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The brains of high functioning autistic individuals do not synchronize with those of others

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ABSTRACT

Multifaceted and idiosyncratic aberrancies in social cognition characterize autism spectrum disorders (ASDs). To advance understanding of underlying neural mechanisms, we measured brain hemodynamic activity with functional magnetic resonance imaging (fMRI) in individuals with ASD and matched-pair neurotypical (NT) controls while they were viewing a feature film portraying social interactions. Pearson's correlation coefficient was used as a measure of voxelwise similarity of brain activity (InterSubject Correlations—ISCs). Individuals with ASD showed lower ISC than NT controls in brain regions implicated in processing social information including the insula, posterior and anterior cingulate cortex, caudate nucleus, precuneus, lateral occipital cortex, and supramarginal gyrus. Curiously, also within NT group, autism-quotient scores predicted ISC in overlapping areas, including, e.g., supramarginal gyrus and precuneus. In ASD participants, functional connectivity was decreased between the frontal pole and the superior frontal gyrus, angular gyrus, superior parietal lobule, precentral gyrus, precuneus, and anterior/posterior cingulate gyrus. Taken together these results suggest that ISC and functional connectivity measure distinct features of atypical brain function in high-functioning autistic individuals during free viewing of acted social interactions. Our ISC results suggest that the minds of ASD individuals do not 'tick together' with others while perceiving identical dynamic social interactions.

1. Introduction

Autism spectrum disorders (ASD), affecting about 1% of adult populations (Brugha et al., 2011), are characterized by abnormal social interaction, communication, restricted interests, and repetitive behavior (Baron-Cohen and Belmonte, 2005; Baskin et al., 2006; Woodbury-Smith and Volkmar, 2009). Individual ASD phenotypes evolve in complex nature–nurture interactions (Jones and Klin, 2009; Pelphrey et al., 2011) and are difficult to characterize. Widely used tests measuring specific aspects of social cognition such as facial expression recognition (Falck-Ytter and von Hofsten, 2011), mentalizing of others' thoughts (Happe, 1993; Ziatas et al., 2003), and understanding or imitating others' actions (Hamilton, 2009), each capture some aspects of the multifaceted social cognition impairments. With such tasks it has been challenging to characterize especially high-functioning ASD individuals who often compensate their poor performance in tasks probing isolated social functions by adopting alternative strategies (Frith, 2004). For instance, images of facial expression of happiness can be recognized by analyzing facial features around mouth and eyes, while in real-life recognition of other person's happiness requires, in addition to fast detection of facial expression, an ability to interpret contextual cues and goals of behavior. Therefore, performance in typical behavioral tests does not predict how patients with ASD guide their social interactions in complex natural environments. Brain imaging studies probing the neural basis of ASDs using similar tasks as in behavioral studies (Behrmann et al., 2006; Iacoboni and Dapretto, 2006; Zilbovicius et al., 2006) naturally share these limitations.

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Challenges in measuring autistic traits and underlying brain functions have required development of novel paradigms that enable characterization of behavior in complex, dynamic social conditions that better imitate real life. Such paradigms, when they are used to measure spontaneous recognition of social cues (Golan et al., 2006; Heavey et al., 2000; Klin et al., 2002; Loveland et al., 1997; Speer et al., 2007) or interpretation of social interaction (Barnes et al., 2009; Dziobek et al., 2006) portrayed in movies, have indeed turned out to be successful in characterizing social-cognitive impairments in ASDs. Importantly, novel brain imaging methods allow investigation of hemodynamic activity associated with viewing social interactions portrayed in a movie (Bartels and Zeki, 2005; Hasson et al., 2004, 2010; Jääskeläinen et al., 2008; Lahnakoski et al., 2012a,b; Nummenmaa et al., 2012a). In a pioneering study, Hasson et al. (2004) used spatiotemporal activity patterns of one brain to predict activity in another brains, and found a strong voxel-by-voxel synchronization in several cortical areas. It seems that naturalistic stimuli are very efficient in eliciting reliable responses in the human brain (Hasson et al., 2010). Hasson et al. (2009) also demonstrated that in autistic participants regional temporal synchronization of fMRI signals, intersubject correlation (ISC), was decreased during free viewing of a movie excerpt in multiple brain areas, including visual and auditory cortices, suggesting that autistic persons respond to dynamic naturalistic stimulation in more individualistic ways than neurotypical (NT) controls.

Experiments using simple stimuli and isolated behavioral tasks and those using very rich naturalistic free viewing conditions may offer complementary insight into brain basis of ASD. Traditional experiments are tuned to carefully tease apart specific aspects of stimulus processing and task demands. However, it may be difficult to predict how such findings generalize to more complex ecological stimulus conditions. For instance, even responses of early sensory neurons to complex naturalistic stimuli are difficult to predict based on their responses to simple static stimuli (Touryan et al., 2005; Yao et al., 2007). Studying brain activity of ASD versus control subjects in more naturalistic settings, such as while viewing complex social interactions depicted in a movie, may enhance understanding how the brain is functioning in real life. Nevertheless, the obvious drawback is that in such experiments it may be very difficult to determine specific associations between stimulus features and corresponding brain activity.

Recent functional brain imaging studies on ASDs, measuring the functional connectivity among brain areas, have characterized distributed brain networks participating in social cognition (for reviews see (Just et al., 2012; Müller et al., 2011; Schipul et al., 2011)). Several studies report decreased frontal-posterior connectivity in ASD participants during simple behavioral tasks (Courchesne and Pierce, 2005; Just et al., 2004, 2007; Kleinhans et al., 2008; Koshino et al., 2005; Monk et al., 2010; Mostofsky et al., 2009; Solomon et al., 2009) and during resting state (Kennedy et al., 2006; Monk et al., 2009; Weng et al., 2010). Although the validity of these findings has recently been questioned by studies demonstrating that the methods that were used are sensitive to spurious effects caused by movement of the participants during scanning (Power et al., 2012; Van Dijk et al., 2012), these studies have significantly shaped views of autism-related brain functions. Instead of local amplitude changes in brain responses, several studies provided evidence of atypical large-scale brain network structure in ASDs, such as increase of randomness in local brain activity (Dinstein et al., 2012) or brain network structure (Lai et al., 2010). Theories of autism are therefore now accounting for findings related to distributed brain networks, typically relating autistic traits to delays in fast interactions among brain areas which characterize most of the social brain functions (Gepner and Féron, 2009). Brain imaging studies using complex dynamic stimuli such as movies that portray human social interactions may thus be well suited for addressing brain connectivity in ASD, as they provide optimal, large and time-variable dataset for functional connectivity analyses.

In this study, we examined using ISC and functional connectivity measures the neural basis of social impairments in ASD during naturalistic stimulation. We measured brain activity of 13 carefully diagnosed and characterized ASD participants and 13 matched-pair NT controls with fMRI while they were viewing a film depicting core aspects of social cognition (social interaction, goal-directed action, and facial and bodily emotional expressions). This movie reliably activates brain networks involved in social information processing in NT participants (Lahnakoski et al., 2012a). We included only high-functioning participants with ASD diagnosis that matched the NT controls in other domains of intellectual performance excluding social cognition, and restricted and/or stereotyped behavior. We also studied the link between the severity of the autistic traits and synchronization of brain activity. Whole brain functional connectivity analyses were performed using fourteen regions of interest (ROIs) as seeds. The selection of ROIs was based on our recent study localizing key areas involved in perception of dynamic social events containing faces, bodies, biological motion, goal-oriented action, emotions, social interaction, pain, or speech (Lahnakoski et al., 2012b). We predicted finding group differences in ISC especially in brain areas that have a key role in social perception and cognition, including the occipito-temporal fusiform cortex (Kanwisher et al., 1997), the inferior frontal gyrus (Dapretto et al., 2006), the superior temporal sulcus (Koldewyn et al., 2011; Pelphrey and Carter, 2008), and medial prefrontal cortex (Spengler et al., 2010). Furthermore, encouraged by our recent study demonstrating a link between similarity of brain activity during movie viewing and similarity of participants emotional experiences (Nummenmaa et al., 2012a), we expected that the synchronization of brain activity in the social brain areas is associated with social skills measured by the autism quotient (AQ) also in the NT group (Nummenmaa et al., 2012b; von dem Hagen et al., 2011). Finally, we expected to find decreased functional connectivity between the frontal and posterior brain areas in ASD participants, previously reported during simple behavioral tasks and resting state.

2. Material and methods

2.1. Participants

We studied 13 adult ASD males (mean age = 29 years, S.E.M = 1.7 years, age range = 20–41 years) and 13 NT adult male matched-pair control subjects (mean age = 29 years, S.E.M = 2.1 years, age range 19–47 years). The individuals with ASD filled the criteria for Asperger syndrome based on ICD-10 criteria. The diagnostic process included a detailed developmental history. Current symptoms were assessed with a review of diagnostic criteria and participants filled in the autism-spectrum quotient (AQ) questionnaire (Baron-Cohen et al., 2001a). AQ is a self-rating scale developed for assessment of the degree to which an individual with normal intelligence has the traits associated with the autism spectrum, validated in several studies (Allison et al., 2012; Hoekstra et al., 2011; Woodbury-Smith et al., 2005). Five additional participants were scanned for both groups, however, two ASD participants were excluded for not meeting all the required criteria (due to the usage of medication, remission of particular symptoms, and additional diagnosis) and three ASD participants were excluded from the analysis due to excessive head movements (>3 mm absolute movement, i.e. more than one voxel in any direction) during scanning. One of the included ASD participants diagnosed in childhood had a remission of excessive routines and rituals and the concurrent symptoms were therefore more accurately characterized by the diagnosis of PDD-NOS. The matched-pair (NT) controls of the excluded ASD participants were also excluded. All participants had normal or corrected-to-normal vision, and normal hearing and spoke Finnish as their native language. Moreover, they had no other neurological or psychiatric diagnoses, and none of them were currently receiving medication affecting the central nervous system. Exclusion of psychiatric symptoms for the NT controls was confirmed with Structured Clinical Interview for DSM-IV. Groups were matched by age, and on each individual test on the Wechsler Adult Intelligence Scale III (Table 1). AQ, (Baron-Cohen