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# Individual differences in symptom severity and behavior predict neural activation during face processing in adolescents with autism

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ABSTRACT

Despite the impressive literature describing atypical neural activation in visuoperceptual face processing regions in autism, almost nothing is known about whether these perturbations extend to more affective regions in the circuitry and whether they bear any relationship to symptom severity or atypical behavior. Using fMRI, we compared face-, object-, and house-related activation in adolescent males with high-functioning autism (HFA) and typically developing (TD) matched controls. HFA adolescents exhibited hypo-activation throughout the core visuoperceptual regions, particularly in the right hemisphere, as well as in some of the affective/motivational face-processing regions, including the posterior cingulate cortex and right anterior temporal lobe. Conclusions about the relative hyper- or hypo-activation of the amygdala depended on the nature of the contrast that was used to define the activation. Individual differences in symptom severity predicted the magnitude of face activation, particularly in the right fusiform gyrus. Also, among the HFA adolescents, face recognition performance predicted the magnitude of face activation in the right anterior temporal lobe, a region that supports face individuation in TD adults. Our findings reveal a systematic relation between the magnitude of neural dysfunction, severity of autism symptoms, and variation in face recognition behavior in adolescents with autism. In so doing, we uncover brain–behavior relations that underlie one of the most prominent social deficits in autism and help resolve discrepancies in the literature.



## 1. Introduction

Although not a diagnostic symptom of autism spectrum disorder (ASD), deficits in face processing represent a model domain in which to understand some of the core behavioral and neural features of autism. For example, many components of face processing (e.g., identity recognition, expression recognition) are developing at the very time that behavioral symptoms of autism are emerging and changing developmentally (infancy through young adulthood), allowing researchers to track aberrant developmental trajectories, and thus identify vulnerable developmental periods. In addition, many of the individual neural regions comprising the broadly distributed circuitry that subserves face recognition abilities (Gobbini and Haxby, 2007) are located within anatomical regions that show pathological structural growth patterns during infancy, toddlerhood, and adolescence in autism. These regions include the temporal and frontal lobes as well as the amygdala (Schumann et al., 2010), suggesting that they may be particularly vulnerable throughout the developmental course of the disorder. Finally, given that faces are the pre-eminent social stimulus from which we extract multiple kinds of social information that guide behavior, they provide a useful index of atypical neural organization of social-information processing across a spectrum of social–emotional disorders (e.g., Evans et al., 2008; Kucharska-Pietura et al., 2005; Marsh and Blair, 2008). Therefore, understanding the profile of atypical neural activation during face processing in autism, particularly during vulnerable developmental periods, is a fruitful approach to studying a core feature of autism; that is, disruption of the social brain and social information processing more generally.

The central goal of the current project was to evaluate the nature and extent of disruption in the social brain during face processing in autism, particularly during adolescence. We focus specifically on adolescence (i.e., the second decade of life) as this is a developmental period of emerging vulnerability for individuals with autism in terms of face processing behavior (O'Hearn et al., 2010) and neural circuitry (Dalton et al., 2005; Scherf et al., 2010; Wang et al., 2004). Also, an estimated

*Abbreviations:* TD, typical developing; HFA, high functioning autism; fMRI, functional magnetic iresonance maging; BOLD, blood oxygen level dependent.

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one-third of children with autism experience deterioration in functioning during adolescence, which is associated with concomitant neurological complications (Gillberg and Steffenburg, 1987; Kanne et al., 2011), a substantial increase in social withdrawal (Anderson et al., 2011), and a potential heightened risk for developing comorbid depression and anxiety (Brereton et al., 2006; Kuusikko et al., 2008; Mayes et al., 2011; McPheeters et al., 2011).

In this work, we include a particular focus on the functional profile of activation within the fusiform face area (FFA; Kanwisher et al., 1997) of the temporal lobe and the amygdala, two critical regions supporting multiple aspects of face processing (i.e., identity recognition, affective processing, trait attribution). Our focus on atypical activation within the FFA and amygdala in autism stems from contradictions within the existing literature that have made it difficult to ascertain a profile of atypical functional activation and organization among these regions even in adulthood autism. Importantly, while the amygdala is central for processing affective information about faces, it is only one of several other critical regions that make up the extended face network (Gobbini and Haxby, 2007). Surprisingly, little is known about the neural profile of these extended regions in autism, which might be especially disrupted given the known social and affective impairments in autism.

### 1.1. Discrepancies concerning atypical face-related activation in autism

The FFA in the fusiform gyrus (FG) together with a lateral region in the inferior occipital cortex ["occipital face area" (OFA); Gauthier et al., 2000] and the posterior superior temporal sulcus (STS; Hoffman and Haxby, 2000) comprise the "core regions" in the broadly distributed neural circuitry supporting face processing (Gobbini and Haxby, 2007; Haxby et al., 2000). Although these core regions are strongly implicated in supporting the visuoperceptual and cognitive analysis of faces, they also receive strong inputs from the extended regions, which are implicated in the more social and emotional aspects of face processing (Said et al., 2010, 2011). The extended face processing regions include the amygdala, insula, and medial prefrontal cortex, regions in the anterior paracingulate cortex, and the anterior temporal lobe (Gobbini and Haxby, 2007). These extended regions process more changeable aspects of faces, such as facial expressions and associating "person knowledge" with faces, including personal traits, attitudes, mental states, and intentions. The overwhelming majority of studies investigating the neural basis of face processing in autism have focused on understanding whether face-related activation in the FFA and the amygdala is atypical.

#### 1.1.1. Fusiform face area

Many studies report hypo-activation in the FFA in individuals with autism during unfamiliar face processing (Dalton et al., 2005; Domes et al., 2013; Grelotti et al., 2005; Humphreys et al., 2008; Kleinhans et al., 2011; Malisza et al., 2011; Pelphrey et al., 2007; Pierce et al., 2001; Pierce and Redcay, 2008; Pinkham et al., 2008; Richey et al., 2014; Sato et al., 2012; Schultz et al., 2000; Wang et al., 2004). For example, we previously reported that during passive viewing of movies of faces, hypo-activation is evident in the FFA as well as other core (i.e., perceptual) regions of the face-processing network in adults (Humphreys et al., 2008) and adolescents (Scherf et al., 2010) with high-functioning autism (HFA). However, there are several studies that fail to find atypical activation within the fusiform gyrus (Bird et al., 2006; Dapretto et al., 2006; Hadjikhani et al., 2004, 2007; Kleinshans et al., 2008) in autism. For example, in contrast to our previous finding, Hadjikhani et al., who used a passive viewing task of static face photographs but asked participants to fixate a red fixation cross positioned on the bridge of the nose of the face images, failed to find differences in face-related activation in the FG of adults with autism (Hadjikhani et al., 2007). It would seem that encouraging participants with autism to fixate the face improves signal in the FFA; however, a similar a study of adults with autism using the same procedure reported face-related hypo-activation in the FG (Humphreys et al., 2008). One important difference between these two studies is that the participants in the studies varied in the magnitude of their symptom severity with the participants in the study by Hadjikhani and colleagues consisting of almost an equal distribution of autism, and Asperger's/PDD participants whereas the study by Humphrey and colleagues only included participants with autism.

A review of this literature suggests that the pattern of mixed findings of face-related activation in the fusiform gyrus is not likely to be related to differences in task demands (e.g., passive viewing versus face matching) or the specific contrast used to define the face activation (e.g., affective faces versus neutral faces, faces versus objects, faces versus shapes). Patterns of both hypo- and comparable face-related activation in the FFA have been observed under the full range of these conditions. The pattern of mixed findings is also not likely to be related to the familiarity of the face stimuli since findings of both hypo- and comparable face-related activation have been observed when the face stimuli are familiar to participants (hypo-active, Dalton et al., 2005; comparable, Pierce et al., 2004; Pierce and Redcay, 2008). Instead, the studies appear to differ in terms of the relative severity of the autism participants. Specifically, all the studies reporting comparable face-related activation in people with autism, particularly in the FFA, have included a large proportion of participants with Asperger's Syndrome and PDD-NOS, who are less severely impacted symptomatically than those with an autism diagnosis. In contrast, the studies reporting hypo-activation in the FFA have largely included participants with a diagnosis of autism who are more severely affected by the disorder.

Based on these findings, we suggest that the discrepancies in the existing literature, particularly with respect to face-related activation in the fusiform gyrus, may actually reflect a systematic relation between the magnitude of activation and the severity of autism symptoms and/or variation in face recognition behavior. Importantly, this hypothesis has not been systematically examined. Understanding the potential relation between symptom severity, face recognition behavior, and FFA activation in response to faces may provide a critical step in reconciling the notable discrepancies about the development of the social brain in autism.

#### 1.1.2. Amygdala

Findings about atypical amygdala activation during face processing in autism are equally discrepant. Given the social impairments of autism and the reported difficulties in processing emotional expressions (Adolphs et al., 2001; Dawson et al., 2005), amygdala activation is likely to be atypical, particularly in response to affective faces. However, the nature of this atypicality is controversial and the existing results conflict, with many reporting hypo-activation (Ashwin et al., 2007; Bookheimer et al., 2008; Corbett et al., 2009; Critchley et al., 2000; Grelotti et al., 2005; Hadjikhani et al., 2007; Iidaka et al., 2012; Pelphrey et al., 2007; Pierce et al., 2001), some reporting hyper-activation (Dalton et al., 2005; Monk et al., 2010; Swartz et al., 2013; Tottenham et al., 2014; Weng et al., 2011), and still others reporting comparable activation (Pierce et al., 2004; Wang et al., 2004) in the amygdala compared to typically developing (TD) individuals.

Our review of this literature suggests that, instead of symptom severity, the discrepancy in findings about amygdala activation in autism may be related to methodological differences in the way neural activation is defined, particularly with respect to the comparison baseline condition. For example, studies reporting amygdala hyper-activation in autism generally contrast affective faces (e.g., sad, happy) with fixation (e.g., Dalton et al., 2005; Tottenham et al., 2014; Weng et al., 2011). Under these conditions, hyper-activation compared to controls could result from either higher magnitude responses to the faces and/or lower responses to the fixation, which could both contribute to a larger difference score (i.e., hyper-activation) across these two conditions. In contrast, studies reporting amygdala hypo-activation in autism have employed a variety of contrasts in which affective or neural faces are compared with other visual objects, shapes, or scrambled images