

Model syndromes for investigating social cognitive and affective neuroscience: a comparison of autism and Williams syndrome

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Autism and Williams syndrome are genetically based neurodevelopmental disorders that present strikingly different social phenotypes. Autism involves fundamental impairments in social reciprocity and communication, whereas people with Williams syndrome are highly sociable and engaging. This article reviews the behavioral and neuroimaging literature that has explored the neurocognitive mechanisms that underlie these contrasting social phenotypes, focusing on studies of face processing. The article concludes with a discussion of how the social phenotypes of both syndromes may be characterized by impaired connectivity between the amygdala and other critical regions in the 'social brain'.

Keywords: autism; Williams syndrome; face processing; emotion processing; amygdala

INTRODUCTION

For the past two decades autism, (ASD)¹ and Williams syndrome (WMS) have captured the interest and imagination of cognitive neuroscientists. These neurodevelopmental disorders present striking phenotypes that hold out the promise of advancing our understanding of the biological bases of essential human capacities including language, visual-spatial and social cognition. In this article, we selectively review some of the research that has investigated social cognition in these disorders with a specific focus on face processing to explore what we have learned about the neurocognitive mechanisms that underlie human social behavior.

ASD and WMS are examples of genetically based syndromes: WMS is caused by a hemizygous deletion of about 21 genes on chromosome 7 (Osborne, 2006), whereas autism is a highly heritable complex disorder that is assumed to involve elevated risk alleles on several genes that have yet to be identified (Santangelo and Folstein, 1999). The specific genetic abnormalities associated with ASD and WMS are presumed to disrupt normal brain development, which leads to the distinct phenotypic outcomes associated with each disorder. Even though ASD and WMS may be defined by highly characteristic and distinctive behavioral profiles there is considerable heterogeneity in the expression of core

phenotypic features as well as in IQ and language skills. This variability within each syndrome is important in considering the design and interpretation of experimental studies on social cognition and may contribute to the often conflicting findings that are reported in the literature (Tager-Flusberg, 2005; Sasson, 2006).

The most salient difference between people with ASD and people with WMS is their social behavior. ASD is defined on the basis of profound impairments in social functioning, including difficulties interacting with others, attending to people, and decoding nonverbal cues, and impairments in social emotional reciprocity. In contrast, people with WMS show an unusually strong interest in people, including strangers; they are warm and engaging and seem highly empathic toward others. Side-by-side, these syndromes appear to be mirror images of one another, suggesting that what is impaired in ASD may be specifically spared in WMS. This potential for a double dissociation has fueled the notion that ASD and WMS may offer unique perspectives on the genetic and neurobiological bases of social cognitive and affective processes.

Social cognition encompasses a wide range of abilities including interpretation of cues, social attribution, communication, interaction and social inferencing, all subserved by a set of complex interacting distributed neural systems (e.g. Ochsner, 2004; Amodio and Frith, 2006). Probably the most significant stimulus for human social information processing is the *face*. Faces are important for identifying one's social partner, interpreting communicative intent and emotional response as well as for inferring more complex social attributions, stereotypes and appraisals. It is, therefore, not surprising that so many social cognitive studies have focused on face processing, including studies on ASD and WMS.

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¹ Because studies on social cognition have often included different subtypes of individuals with autism spectrum disorders, including classic autism, PDD-NOS or Asperger syndrome, we use the acronym ASD throughout this review.

FACE RECOGNITION

The remarkable ease with which people can instantly recognize a face has been argued to depend on *holistic* perceptual and encoding processes, as evident, for example, in our superior ability to recognize faces in upright rather than inverted orientation (Farah *et al.*, 1995). Changing the orientation disrupts the normal holistic processing of faces, forcing one to rely more on featural processing. At the neural level, the so-called fusiform face area (FFA) in the fusiform gyrus is considered to be an area specialized for faces as one component in a more distributed neural system (Haxby *et al.*, 2002), and is presumed to be functionally related to holistic processing (Kanwisher, *et al.*, 1997). Holistic face processing emerges early in development (Tanaka and Farah, 1993; de Haan and Nelson, 1999). One study, using PET, found FFA activation to a woman's face in 2-month-old infants (Tzourio-Mazoyer *et al.*, 2002). While the foundations for specialized face processing mechanisms are present during the first few months of life, developmental changes take place during childhood, especially in the processing of higher order configural relations in faces, which accounts for the increasing expertise in face recognition in older children (Mondloch *et al.*, 2003).

At the level of face recognition skills, there are significant and robust differences between ASD and WMS. On standardized tests of face recognition, children and adults with ASD perform well below standard norms (Klin *et al.*, 1999; Schultz, 2005), whereas people with WMS generally perform within the normal range and significantly better than mental-age-matched controls (Bellugi *et al.*, 1994; Tager-Flusberg *et al.*, 2003). These differences are consistent with the contrast between a syndrome characterized by severe social impairment and a syndrome characterized by unusual social interest. Yet, despite these differences in face recognition ability, it has been claimed that both ASD and WMS involve the same atypical face processing strategies: a failure to encode faces holistically and a greater reliance on local part processing (e.g. Elgar and Campbell, 2001; Karmiloff-Smith *et al.*, 2002).

Early studies by Langdell (1978) as well as Hobson and his colleagues (1988) demonstrated that children with ASD do not show the inversion effect. Langdell also noted that the children with ASD in his study relied more on the mouth for recognizing faces, rather than primarily on the eyes, which is the more typical pattern. Joseph and Tanaka (2003) followed up on these studies using a whole-part paradigm, which compares recognition of face features (eyes, mouth) presented in the context of the whole face or in isolation for upright and inverted faces (Tanaka and Farah, 1993). Children with ASD were compared to controls using a match-to-sample procedure. Performance of both groups was significantly better for the whole face in the upright condition, suggesting holistic processing strategies. However, for the children with ASD, this advantage only held on trials on which recognition depended on

the mouth, not the eyes. The findings suggest that children with ASD do not have a global impairment in holistic processing of faces, but rather that the difference for this population lies in the processing of eyes.

Early studies on WMS claimed that people with WMS do not show the inversion effect and hence fail to process faces holistically (Deruelle *et al.*, 1999; Karmiloff-Smith, 1997). However, these studies included small samples of widely varying ages and ability levels. Tager-Flusberg *et al.* (2003) used the same whole-part task employed by Joseph and Tanaka (2003) with a large group of adolescents and adults with WMS and age-matched controls. Both groups showed the same pattern of results: better performance in the whole-face condition for upright but not inverted faces. This pattern held for all face features, including the eyes, and provided strong evidence that people with WMS process faces holistically. There is still a debate over whether people with WMS are impaired in configural processing of higher order relations in faces (Karmiloff-Smith *et al.*, 2004). However, this impairment may be more related to developmental delays and mental retardation than to syndrome-specific differences in face processing mechanisms.

The evidence from these studies on face recognition does not support the hypothesis that people with ASD or WMS process faces atypically; both groups are able to process faces holistically (Jemel *et al.*, 2006; Tager-Flusberg and Plesa Skwerer, 2006). In the case of ASD, however, there are unique differences in the way that *eyes* are processed. Children with ASD rely less on the eye region of the face for recognizing people, and holistic face processing strategies are disrupted when recognition depends on discriminating eyes. These findings are consistent with studies that have employed eye-tracking methods to determine fixation points and scan paths when people with ASD observe social stimuli. Pelphrey and his colleagues reported that a small group of young adults with ASD spent significantly less time than controls looking at internal facial features on static faces; instead they tended to scan either peripheral features (e.g. hair line) or outside the face. Using dynamic social videos, Klin and his colleagues (2002) found that compared to controls, adolescents and adults with ASD spent less time looking at eyes and relatively more time looking at the mouths of actors engaged in conversation. These findings demonstrate that people with ASD show atypical attention to eyes which presumably influences their face recognition skills. To date, there have been no comparable studies using eye-tracking methods on people with WMS, so we do not know whether they too deploy unusual attentional strategies when they look at faces.

Several studies have investigated brain activation patterns to faces in people with ASD using fMRI. Schultz and his colleagues (2000) were the first to report that adults with ASD fail to activate FFA when engaged in a face

discrimination task. In comparison to well-matched control groups, ASD participants showed significantly less FFA activation and significantly greater activation in the inferior temporal gyrus, an area that is usually responsive to objects. Numerous other neuroimaging studies also reported reduced FFA activation in people with ASD (for a recent review, see *Jemel et al., 2006*). However, using a different paradigm *Hadjikhani et al. (2004, 2006)* found no differences in FFA activation between adults with ASD and controls. In these studies participants were asked to fixate a centrally located cross during a passive viewing task, which ensured that they would focus their attention directly on the eye region of the faces that were presented in the scanner. A recent study by *Dalton et al. (2005)* combined fMRI with behavioral and eye-tracking measures to investigate individual variation in face processing and FFA activation in adolescents with ASD in two experimental paradigms. Using this multi-method approach, this study provided some resolution to the conflicting findings on FFA activation. Consistent with the findings from most studies, the ASD group showed hypoactivation in FFA relative to age-matched controls. However, there was variation within the ASD group: the degree of FFA activation was significantly correlated with the time spent fixating on the eye region of the face. Taken together, these studies suggest that this neurobiological substrate for face processing is not specifically deviant in ASD.

Several studies have investigated FFA activation in adults with WMS. *Schultz et al. (2001)* found normal FFA activation on a face processing task in a small group of adults with WMS. There was no difference between the WMS and control groups in either location or intensity of FFA activation. Similar findings were reported by *Meyer-Lindenberg and colleagues (2004)*, who studied only adults with WMS and normal intelligence. Finally, *Mobbs et al. (2004)* compared a group of adults with WMS to age matched controls on a more complex face processing task. In their analyses focusing on specific regions of interest, there were no group differences in FFA activation, although they did find differences in some other regions that were not easily interpretable.

Across both ASD and WMS, the evidence points to neurocognitive face processing mechanisms that are generally similar to those in normal populations. The one source of deviance that is consistent across both behavioral and neuroimaging studies lies in the atypical processing of eyes in people with ASD, which contributes to their face processing impairments and atypical neural activation patterns. Eyes are especially salient facial features in that they are crucial for *communication*, including conveying intentional and emotional states. Eyes thus have special significance for online mental state attribution. Impaired processing of eyes therefore contributes to the broader social cognitive deficits that characterize ASD (*Baron-Cohen, 1995*).

It is not clear why people with ASD look significantly less at faces. Some have argued that it is rooted in a decrease in the reward value associated with faces in infancy and impaired social motivation (e.g. *Klin et al., 2003; Dawson et al., 2005*), while others suggest that faces are associated with heightened arousal in people with ASD, leading to their avoidance of face and eye contact (*Dalton et al., 2005; Nacewicz et al., in press*).

EMOTION PROCESSING

Faces are important for expressing a wide range of basic and more complex emotional states. Given the significance of the eye region for the identification of emotions, one would predict significant impairments in children and adults with ASD. There is, however, conflicting evidence for behavioral deficits in decoding facial expressions in ASD. A large number of studies have been conducted, usually including standard face emotion stimuli, such as the Ekman faces (*Ekman and Friesen, 1976*). In general, when the studies include well-matched control groups, the data suggest that people with ASD are not specifically impaired in identifying basic emotional expressions, though there is considerable variability in performance (*Hefter et al., 2005*). Key predictors of performance include age, cognitive level and language (*Ozonoff, Pennington and Rogers, 1990; Buitelaar et al., 1999*) and there is evidence that identification of facially expressed is verbally mediated in ASD (*Grossman et al., 2000*). *Gross (2004)* compared emotion identification from standard and partial faces in children with ASD. Errors made by the children on the standard faces suggested that they were relying on information from the lower half of the face and their performance on stimuli depicting only the upper half of the face was at chance level. Distinguishing between different negative emotions depends more heavily on information in the upper portion of the face, especially the eye region. *Pelphrey et al. (2002)* found impaired performance in recognizing fear, and using a graded test of basic emotions, *Joseph and his colleagues (2005)* found impaired performance at lower levels of intensity for negative emotions (*sad, fear, anger*) in adolescents with ASD. *Baron-Cohen and his colleagues* developed a test for recognizing complex emotional and other mental states just from the eye region of the face (*Baron-Cohen et al., 1997; Baron-Cohen et al., 2001*). Adults with ASD perform significantly worse on the 'eyes' test than age and gender-matched controls. Thus, it seems that when more challenging measures of facial emotion identification are used, including more subtle or complex emotional expressions, or ones that are more reliant on discriminating expressions from the eyes, children and adults with ASD do show impairments in recognizing emotions.

Contrary to expectations, children and adults with WMS are not especially proficient in recognizing emotional expressions. Despite their empathic personality, children with WMS are no better than well-matched controls of

comparable mental age or level of mental retardation in labeling basic emotions (Tager-Flusberg and Sullivan, 2000; Gagliardi *et al.*, 2003). On a standardized test of basic emotions, adolescents and adults with WMS scored at the same level as language and IQ-matched individuals with mental retardation, and both groups performed worse than age-matched normal controls on negative emotions (*sad*, *fear*, *anger*) but at the same level on *happy* (Plesa Skwerer *et al.*, 2006a). In an early study using the original version of the 'eyes' task, Tager-Flusberg *et al.* (1998) found that adults with WMS were better than adults with a different mental retardation syndrome, Prader-Willi syndrome, and that about half the WMS group performed at the same level as age-matched controls. However, in a more recent study, using the revised 'eyes' task which, unlike the original, requires more than simply discriminating between positive and negative valenced mental states (e.g. *sympathetic*, *not sympathetic*), people with WMS performed significantly worse than normal controls and at the same level as an age- and IQ-matched comparison group (Plesa Skwerer *et al.*, 2006b). Unlike face identity recognition, face emotion recognition is not a spared capacity in WMS.

The neural circuitry for processing facial expressions of emotions involves a complex network of cortical and subcortical regions that are part of the 'social brain' (Brothers, 1990). The main region of interest for the majority of studies on ASD and WMS has been the amygdala, although there is still some controversy over the precise role of the amygdala in processing different types of emotions (Adolphs, 2003; Davis and Whalen, 2001). Baron-Cohen *et al.* (1999) were the first to investigate neural processing of facial expressions using the 'eyes' task. In contrast to normal controls, adults with ASD showed significantly reduced activation in the amygdala. Reduced amygdala activation has also been reported in other studies using standard face emotions (Critchley *et al.*, 2000; Wang *et al.*, 2004), but some other studies have found no difference in amygdala activation (Piggot *et al.*, 2004) or increased activation (Dalton *et al.*, 2005). The latter study, described in the previous section, incorporated eye-tracking into an fMRI experiment in which subjects were asked to judge whether the faces presented in the scanner were emotional or neutral in expression. Increased amygdala activation in participants with ASD, but not controls, was correlated with the amount of time spent looking at the eye region of both the neutral and emotional faces, as well as with FFA activation (see also Hadjikhani *et al.*, 2006), suggesting a heightened emotional response to looking directly at faces in ASD. The ASD group in this study also showed increased activation in the orbitofrontal gyrus to the emotional faces compared to the controls, suggesting that processing social emotional information leads to increased activation of affective neural circuitry in ASD (Dalton *et al.*, 2005).

Only one study has investigated the neural correlates of emotional face processing in WMS (Meyer-Lindenberg *et al.*, 2005). High functioning adults with WMS were compared to age and IQ-matched controls on tasks requiring them to match angry or fearful faces or similarly threatening non-social scenes. The WMS group showed reduced amygdala activation to the emotional faces but heightened activation to the emotional scenes relative to the controls. Furthermore, whereas controls differentially activated areas of prefrontal cortex (PFC) including dorsolateral, medial and orbitofrontal (OFC) cortex in response to social stimuli, a different pattern was obtained for the WMS group. Most striking was the absence of activation in OFC. Path analyses revealed that there was no connection between amygdala and OFC activation in the WMS group, although the patterns of connectivity between medial and dorsolateral PFC was similar to the controls.

The picture to emerge from current behavioral and neuroimaging studies of emotional processing in ASD and WMS is less clear than for face recognition. Face identity and facial expressions of emotion are subserved by distinct but overlapping neural circuitry (Haxby *et al.*, 2002). At the behavioral level, it seems that they are not related to one another in either ASD (Hefter *et al.*, 2005) or WMS (Plesa Skwerer *et al.*, 2006a). At the neurobiological level, abnormalities in amygdala activation have been implicated in the processing of facial emotions in both populations. However, because there have been so few studies, each employing different types of tasks and methods, we cannot yet specify the nature of the amygdala dysfunction for either ASD or WMS.

AMYGDALA ABNORMALITIES IN ASD AND WMS

The hypothesis that ASD involves abnormalities in amygdala functioning was suggested by Baron-Cohen and his colleagues (Baron-Cohen *et al.*, 2000) based on their initial fMRI study (Baron-Cohen *et al.*, 1999). While several different research groups have endorsed this proposal, especially as it is consistent with evidence of structural abnormalities of the amygdala in both *postmortem* (Bauman and Kemper, 1985; Schumann and Amaral, 2006) and *in vivo* MRI studies (Schumann *et al.*, 2004; Nacewicz *et al.*, in press), there is little consensus on the scope of the dysfunction. Schultz (2005) focuses on the connectivity between the amygdala and FFA, and argues that early impairments in the amygdala have a cascading developmental influence on cortical areas involved in face processing, including FFA as well as other temporal regions. Other groups highlight abnormalities in the *development* of amygdala-cortical connectivity in ASD and particularly with prefrontal regions that are associated with social information processing (Adolphs *et al.*, 2001; Pelphrey *et al.*, 2004; Dalton *et al.*, 2005; Bachevalier and Loveland, 2006). Amaral *et al.* (2003), however, argue that amygdala abnormalities may be more proximally related to

generalized anxiety, and only secondarily related to social functioning in ASD. Amygdala dysfunction in ASD is likely to be quite variable across different individuals at different ages and to involve abnormal cortical connectivity.

Amygdala dysfunction in WMS also involves abnormal connectivity, specifically with prefrontal regions important in social information processing (Meyer-Lindenberg *et al.*, 2005). This neurobiological impairment has been linked to more complex aspects of the social phenotype of WMS (Meyer-Lindenberg *et al.*, 2006). Despite the appearance that WMS and ASD present as contrasting syndromes by virtue of differences in their social behavior, people with WMS also have social impairments. While they are indeed socially engaging and very interested in people, they are not especially good at discriminating facial expressions or other social cues, they have difficulty forming social relationships, and they have poor social judgment (Dykens and Rosner, 1999). Moreover, their interest in other people is unusual in its intensity and their social behavior is generally characterized as disinhibited (Jones *et al.*, 2000; Mervis *et al.*, 2003; Tager-Flusberg and Plesa Skwerer, 2006). Meyer-Lindenberg *et al.* (2006) attribute these unusual aspects of the social phenotype in WMS to the self-regulatory deficits arising from decreased connectivity between OFC and amygdala.

Further evidence for the hypothesis that ASD and WMS involve impaired amygdala connectivity comes from studies of social appraisal. People with ASD (Adolphs *et al.*, 2001) and WMS (Bellugi *et al.*, 1999) rated photographs of faces as more approachable and trustworthy than controls. Their social judgments were similar to those offered by people with bilateral amygdala lesions who are impaired in the perception of social threat (Adolphs *et al.*, 1998).

The amygdala plays an important role in mediating activation of the autonomic nervous system (Davidson and Irwin, 1999). There is evidence that children and adolescents with ASD tend to show heightened arousal to social stimuli, as measured by skin conductance responses (SCR; Hirstein *et al.*, 2001; Joseph *et al.*, 2005; Kylliainen and Hietanen, 2006). Although there is individual variability, most children show hyperarousal, and only a relatively small minority show hypoarousal (Hirstein *et al.*, 2001). In contrast, adolescents and adults with WMS tend to be hypoaroused when viewing dynamic facial stimuli compared to either normal controls or IQ-matched comparison groups (Plesa Skwerer *et al.*, 2005), a pattern similar to what has been reported in patients with amygdala damage. There are still many unanswered questions about the significance of SCR abnormalities in ASD and WMS and what they reveal about impairments in amygdala connectivity. Nevertheless, these preliminary studies suggest that this is a promising methodology for pursuing the relationship between social information processing, anxiety, and affective responsiveness at the behavioral and neurobiological levels in these populations.

CONCLUSIONS

As research on the social behavior of ASD and WMS has progressed, our understanding of the nature of the neurocognitive mechanisms implicated in these disorders has become far more complex than was originally envisioned. Genetic mutations associated with these syndromes do not lead to simple lesions or enhanced growth in the neural circuitry for social cognition, or concomitantly, in the complete absence or preservation of social functioning. Neurodevelopmental disorders are fundamentally different from acquired disorders and only limited parallels can be drawn between them (Karmiloff-Smith, 1997; Tager-Flusberg, 1999). The selective review of face processing studies of ASD and WMS summarized in this article highlights both the advances and unanswered questions that remain in relation to just two aspects of social perception: recognition of identity and emotion in faces. A more complete account of the neurocognitive bases of the social phenotypes of ASD and WMS must address processing of many other types of social stimuli, including eye gaze, biological motion, and auditory cues, and how effectively these aspects of social perception are integrated with one another as well as with explicit social and cultural knowledge. Such inquiry will benefit from the rapid theoretical and methodological advances being made in the broader field of social cognitive neuroscience.

As the field moves forward, research on neurodevelopmental disorders should attend to some of the lessons learned from current studies on both ASD and WMS. First, it is important to take a developmental perspective, taking into consideration age-related changes at both behavioral and neurobiological levels. Studies that combine subjects of widely differing ages risk obscuring important syndrome-specific differences in developmental trajectories, as has been demonstrated in the case of amygdala growth in ASD (Schumann *et al.*, 2004). Second, we are likely to learn as much or more from a fine-grained analysis of within syndrome variation as we have done from comparing one syndrome to another or to well-matched controls. Combining children with ASD who are hyperaroused with those who are hypoaroused might erroneously lead to the conclusion that there are no differences in arousal levels in ASD. It is quite possible that the different patterns of skin conductance found among children with ASD in Hirstein *et al.*'s (2001) study represent important subtype distinctions that are associated with different underlying neuropathology and genetic mutations. Thus, investigating individual differences among children or adults with ASD or WMS is more likely to facilitate the search for links between genes, brain and social behavior than simply comparing group behavior or neural activation levels. Third, other important advances will come from taking a multi-method approach, building on the example of Dalton *et al.*'s (2005) study that combined eye-tracking with behavioral performance

measures and neural activation patterns in investigating individual variation in face processing among adolescents with ASD. Each measure of social information processing discussed in this review, including level of performance, evaluation ratings, speed of processing, eye-tracking, location and intensity of neural activation, and autonomic arousal provides complementary evidence for how a person perceives, encodes and responds to a social stimulus. We can also add to this list regional measures of neurotransmitter levels using spectroscopy or measures of functional connectivity such as diffusion tensor imaging, which are likely to be important in providing more direct tests of the hypothesis that both ASD and WMS may best be characterized by abnormalities in cortical–amygdala neural circuitry. By combining different measures and employing similar experimental tasks and methods in investigations of ASD and WMS, future studies will reveal what distinguishes or is shared in the underlying pathology of these very different syndromes.

The relationships between the ASD and WMS social phenotypes and the amygdala are likely to be multifaceted, related to atypical connectivity both within the amygdala and between the amygdala and other critical cortical (e.g. prefrontal and/or temporal regions) and subcortical brain areas (e.g. hippocampus; hypothalamus). Functional differences or impairments in disorders such as ASD or WMS may result from changes in one or more of the inhibitory or excitatory pathways connecting the amygdala to these other regions, or to abnormalities in these other regions that influence amygdala functioning. As research progresses in uncovering these and other pathways that are critical to the neural circuitry involved in ASD and WMS, the findings are expected to contribute to a more complete understanding of the genetic and neurobiological substrates of social behavior.

Conflict of Interest

None declared.

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