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Atypical activation of action-semantic network in adolescents with autism spectrum disorder

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ABSTRACT

In typical adults, fMRI studies have shown activation of primary and pre-motor regions during action word processing. Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social and communication impairments. ASD studies have shown atypical semantic processing and motor deficits. The objective of this study was to examine semantic processing of verbs in ASD. 15 ASD adolescents and 19 typically developing adolescents, 11–16 years, completed a semantic similarity judgment task during fMRI. There were no differences in task accuracy or reaction time. At the group level, both groups had activation in left language areas; controls, but not ASD, also had activation in the left pre-supplementary motor area (pre-SMA). In ASD, less left frontal activation and reduced left lateralization of activation within these regions was associated with shorter reaction times and better language skills. More left temporal activation was associated with better language abilities in ASD. Differences in pre-SMA activation may relate to motor planning deficits or differences in approach to the semantic task in ASD. Results suggest that left frontal language areas may be less efficient in ASD and those who can compensate by recruiting more right hemisphere homologues may result in better language abilities.

1. Introduction

A number of fMRI studies have found activation of primary motor and pre-motor areas, in addition to critical language regions, during language processing of action words in typical adults (Aziz-Zadeh, Wilson, Rizzolatti, & Iacoboni, 2006; Kemmerer, Castillo, Talavage, Patterson, & Wiley, 2008; Pulvermuller, Cook, & Hauk, 2012; for review, Kiefer & Pulvermuller, 2012). This activation is somatotopically organized, such that action words referring to leg movements activate the leg region of primary motor cortex, arm words activate arm motor cortex, etc. This activation has also been found to overlap with regions activated by performance of the action (Hauk, Johnsrude, & Pulvermüller, 2004) and it has been proposed that it involves the mirror neuron system (for review, Chersi, Thill, Ziemke, & Borghi, 2010). Some have argued that this motor activation is due to imagery or covert performance of the actions, however, recent studies have demonstrated that this activation is automatic, occurring early in processing, within 200 ms, and even when subjects do not attend to the stimuli (Mahon & Caramazza, 2008; for review, Pulvermuller, 2013). Supporting automatic processing, Boulenger et al. (2008) found effects on motor movement when action words were subliminally presented.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication with the presence of specialized interests or repetitive behaviors (American Psychiatric Association, 2013). Although a range of language abilities occur in ASD, language and communication difficulties are a core feature of the disorder. Differences in activation, during a variety of language tasks, have been found in ASD relative to controls (Boddaert et al., 2003, 2004; Gaffrey et al., 2007; Gervais et al., 2004; Harris et al., 2006; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; Kleinhans, Müller, Cohen, & Courchesne, 2008; Knaus, Silver, Lindgren, Hadjikhani, & Tager-Flusberg, 2008; Moseley

Abbreviations: ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; AQ, asymmetry quotient; ASD, autism spectrum disorder; OWLS, Oral and Written Language Scales; POP, pars opercularis; pre-SMA, pre-supplementary motor area; PTR, pars triangularis; pSTG, posterior superior temporal gyrus; ROI, region of interest; SCQ, Social Communication Questionnaire; WISC, Wechsler Intelligence Scale for Children

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et al., 2013; Müller et al., 1998, 1999; Redcay & Courchesne, 2008). Atypical semantic processing or organization has been found in ASD. In one study, subjects indicated whether a visually presented word was positive or negative and there was reduced inferior frontal gyrus activation, due to increased activation during the perceptual task, and increased middle temporal gyrus activation in the ASD group compared to controls (Harris et al., 2006). Gaffrey et al. (2007) had subjects determine whether a visually presented word belonged to a specified category and found increased extrastriate visual cortex activation in the ASD group, which corresponded to increased errors. They also found that the ASD group had slightly smaller clusters of activation in left inferior frontal regions. In our prior study, using a visual response-naming task, adolescents with ASD had more activation in inferior frontal gyrus, which was less left lateralized, compared to controls (Knaus et al., 2008). The ASD group also had more regions activated relative to the control group. Moseley et al. (2013) examined action word processing in high-functioning adults with ASD and demonstrated reduced activation of inferior frontal and pre-motor cortex in ASD compared to typical controls. Most fMRI studies examining semantic processing in ASD have been limited to high-functioning individuals and have not explored associations with behavioral measures.

The objective of this study was to examine semantic processing of verbs in adolescents with ASD compared to typically developing adolescents and to examine associations with behavioral measures. Since verb processing was examined, we expected activation of motor-related regions, in addition to critical language areas, in typically developing adolescents and that motor area activation would be decreased in ASD, based on the previous study of action word processing in adults (Moseley et al., 2013). Reduced or reversed left lateralization of activation during language processing in ASD is one of the most consistent findings (Boddaert et al., 2003, 2004; Gervais et al., 2004; Knaus et al., 2008; Müller et al., 1998, 1999; Redcay & Courchesne, 2008). We, therefore, hypothesized decreased left lateralization of activation in frontal and temporal language regions during semantic processing in the ASD group relative to the typically developing group. We expected increased left lateralization would be associated with higher language scores in the ASD group. Based on our previous finding (Knaus et al., 2008), we also hypothesized increased activation of frontal language regions in the ASD group compared to typically developing adolescents.

2. Material and methods

2.1. Subjects

Subjects included 15 adolescents with ASD (2 females) and 19 typically developing adolescents (3 females), 11–16 years old. All subjects had English as their first language. Based on the Almli Handedness Assessment (Almli, 2006), there were 3 non-right-handers in each group. Individuals with frank neurological damage, with a known genetic disorder, who were born prematurely (less than 36 weeks), or who had had seizures within the last 3 years were excluded from the study. About half of the ASD subjects (n = 7) were taking medications, including ADHD medications and mood stabilizers. However, when those on medication were compared to those not on medication, there were no differences in activation for any ROI. Typically developing individuals also had no history or current diagnosis of developmental, learning, psychiatric, or neurologic disorders and no immediate family members with an ASD diagnosis.

For ASD participants, diagnosis was based on DSM-IV criteria (APA, 1994) and therefore included individuals with a diagnosis of autism, pervasive developmental disorder-not otherwise specified, or Asperger syndrome. The Autism Diagnostic Observation Schedule – 2nd Edition, Module 3 or 4 (ADOS-2; Lord et al., 2012) and the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) or Lifetime Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003) was used to confirm diagnosis.

Parents and participants were informed of the procedures and parents gave written consent and children written assent, prior to the child's participation in the study. All data in this manuscript were collected in compliance with the Louisiana State University Health Sciences Center and Children's Hospital Institutional Review Boards.

2.2. Standardized tests

Subtests of the Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV; Wechsler, 2003) were administered to all subjects to assess verbal and non-verbal IQ. The Oral and Written Language Scales (OWLS; Carrow-Woolfolk, 1995) was administered to each subject in order to assess receptive and expressive language abilities.

2.3. MRI acquisition

All participants were trained in a mock scanner prior to the actual MR scanning where the fMRI task was also practiced using different stimuli. All MRI scans were acquired at Touro Imaging Center, on a Siemens 3 T Verio scanner. Volumetric T1-weighted images were obtained as a series of 144–176, 1 mm gapless sagittal images. MPRage was used, with technical factors of: TR = 1900 ms, TE = 2.48, 256 × 256 pixel matrix, 250 mm field of view, and 9° flip angle. Data sets were rotated into alignment in the sagittal, axial, and coronal planes in order to eliminate any head rotation and MRI scans were maintained in real space. EPI axial sequences aligned parallel to the intercommisural plane were acquired. fMRI scans were acquired using Blood Oxygen Level Dependent contrast with the following parameters: TR = 3000 ms, TE = 30 ms, FOV = 230 mm, pixel matrix = 64 × 64, flip angle = 90 degrees, 31 contiguous slices, slice thickness = 4 mm. Each MRI scan series was assigned a blind number to assure subject confidentiality and to ensure all analyses were performed blind to subject.

2.4. fMRI task

A block design was used with a semantic similarity judgment task and a control symbol judgment task (Kemmerer et al., 2008; Sabsevitz, Medler, Seidenberg, & Binder, 2005). For the semantic judgment, 3 verbs were shown in a triangular arrangement, with the target word at the top center. Subjects indicated, with a button press, which of the bottom 2 words was most similar in meaning to the target. See Appendix A for stimuli used in the scanner. For the control task, character strings in Wingdings font were presented, again with the target string at the top center. Similar to the semantic task, participants indicated, with a button press, which of the 2 bottom strings was the same as the target. Stimuli were presented via E-Prime every 5 s. The run consisted of 8, 12.5 s rest blocks, consisting of just a crosshair, 4, 25 s semantic judgment blocks, and 4, 25 s Wingdings blocks, for a total time of 5 min.

2.5. Analyses

2.5.1. Behavioral measures

To examine group differences in age, an ANOVA was performed with group (ASD, control) as the independent variable and age as the dependent variable. To investigate differences in IQ and language scores, MANOVAs were calculated with group as the independent variable and verbal and non-verbal IQ or receptive and expressive language scores as dependent variables. To examine differences in accuracy and reaction time on the fMRI task, 2-factor ANOVAs were done with group and task (words, symbols) as factors and accuracy or reaction time as dependent variables.

2.5.2. fMRI

All fMRI data analyses were completed with FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library,