 34) = 0.27, p = .61$ ). Although the functional connectivity decreased with Euclidean distance between ROI centroids ( $F(1, 34) = 324.85, p < .0001$ ), it did so similarly for both autism and control groups. By contrast, underconnectivity theory posits that the connection distance is not as critical as whether the connection is between a frontal area and a posterior cortical area. Indeed, the underconnectivity theory correctly predicts an interaction between group and the frontal-parietal vs. other-pairs variable ( $F(1, 34) = 6.30, p < .02$ ), with the autism group showing reliably lower functional connectivity only for frontal-parietal pairs (Just et al., 2007).

While it may seem improbable that a neurobiological factor could selectively affect frontal-posterior tracts, but not other long-distance connections, it is actually biologically plausible. The frontal lobes are implicated in many of the developmental mechanisms that may be relevant to autism, including glial activation and neuroinflammation (Vargas et al., 2005); minicolumnopathy (Casanova et al., 2006); increase in neuron number (Courchesne et al., 2011); and early brain overgrowth (Carper et al., 2002, Carper & Courchesne, 2005; Herbert et al., 2004). Given the protracted maturation of frontal lobe circuitry, these abnormalities could affect only frontal-posterior tracts, resulting in underconnectivity specifically along white matter connecting cortical centers in those areas (Courchesne & Pierce, 2005a, 2005b). Based on the fMRI

studies of functional connectivity and the DTI studies of structural connectivity reviewed here, it is clear that connections involving the frontal lobes are affected more than others.

## QUESTIONS RAISED BY THE THEORY

The underconnectivity theory provides a useful theoretical framework, but it has not yet been applied to investigations of several outstanding questions about autism. In its current form, we view the theory as preliminary, anticipating that future research will result in considerable refinement, expansion, and modification. Below we raise some key, but unanswered, questions generated by the theory.

### *Other Connectivity Disturbances*

Several types of other connectivity abnormalities besides functional underconnectivity could emerge, through the use of fMRI or other techniques. Further study could find alterations in connectivity among neural systems or intraregional communication, including the possibility of *increased* connectivity between some areas. Other techniques that could be brought to bear on studies of neural connectivity in autism include histology, electrophysiology, morphometry, and diffusion imaging. Specifically, it will be most interesting to use some combination of these approaches to investigate white matter and gray matter abnormalities, as well as the relation between functional and anatomical abnormalities in autism.

### *Task Effects in Connectivity*

Although we have reported functional underconnectivity in a number of different types of thinking relevant to autism (executive function, perception, language, social processing, inhibition), this phenomenon has not been studied in many other types of relevant tasks, including tasks without frontal involvement, tasks with non-visual input (auditory, haptic, gustatory, or olfactory), and simple motor tasks. We assume that the disruption in connectivity only applies between frontal and posterior regions because the studies supporting this theory focused on tasks with frontal involvement, but ensuing studies could falsify this assumption.

### *Investigation with Lower-Functioning and Younger Participants*

Most of the functional connectivity studies to date have been conducted with high-functioning individuals with autism, but this research should be extended to include lower-functioning participants. Although it is more difficult to

acquire imaging data from low-functioning individuals, it should be possible to study this population's resting state functional connectivity, which has been shown to be impaired in high-functioning autism (Cherkassky et al., 2006; Kennedy & Courchesne, 2008; Monk et al., 2009). Another extension might examine younger participants with autism in order to understand the ontology of functional underconnectivity and the development of white matter that supports cortical connectivity.

### *Relation of Underconnectivity Theory to Other Clinical Populations*

Comparison of possible cortical communication disturbances across neurological conditions could be informative about the nature of connectivity. For example, Herbert et al. (2004) found several areas of white matter that were larger in autism and also in participants with developmental language delay, compared to controls, although there were some areas affected only in one disorder and not the other. Understanding the patterns of commonalities and specificities in disordered anatomical and functional connectivity may reveal possible branching points in development of different syndromes.

Another disorder that involves disruption of white matter, like autism and developmental language delay, is dyslexia (e.g., Deutsch et al., 2005). Recently, we demonstrated that the white matter abnormalities associated with poor reading skills in children can be improved with training (Keller & Just, 2009b). If white matter is modifiable with behavioral therapies, as this study showed, there is hope that behavioral therapies for autism might also be able to modify a connectivity deficit.

### *Etiology of Underconnectivity*

Underconnectivity theory does not attempt to account for the pathophysiological origins of autism, although it provides guidance for such a search. Under-connectivity theory could be easily linked to genomics, since it already integrates some of the known pathophysiological and neuropsychological aspects of autism. For instance, one tentative hypothesis proposes that autism is caused by developmental dysregulation of inter-regional brain connectivity (Geschwind & Levitt, 2007).

## SUMMARY

Underconnectivity theory proposes that autism can be characterized as a neural systems disorder marked by frontal-posterior communication impairments caused by lowered bandwidth. The abnormal flow of information between frontal and posterior areas results in deficits in tasks that require substantial frontal contributions, as well as increased reliance on posterior cortical

regions. This increased dependence on processing in more posterior regions could hamper performance during tasks that necessitate inputs from the frontal cortex, including for higher-level strategies and concepts. The diversity of behavioral symptoms in autism may be due to the wide range of activities that involve substantial frontal participation.

The 4CAPS computational model of autism (Just et al., 2012) provides a sufficiency proof of underconnectivity theory. By recreating the conditions proposed by underconnectivity theory—that is, lower frontal-posterior bandwidth and more autonomy of posterior cortical centers—the model reproduces several key phenomena observed in fMRI studies of autism using the TOL task, including observed reaction times, fMRI activation, and group and individual differences in functional connectivity. In addition, the model accounts for group differences in a wide variety of tasks across different domains (as shown in Table 3.1).

Although white matter differences form at least part of the biological basis of autism, future studies should search for concomitant or even causal gray matter abnormalities. New imaging technologies can trace white matter tracts in great detail, thereby transforming some of these theoretical considerations into empirical issues. A theory of frontal-posterior underconnectivity in autism provides an initial framework to guide such future research.

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## NOTE

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