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SYMPOSIUM—INTRODUCTION

Cognitive neuroscience of autism

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The past decade has witnessed an exponential growth in research on autism, a neurodevelopmental disorder affecting social, language, communication, and behavioral development. This growth is fuelled by many factors, including rising prevalence rates; increased media attention and public awareness; the creation of new parent-based research foundations; and targeted federal funding opportunities. Researchers have taken advantage of new theoretical frameworks and exciting scientific technologies that are now being employed to address key questions about the underlying causes and pathophysiology of autism. Advances in developmental neuropsychology and cognitive neuroscience, including the application of magnetic resonance imaging (MRI) methods, have had a particularly significant impact in providing insights into the neurobiology of autism. Several of these key advances, which are closely tied to changes in the way the developmental phenotype of autism has been conceptualized, are highlighted in the papers comprising this Symposium issue.

AUTISM SPECTRUM DISORDERS

The core features of autism as first described by Kanner (1943) include impairments in social functioning, communication, as well as repetitive behaviors, resistance to change and restricted interests. These are the clinical symptoms that are shared by all individuals with an autism diagnosis of differing severities. In addition to the core features, there are numerous other characteristics seen in many individuals with autism, but the hallmark of these related characteristics is *heterogeneity* in their expression. For example about 50% of the autism population has co-morbid mental retardation, and about 70% has impaired language, which goes beyond the universal difficulties in communication (Lord & Rutter, 1994). Variability in symptom severity, mental retardation and language are reflected in diagnostic categories, which include autistic disorder, pervasive developmental disorder-not otherwise specified, and Asperger syndrome (American Psychiatric Association, 1994). Collectively, these are referred to as autism spectrum disorders (ASD), reflecting the assumption that this set of complex disorders share an underlying etiology and pathology (Di-Cicco-Bloom et al., 2006). Yet the challenge for researchers is to balance this assumption against the known individual variation and heterogeneity.

Not surprisingly from a clinical standpoint, much of the focus in diagnostic evaluations and research has been on the impairments that severely affect adaptive functioning. At the same time, ASD may also include areas of spared or even superior abilities. These include savant skills (e.g., calendrical or other mathematical calculation skills; musical talent; artistic ability), good memory and enhanced visual-spatial attentional skills. A complete understanding of the pathophysiology of ASD will only be possible by investigating the strengths as well as the weaknesses together with the heterogeneity in expression that is encompassed by the ASD phenotype.

In recent years, the deeper significance of ASD as a *developmental* disorder has begun to be recognized. As such, classic neuropsychological models of brain organization have only limited application (cf. Karmiloff-Smith, 1997) although there is no evidence that the essential organization of brain functions (e.g., vision, memory, language) is fundamentally different in ASD than in the normal population. The developmental nature of ASD is manifest in alterations in the *timing* and *rate* of brain and behavioral growth. These changes in developmental trajectories, which may have their roots in the prenatal period of brain development (e.g., Kemper & Bauman, 1993), typically begin some time during the first two years of life and appear to continue through childhood. These alterations in development have long been known at the behavioral level, based on retrospective parental reports of the emergence of autism symptoms after a period of normal development in early infancy. Current prospective studies of infants at risk for autism have confirmed these reports, showing that ASD is initially observed in the

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failure to acquire key social-communicative and language milestones and subtle motor patterns at around the age of 10–15 months (Yirmiya & Ozonoff, 2007).

NEUROBIOLOGY OF ASD

Neuroanatomical studies of ASD complement these behavioral findings. Enlarged head size was initially observed by Kanner (1943) in some of his patients, and then followed up by studies of head circumference, a proxy for brain size (Lainhart et al., 1997). These observations, coupled with recent MRI studies of very young children with ASD, have led to one of the most significant theories of developmental neuropathology in autism. Several lines of evidence suggest that some time during the second half of the first year of life, the brain undergoes a period of accelerated growth followed by a slowing or deceleration (e.g., Courchesne et al., 2003; Hazlett et al., 2005). Thus far, this hypothesis of early brain overgrowth in ASD has been based mostly on cross-sectional studies that await confirmation from prospective longitudinal investigations including detailed information about both behavioral and brain developmental trajectories. The hypothesis also opens up several follow-up questions: Does brain overgrowth affect all areas of the brain or is it region specific? How do changes in developmental timing and rate of brain development influence the formation of neural circuitry associated with specific functions, including regional connectivity? Does it affect changes in both white and grey matter equally? What accounts for the brain overgrowth—numbers of neurons; synaptic development; failure in pruning, etc.? Do environmental factors (e.g., postnatal experiences and interactions with the social world) contribute or modify these atypical developmental patterns? A complete account of the neuropathology of ASD must address these kinds of questions. To accomplish this goal will take a multidisciplinary program of research, within which cognitive neuroscience can play a central role.

REGIONAL SPECIFICITY

MRI studies of children and adolescents with ASD have identified abnormalities in the volume and in some cases shape and sulcul patterns in brain regions that are associated with the core impairments. As summarized by Amaral and his colleagues (Amaral et al., 2008), these include areas associated with social impairments (frontal and anterior cingulate cortex, superior temporal sulcus, fusiform gyrus, posterior parietal cortex and amygdala), language and communication impairments (inferior frontal gyrus, thalamus, cerebellum) and repetitive behaviors (basal ganglia).

NEURAL BASIS OF FACE PROCESSING

Given the centrality of the social impairments, these have been the focus of many behavioral and neuroimaging studies in an effort to understand the neurocognitive mechanisms that underlie them. For human social interactions, faces are highly significant stimuli necessary for identifying individuals, communication, and emotional expression. People with autism have deficits in face processing that encompass all these components (Sasson, 2006). The importance of the fusiform gyrus in face processing, specifically the face fusiform area (FFA), has led to a number of functional MRI studies of adults with ASD, designed to investigate whether abnormalities in activation to faces are found in this region. Early studies reported that, indeed, there was absent or reduced FFA activation in ASD (e.g., Schultz et al., 2000), however later studies suggested that this reduction was most likely related to failure to look directly at the central features of the face, especially the eyes (Dalton et al., 2005; Hadjikhani et al., 2004). The paper by Bookheimer and colleagues (Bookheimer et al., 2008, this issue) follows this line of work, comparing children and adolescents with ASD as they processed upright and inverted faces. As in other recent investigations, these researchers did not find group differences in FFA activation. However, the ASD group showed reduced activation in other components of the neural circuitry underling social information processing, including the amygdala as well as frontal-parietal areas that are thought to be part of the human mirror neuron system.

Conturo and his colleagues (Conturo et al., 2008, this issue) also pursue the neural circuitry related to face processing, exploring the connectivity between the FFA and the hippocampus and amygdala. Using MR diffusion tensor imaging (DTI) and diffusion tensor tracking (DTT), they found reduced across-fiber diffusivity in the hippocampus-FFA pathway in the right hemisphere, which was significantly related to poor face recognition scores in the ASD group. This finding is interpreted as evidence for early pathological processes affecting axonal development. Conturo et al., 2008, also found increased diffusivity in this pathway in the left hemisphere as well as in both amygdala pathways (left and right hemispheres) which they interpret as evidence for decreases in myelination and/or axonal loss that are more likely occurring later in development. Their findings complement the picture emerging from structural MRI and neuropathological studies of ASD regarding the atypical developmental trajectory of the amygdala (Nacewicz et al., 2006; Schumann et al., 2004).

Poor face recognition (and FFA activation) in ASD is related to the amount of time spent looking at the eye region of the face. Why do individuals with ASD avoid looking at eyes? Is it because they lack social interest or is it to actively avoid a stimulus that they find aversive? Joseph and his colleagues (Joseph et al., 2008, this issue), investigate this question using psychophysiological measures, specifically skin conductance responses (SCR) to faces. They found that the SCRs in the ASD group were significantly higher than in the control group, and that the amplitude of SCRs to faces with a full view of both eyes directed toward the observer, was inversely related to accuracy on a face rec-

ognition task. Thus, these results provide support for the hypothesis that direct eye contact is overly arousing for people with ASD and interferes with their processing of faces. This hypothesis fits well with the findings from the neuroimaging studies that also implicate the amygdala as playing a major role in the neural systems associated with face processing as well as with broader social impairments in this population (cf. Nacewicz et al., 2006).

DEVELOPMENTAL HISTORY

There are major limitations in the application of sophisticated cognitive and functional imaging methods to studies of very young children. Yet, given the emphasis on atypical developmental patterns, especially during the early years of childhood, it is critical not to neglect this age group. The study reported in the paper by Munson et al. (2008, this issue) takes advantage of neuropsychological tasks that are putatively associated with prefrontal and temporal lobe functioning to predict individual differences in the rate of social communicative functioning in a relatively large sample of preschoolers with ASD. Their outcome measures were social and communication subdomain scores on the Vineland, which correlate with symptom severity in ASD. Munson et al. (2008), found that performance on tasks tapping reward learning, deferred imitation and novelty preference, which depend on the integrity of ventromedial prefrontal and medial temporal lobe cortical systems (Diamond, 2002; Zelazo et al., 2005), predicted rate of social and communication development. In contrast, tasks tapping spatial memory were not predictive. The specificity of the relationship between these neuropsychological tasks and rate of development underscores the importance of conducting longitudinal studies that capture trajectories over time.

FUNCTIONAL LATERALITY

The majority of children with ASD are delayed in the onset of language milestones. While some of these children catch up with their peers, subtle differences in the efficiency of processing linguistic stimuli, including phonological, semantic and grammatical forms may persist through adulthood, even though they are not reflected in standardized language test scores (Tager-Flusberg et al., 2005). Initial functional imaging studies of language processing in high functioning adults with ASD found reduced activation in Broca's area, and reduced functional connectivity between Broca's and Wernicke's areas in the left hemisphere (e.g., Harris et al., 2006; Just et al., 2004) that may underlie these subtle impairments. The study by Knaus et al. (2008, this issue), involved adolescents with ASD as well as matched controls to explore activation in response to a semantic generation task. The inclusion of adolescents is significant given that cortical areas associated with language functions continue to develop through the end of adolescence. Thus, for the participants in this study, the neural bases of language would not have reached maturity and the findings might be more revealing on ongoing developmental processes. In contrast to the earlier research, the adolescents in this study showed increased activation in Broca's area, relative to controls but it was less left lateralized and not correlated with activation in Wernicke's area. Reduced functional lateralization may be the result of delayed language development a pattern found in most children with ASD.

The impact of early language delay on lateralization of function is explicitly explored in the paper by Takarae and his colleagues (Takarae et al., 2008, this issue). They divided their sample of participants with autism into those with and those without language delay. The participants were given tasks tapping visual motion coherence and visual pursuit, which are known to be impaired in ASD, presenting them separately to the left and right visual fields. Performance on both tasks was significantly correlated but the patterns of impairment differed based on history of language delay. The group with language delay had bilateral impairments on the motion coherence tasks whereas the group without delay had impairments only in the left hemifield. This group also failed to show the typical right directional advantage in the visual pursuit tasks. The study underscores the significance of differences in early developmental trajectories in predicting later sensori-motor functioning in ASD.

NEURAL BASIS OF UNIMPAIRED COGNITION IN ASD

One of the domains in which people with ASD often excel is visual search tasks (e.g., O'Riordan, 2004). Individuals with ASD are faster and more efficient in determining the presence or absence of a target stimulus, even under very challenging conditions. The paper by Keehn et al. (2008, this issue) explores the neural underpinnings of this area of strength in adolescents with ASD to investigate whether it is based on greater reliance on lower level occipital regions or on top-down control processes. Unexpectedly, they found evidence for both lower- and higher-level involvement in the search efficiency for the ASD group, with increased activation in the frontal-parietal network associated with visual attention. Furthermore, their findings did not support the hypothesis that there is decreased connectivity in this network, suggesting that underconnectivity is not a hallmark feature of all aspects of brain functioning in ASD (cf. Just et al., 2004).

CONCLUSIONS

Taken together, the papers in this symposium highlight the range of methods and approaches that are currently employed in clinical investigations of the underlying pathophysiology of ASD. Several of the papers report on neuroimaging studies that have provided important insights into the neural mechanisms associated with impaired as well as spared aspects of functioning in this population. No single type of pathology or atypical pattern (e.g., underconnectivity, altered

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laterality, hypoactivation) is seen across all studies; rather the findings suggest regional and system-specificity, depending on the types of task and domain under investigation. Because of limits in the application of fMRI to higher-functioning older individuals, the picture we have from studies on the cognitive neuroscience of autism is based on a relatively small proportion of the population and does not capture the full range of phenotypic expression for either behavior or brain function. Moreover, none of the research to date using fMRI has followed the same individuals over time so we have no idea how brain organization and functional activity may change over time.

Studies using structural MRI (with sedation), neuropsychological or other behavioral methods can be conducted with a broader range of individuals, including very young children. These are especially important given all the evidence that ASD is the result of abnormalities in the rate of early brain development. Future research needs to build on the cross-sectional studies that dominate the field to provide more detailed understanding of the developmental changes that define the syndrome. It will also be important for future research on the developmental neurobiology of ASD to intersect more closely with genetics studies. Of special note is the recent discovery that several of the genes that have been found to be implicated in autism play an important role in synaptic changes that are associated with learning (Morrow et al., 2008). Expression of these genes seems to be dependent on early experience, which may account for the appearance of autism symptoms toward the end of the first year of life. These symptoms in social-communication are critically dependent on social experiences during this period of development. As work advances in both genetics and cognitive neuroscience, we will begin to understand more deeply the mechanisms that lead to autism. In turn, this knowledge has the potential to lead to novel interventions that may prevent the emergence of this devastating disorder.

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