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BRIEF REPORT

# Brief Report: Brain Activation to Social Words in a Sedated Child with Autism

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**Abstract** A functional magnetic resonance imaging (fMRI) study was performed on a 4-year-old girl with autism. While sedated, she listened to three utterances (numbers, hello, her own first name) played through headphones. Based on analyses of the fMRI data, the amount of total brain activation varied with the content of the utterance. The greatest volume of overall activation was in response to numbers, followed by the word 'hello', with the least activation to her name. Frontal cortex activation was greatest in response to her name, with less activation for numbers, and the least for the word 'hello.' These findings indicate that fMRI can identify and quantify the brain regions that are activated in response to words in children with autism under sedation.

**Keywords** Autism · fMRI · Self-awareness

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## Social Communication Skills are Impaired or Absent in Children with Autism

Clinical studies have reported that many children with autism fail to respond when their own name is called although their hearing abilities appear intact (Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000); in addition, some children with autism exhibit a verbal auditory agnosia, or a word deafness, as suggested by Rapin (1997). The failure to respond to one's own name suggests that some children with autism may lack a sense of personal identity, thus affecting the ability to develop a theory of mind because of difficulties in the cognitive representation of 'me' (Lewis, 2003).

We are interested in knowing which brain regions are activated in autism when hearing one's own name. As a basis of typical functioning in response to this unique stimulus, neuroimaging studies have examined adults listening to their own names. Perrin et al. (2005) using EEG, as well as positron emission tomography (PET), found activation of the right medial prefrontal cortex when adults heard their own first name. Using functional magnetic resonance imaging (fMRI), Carmody and Lewis (2006) showed that adults hearing their own first name activated both the anterior regions of middle frontal cortex and superior frontal cortex, as well as posterior regions of middle and superior temporal cortex, and cuneus.

Whereas fMRI permits the mapping of brain functions during task performance, the two challenges to the use of fMRI in pediatric populations are subject movement and subject compliance with the task. Both concerns are managed by sedation, and propofol has been shown to be safe with pediatric patients undergoing neuroimaging studies (Kain, Gaal, Kain, Jaeger, & Rimar, 1994; Merola, Albarracin, Lebowitz, Bienkowski, & Barst, 1995). In addition, fMRI studies of infants and young children have shown that brain regions are activated in response to visual and auditory stimulation under pentobarbital or chloral hydrate sedation (Altman & Bernal, 2001) and in response to visual, auditory, and tactile stimulation under propofol sedation (Souweidane et al., 1999).

Our interest in the current study is to identify brain regions that are activated when a child with autism hears her first name, social stimuli, and numbers. We hypothesized that the regions of brain activation would be different for the social stimuli than for the non-social stimuli. To test this hypothesis, we conducted a neuroimaging study of brain activity in a young child with autism under sedation while listening passively to the utterances.

## Methods

### Participant

A girl diagnosed with autism was assessed by MRI evaluation, psychological examination, and a neurodevelopmental evaluation. Psychological testing was conducted at 40 and 64 months of age, and MRI was conducted at 46 months of age.

On the neurodevelopmental evaluation, there was no history of brain injury and no findings of structural neurological impairments, with the exception of café-au-lait spots. The study was approved by the local Institutional Review Board, and treatment of the participant was in accordance with the ethical standards of the American Psychological Association (2002). The parents of the participant signed the informed consent and had the right to refuse participation, terminate the testing sessions, or not complete the tasks.

### Tasks

The assessment instruments were the *Differential Ability Scales* (DAS) (Elliot, 1990), *The Beery Buktenica Developmental Test of Visual Motor Integration* (VMI) (Beery, 1997), the *Vineland Adaptive Behavior Scales* (VABS) (Sparrow, Balla, & Cicchetti, 1984), and the *Autism Diagnostic Observation Schedule* (ADOS)-G module 1 (Lord et al., 2000).

### MRI Procedures

The participant had a clinical MRI procedure under sedation (Propofol IV; Diprivan) to rule out a neurocutaneous disorder as the etiology of her café-au-lait spots and autism. An fMRI sequence was added in the middle of the clinical sequence, after the initial spinal and brain scans, and prior to the administration of contrast for the contrast imaging sequence that was conducted for clinical purposes. During the imaging procedure, pulse, temperature, and blood pressure were monitored.

#### *fMRI Recording*

Scanning was performed with a 1.5 T General Electric Scanner with echoplanar capability and a standard quadrature head coil. The subject was positioned supine on the gantry of the scanner with the head in a midline location in the coil wearing a set of headphones connected to a PC, which presented the stimuli. The scans began with a standard spin echo T1-weighted sequence covering the brain in nine axial slices parallel to the line from the anterior to posterior commissure. Imaging parameters were matrix size = 512 × 512; TR = 416 ms; TE = 8; FOV = 20 cm; NEX = 1; and slice thickness = 10 mm, with 1 mm skip. T2*-weighted images were acquired using echo planar imaging (EPI) gradient echo sequence (matrix size = 128 × 128; TR = 3,000 ms; TE = 60 ms; FOV = 40 cm; flip angle = 75°; slice thickness = 10 mm, with 1 mm skip, interleaved, and 1 NEX) covering the same brain regions and in the same plane as the T1-weighted sequence. During each functional imaging sequence, 52 volumes of nine axial sections were taken. The in-plane resolution of the functional images was 3.2 × 3.2 $mm^2$/voxel.

#### *Stimuli and Task for fMRI*

Three runs of 150 s each were divided into five epochs of 30 s each. The first epoch was silence to allow the hemodynamic signal to accommodate to the scanner noise. During the second and fourth epochs, 20 words were delivered at the rate of one word every 1.5 s, while the third and fifth epochs were silence. On the first run, the word 'hello' was repeated 40 times. The participant's first name was repeated 40 times in

the second run, and during the third run, a random arrangement of 40 numbers ranging from the number one to the number 15 was presented.

*Measures of Brain Activation*

Analyses of brain activation were conducted at two levels. First, statistical parametric maps were created, and then a regional analysis was conducted of the hemodynamic response. Brain regions were analyzed for activation slice-by-slice with the Analyses of Functional Neuroimages Package (AFNI) running under UNIX software (Cox, 1996). The first 10 image sets taken during the initial silent period were excluded in the analysis to ensure steady baseline measures. The data were realigned to the 20th image set to minimize motion-related artifacts. Inspection of the registration graphs indicated less than 2.0 mm of motion in any direction over the course of the session. A cross-correlation analysis was applied on a voxel-by-voxel basis to determine if the MRI signal differed when hearing words relative to listening to silence. All voxels that passed the statistical threshold ($p < 0.01$, uncorrected) in the task-activated datasets were considered activated. In this way, we identified the voxels where the hemodynamic response correlated with the changes in the auditory stimuli from silence to word utterance. This analysis provided statistical parametric maps of voxels of activation, which were smoothed for analyses.

The T1 anatomical images were aligned to the EPI images to localize the regions of activation. A specific region was defined as active for a scan if four or more contiguous pixels were activated (Forman et al., 1995). Identification of the active brain regions was achieved by comparisons to the horizontal standard images available in the Talairach Daemon (Lancaster, Summerlin, Rainey, Freitas, & Fox, 1997). The volumes of activation in brain regions were calculated for the areas that met the minimum of four contiguous active voxels. Volumes of activation were calculated at 102.4 $mm^3$/voxel (10 mm slice thickness and 3.2 $mm^2$/voxel).

## Results

Behavioral Assessment

The subject's high level of activity and inattention impacted the behavioral testing at ages 40 and 64 months. Her performance on the DAS at both ages was estimated to fall within the very low range. Her age equivalent on the VMI was under 2 years and her adaptive behavior composite on the VABS was in the low range for her age on both administrations. On ADOS testing, she had poor eye contact, occasional echolalia, and failed to show shared enjoyment in interactions. However, she gave a responsive smile to social smiles, and although she did shift her gaze when she heard her name, she failed to make eye contact with the examiner who spoke her name. Overall, the child showed behaviors consistent with autism including impairments in communication, reciprocal social interactions, and restricted areas of interest.

fMRI Analyses

A clinical review of the MR images indicated no visible neurological involvement. Inspection of the statistical parametric maps showed that brain activation differed depending on the utterance. Table 1 presents the areas of brain activation in response to the three utterances. The brain regions are defined by the name of the cerebral region; the hemisphere (left or right); the Brodmann area; and the Talairach coordinates, which are given in $x$ (left to right axis), $y$ (anterior to posterior axis), and $z$ (inferior to superior axis) anatomical space (Lancaster et al., 2000). In addition, Table 1 presents the volumes of brain activation. The greatest overall activation was to number (8,091 $mm^3$), followed by the utterance hello (4,918 $mm^3$), with the least activation in response to her own name (1,845 $mm^3$).

A separate analysis identified the regional differences in activation to the three different utterances. Brain regions that were activated in all auditory conditions were the right medial or middle frontal gyrus (Brodmann Area 6), and the volume of frontal activation varied with the sounds. Specifically, the greatest frontal activation was found in the name condition (1,845 $mm^3$), with less activation for numbers (1,434 $mm^3$), and the least activation for the word hello (615 $mm^3$). Brain activation in other regions varied over the conditions. For example, in cingulate regions, there was no activation for name, 410 $mm^3$ of activation for the word hello, and 1,742 $mm^3$ of activation for numbers. Large differences in activation were found in occipital regions with similar volumes of activation for the word hello (2,764 $mm^3$) and for numbers (2,560 $mm^3$), in contrast to no activation for own name.

## Discussion

We used fMRI to examine brain activation in a 4-year-old girl with autism who had impairments in communication and reciprocal social interactions. In order to see if she was responsive to her own name in relation to

**Table 1** Cerebral regions of activation when hearing words relative to silence with the associated hemisphere (*left or right*), Brodmann Areas (*BA*), Talairach coordinates (*x, y, z*), and volume of activation

| Word | Cerebral region | Left or right | BA | x | y | z | Volume ($mm^3$) |
|---|---|---|---|---|---|---|---|
| Own name | Medial frontal gyrus | L | 6 | –9 | 11 | 55 | 410 |
| | | R | 11 | 7 | 43 | –16 | 410 |
| | Middle frontal gyrus | R | 10 | 24 | 52 | 16 | 410 |
| | | R | 6 | 30 | 5 | 55 | 615 |
| | Total activity to own name | | | | | | 1,845 |
| Hello | Middle frontal gyrus | R | 6 | 23 | –14 | 55 | 615 |
| | Cingulate gyrus | L | 23 | –6 | –46 | 24 | 410 |
| | Superior temporal gyrus | L | 42 | –63 | –29 | 16 | 1,126 |
| | Occipital lobe—fusiform gyrus | R | 19 | 34 | –75 | –16 | 2,764 |
| | Total activity to hello | | | | | | 4,915 |
| Numbers | Medial frontal gyrus | R | 6 | 9 | –11 | 55 | 512 |
| | | L | 6 | –10 | –17 | 55 | 512 |
| | Middle frontal gyrus | R | 46 | 41 | 34 | 24 | 410 |
| | Postcentral gyrus | R | 3 | 17 | –30 | 55 | 512 |
| | Precentral gyrus | L | 4 | –29 | –21 | 55 | 1,126 |
| | Precuneus—Parietal | R | 7 | –2 | –73 | 45 | 717 |
| | Anterior cingulate | L | 24 | –6 | 14 | 24 | 922 |
| | Cingulate | R | 31 | 10 | –52 | 24 | 410 |
| | | L | 31 | –14 | –51 | 24 | 410 |
| | Middle occipital gyrus | R | 19 | 39 | –85 | 16 | 410 |
| | Occipital lobe—fusiform gyrus | R | 19 | 35 | –79 | –16 | 2,150 |
| | Total activity to numbers | | | | | | 8,091 |

See method section for details

other social and non-social auditory events, an fMRI study was performed under sedation while she heard repeated presentations of her own name, the utterance 'hello,' and numbers. Brain activation differed in response to the three utterances.

The fMRI analyses indicated two major findings. First, our results confirm previous reports that brain activation in response to words can be measured by fMRI under sedation in children (Souweidane et al., 1999; Altman & Bernal, 2001). For example, in one fMRI study of infants and children under sedation, frontal, temporal, and parietal regions were activated in response to their mother's voice speaking familiar and endearing words (Altman & Bernal, 2001). In an fMRI study using propofol, auditory stimulation with voice recordings of parents activated multiple cortical and subcortical regions, including frontal, temporal, and parietal cortex, as well as occipital cortex and the cuneus (Souweidane et al., 1999). Similarly, we found activation of frontal regions in response to all utterances, social, and non-social, as well as activation in occipital cortex in response to hello and in precuneus regions in response to numbers.

Our second major finding is that the amount of total brain activation differed with the utterances, with the least amount of total activation in response to the subject's own name. However, we did find that the greatest activation of frontal cortex, in Brodmann areas 6 and 10, was in response to the child's own name thus providing evidence of differential neural function to her name. This activation in response to her first name is in agreement with the findings reported by Perrin et al. (2005) using PET scanning as well as Carmody and Lewis (2006) using fMRI who showed evidence of differential brain activity to hearing one's own name versus others' names. Auditory self-recognition has brain activity specific to the frontal and temporal regions, as well as posterior brain regions, including the occipital cortex. Although fMRI provides insight into activity differences in the brains of older, high functioning children, and adults with autism (Luna et al., 2002; Allen & Courchesne, 2003; Müller, Kleinhans, Kemmotsu, Pierce, & Courchesne, 2003; Gervais et al., 2004; Koshino et al., 2005), we have shown the value of a technique to measure function in young patients with severe autistic disorder. In conclusion, fMRI is a technique that may assist in mapping the brain regions that are impacted in the processing of social content in autism.

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