RESEARCH ARTICLE

A Magnetic Resonance Spectroscopy Study of Superior Visual Search Abilities in Children with Autism Spectrum Disorder

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Although diagnosed on the basis of deficits in social communication and interaction, autism spectrum disorder (ASD) is also characterized by superior performance on a variety of visuospatial tasks, including visual search. In neurotypical individuals, region-specific concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) are associated with individual differences in attention and perception. While it has been hypothesized that ASD may be associated with an excitatory–inhibitory imbalance, it remains unclear how this may contribute to accelerated visual search performance in individuals with ASD. To investigate this, 21 children with ASD and 20 typically developing children participated in a visual search task and a magnetic resonance spectroscopy study to detect neurochemical concentrations, including GABA. Region-specific neurochemicals were examined in the right frontal eye fields, right temporal–parietal junction (rTPJ), and bilateral visual cortex (VIS). GABA concentrations did not differ between groups; however, in children with ASD, greater GABA concentration in the VIS was related to more efficient search. Additionally, lower VIS GABA levels were also associated with increased social impairment. Finally, we found reduced N-acetyl aspartate, total creatine, glutamate and glutamine (Glx), GABA/Glx in the rTPJ, suggestive of neuronal dysfunction in a critical network hub. Our results show that GABA concentrations in the VIS are related to efficient search in ASD, thus providing further evidence of enhanced discrimination in ASD. *Autism Res* 2019, 00: 1–13. © 2019 International Society for Autism Research, Wiley Periodicals, Inc.

Lay Summary: Children with autism spectrum disorder (ASD) often perform better than their non-ASD peers on visual search tasks; however, it is unclear how they achieve this superior performance. Using magnetic resonance spectroscopy to measure neurochemicals in the brain, we found that the level of one, gamma-aminobutyric acid, in the visual cortex was directly related to search abilities in children with ASD. These results suggest that faster search may relate to enhanced perceptual functioning in children with ASD.

Keywords: autism spectrum disorder; visual search; magnetic resonance spectroscopy; gamma-aminobutyric acid; frontal eye field; temporal–parietal junction; visual cortex

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder diagnosed based on impairments in social communication and interaction as well as the presence of restricted and repetitive behaviors [APA, 2013]. However, differences in nonsocial attentional functions—including both attentional strengths and weaknesses—have been identified as among the earliest features that distinguish infants likely to develop ASD [Elsabbagh et al., 2013; Gliga et al., 2015]. One particular strength, performance on visual search tasks (VSTs), which require participants to locate a target item embedded within an array of distractors, has been shown in infants at elevated risk for ASD [i.e., infants with an older sibling with ASD; Gliga et al., 2015], as well as toddlers, school-aged children, adolescents, and adults diagnosed with ASD [Kaldy, Giserman, Carter, & Blaser, 2016]. Furthermore, faster, more efficient search abilities are associated with higher levels of ASD symptomatology [Gliga et al., 2015; Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009; Keehn & Joseph, 2016; Keehn, Shih, Brenner, Townsend, & Müller, 2013], suggesting that nonsocial attentional processes, and the differences in brain function that these behaviors reflect, may be of etiological significance in the development of ASD.

However, the precise mechanism(s) underlying enhanced visual search abilities in ASD remain unknown.

That individuals with ASD evidence relatively greater search advantage compared to their typically developing (TD) peers with increasing target-distractor similarity has been used to support the hypothesis that enhanced discrimination contributes to faster search [O'Riordan & Plaisted, 2001], which is consistent with enhanced perceptual functioning in ASD [Mottron, Dawson, Soulières, Hubert, & Burack, 2006]. Alternatively, faster search may be due to more focused attention rather than enhanced lower-level perceptual processing [Blaser, Eglington, Carter, & Kaldy, 2014; Kaldy et al., 2016]. Lastly, evidence of increased perceptual capacity in ASD [Remington, Swettenham, Campbell, & Coleman, 2009; Remington, Swettenham, & Lavie, 2012] may facilitate enhanced peripheral selection, and, thus, faster target detection in ASD [Milne, Dunn, Freeth, & Rosas-Martinez, 2013]. Thus, while evidence of superior visual search in ASD has been shown across the lifespan using a variety of experimental paradigms, there is no consensus about the attentional and/or perceptual processes that may contribute to accelerated search in ASD.

In neurotypical individuals, interindividual differences in attention and perception are associated with region-specific concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [e.g., Edden, Muthukumaraswamy, Freeman, & Singh, 2009; Sumner, Edden, Bompas, Evans, & Singh, 2010]. For example, Sumner et al. [2010] showed that greater GABA levels in the right frontal eye fields (rFEF) (but not the visual cortex [VIS]) were associated with reduced distractor costs in a prosaccade task. Others have also demonstrated that general failures of selective attention are related to cortical GABA levels [Sandberg et al., 2014]. Furthermore, prior research has also shown that sensory perception thresholds are associated with region-specific GABA concentrations [e.g., orientation threshold-VIS: Edden et al., 2009; tactile perception-somatosensory cortex: Puts et al., 2017]. Within the visual domain, occipital and parietal GABA levels uniquely influence perception of different visual features (orientation and size, respectively) [Song, Sandberg, Andersen, Blicher, & Rees, 2017]. Together, these findings indicate that cortical GABA levels, which vary across distinct areas and between individuals, are associated with a variety of attentional and perceptual processes.

One model has hypothesized that ASD may result, in part, from atypically increased cortical excitation due to an imbalance of glutamatergic (excitatory) and GABAergic (inhibitory) signaling [Hussman, 2001; Rubenstein & Merzenich, 2003]. Magnetic resonance spectroscopy (MRS) has been used successfully to measure neurochemicals *in vivo*, including *N*-acetyl aspartate (NAA), total creatine (tCr), total choline (tCho), myo-inositol (mI), with a particular focus on glutamate and glutamine (Glx) and GABA, where reliable GABA measurements requires edited MRS techniques. To date, these studies have provided evidence of equivalent GABA levels compared to TD individuals in the VIS [Gaetz et al., 2014; Robertson, Ratai, & Kanwisher, 2016], striatum [Harada et al., 2011; Horder et al., 2018], and medial prefrontal cortex [Horder et al., 2018], as well as lower GABA concentrations in the sensorimotor cortex [Puts et al., 2017; Sapey-Triomphe, Lamberton, Sonié, Mattout, & Schmitz, 2019], frontal lobe [Harada et al., 2011; Kubas et al., 2012], and auditory cortex [Gaetz et al., 2014; Port et al., 2017; Rojas, Singel, Steinmetz, Hepburn, & Brown, 2014]. While there are several methodological differences between these studies, they suggest that discrete, region-specific differences in GABA may be present in individuals with ASD.

The objective of the present study was to use MRS to examine region-specific differences in GABA concentrations in three areas of interest, and to examine the relationship between GABA levels and visual search performance in ASD. These included two key nodes of dorsal and ventral attentional networks [Corbetta, Patel, & Shulman, 2008], the rFEF, and the right temporal–parietal junction (rTPJ), which play an important role in visual search [Shulman, Astafiev, McAvoy, D'Avossa, & Corbetta, 2007; Shulman et al., 2003]. Furthermore, as discussed, greater GABA levels in the rFEF have been shown to be associated with increased filtering of distracting information [Sumner et al., 2010]. Thus, if the ASD search advantage is related to differences in top-down, attentional filtering, faster performance will be associated with GABA levels in the rFEF. Alternatively, atypical activation and connectivity of the rTPJ in ASD has been shown during visual search [Keehn, Brenner, Palmer, Lincoln, & Müller, 2008; Keehn et al., 2013]. If enhanced search is associated with differences in the reorienting of attention to behaviorally relevant information (i.e., the target), then search metrics may be associated with rTPJ GABA concentrations. Finally, VIS was chosen to determine whether superior search in ASD is associated with enhanced discrimination [O'Riordan & Plaisted, 2001], as occipital GABA levels are associated with orientation perceptual thresholds [Edden et al., 2009; Song et al., 2017]. Finally, because others have hypothesized that an E/I imbalance may contribute to the development of ASD [Hussman, 2001; Rubenstein & Merzenich, 2003], and prior findings have shown an association between GABA and ASD symptom severity [Brix et al., 2015; Carvalho Pereira, Violante, Mouga, Oliveira, & Castelo-Branco, 2018] we examined the relationship between GABA levels and measures of ASD symptomatology.

Methods
Participants

Participants included 21 children with ASD and 20 age-, IQ-, sex-matched TD children (see Table 1). Clinical diagnoses were confirmed using the Autism Diagnostic Observation Schedule, Second Edition, [ADOS-2; Lord,

Table 1. Participant Demographics

		ASD	TD	P value
N (females)		21 (4)	20 (4)	
Age (years)		11.8 (1.2); 9.8–14.5	11.3 (1.7); 9.0–15.0	0.32
	FSIQ	104 (16); 76–132	112 (11); 98–133	0.07
	VIQ	104 (18); 75–154	111 (11); 97–127	0.17
IQ	NVIQ	103 (18); 59–132	110 (12); 94–134	0.13
	Total	75.7 (10.9); 58–90	43.3 (4.7); 37–55	<0.0001
	Social Communication and Interaction	75.3 (10.8); 58–90	42.9 (4.3); 36–53	<0.0001
SRS-2 (t-scores)	Restricted and Repetitive Behavior	74.8 (11.8); 50–90	45.6 (5.6); 41–59	<0.0001
	Social Affect	10.7 (3.8); 5–17	–	
	Restricted and Repetitive Behavior	2.2 (1.4); 0–5	–	
	Total	12.9 (4.4); 7–21	–	
ADOS-2	Comparison score	7.3 (2.1); 4–10	–	

Note. The values are represented as mean (SD); range unless otherwise specified.

Luyster, Gotham, & Guthrie, 2012], Social Communication Questionnaire [SCQ, Rutter, Bailey, & Lord, 2003], and expert clinical judgment according to DSM-5 criteria (R.M.K.). Children with ASD-related medical conditions (e.g., Fragile-X syndrome, tuberous sclerosis) were excluded. Participants in the TD group had no reported family history of ASD and were confirmed via parent report to be free of any other neurological or psychiatric conditions or clinically significant ASD symptoms as measured by the Social Responsiveness Scale, Second Edition [SRS-2; Constantino & Gruber, 2012] and the SCQ. Informed assent and consent were obtained from all participants and their caregivers in accordance with the Purdue University Institutional Review Board.
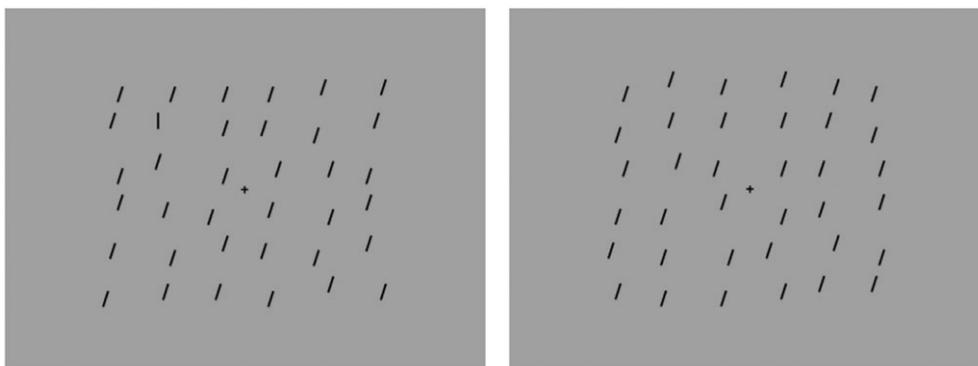
Visual Search Task

The experiment was presented using SR Research Experiment Builder 2.1 on a 19-in. LCD monitor. Participants were seated approximately 60 cm from the display. Manual responses were registered using a Cedrus response pad (RB-740).

The procedure and stimuli were similar to previous studies, which have reported superior search in ASD [Hessels, Hooge, Snijders, & Kemner, 2014; Kemner, Van Ewijk, Van Engeland, & Hooge, 2008; O'Riordan & Plaisted, 2001]. The target was a vertical line and the distractors were oblique lines (tilted 10°; Fig. 1). At a viewing distance of 60 cm, lines had a length of approximately 1.2° visual angle. Target and distractors were drawn in black on a gray background. Stimuli were randomly positioned on a 6×6 array of $1.1° \times 1.1°$ squares. The size of the entire search array was 18.6° by 15.7°. Items were randomly positioned within each square and across the array to produce layout irregularity.

The VST was divided into four blocks, each consisting of 36 trials. Within each block, the target was present on 50% of trials, and target presence (present, absent) and set size (18, 24, 36) were varied in pseudorandom order.

A trial began with a fixation cross ("+") presented alone for 1000 msec. Next, with the fixation cross remaining on the screen, the stimulus array was presented until a response was made or until 7000 msec had elapsed. Children responded with their dominant hand via a two-choice button box on which one button represented target present and the other target absent. The examiner first modeled the task and then participants completed a block of 12 practice trials. Participants were instructed to respond as quickly as possible without making errors. Reaction time (RT) was recorded and the median RT for

Figure 1. Example of visual search task (VST) for target present (left) and target absent (right) conditions (set size 36).

correct trials at each set size was used to measure the slope and y-intercept of the RT × set size function for target present and absent conditions for each participant. Search efficiency is indexed by slope, and reflects the cost of each additional distractor, whereas the y-intercept of the RT × set size function is the RT that would theoretically be observed if search were eliminated from the task.

Social Responsiveness Scale, Second Edition

The SRS-2 [Constantino & Gruber, 2012] is a 65-item caregiver report questionnaire used to measure ASD symptomatology in children from 4 to 18 years of age, across the domains of social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behavior subscales. Social subscales (awareness, cognition, communication, and motivation) are combined to form the Social Communication and Interaction (SCI) scale. The SCI and Restricted and Repetitive Behavior (RRB) DSM-5 Compatible scales and the total score t-scores were used for the correlational analyses.

Magnetic Resonance Imaging and MRS

Magnetic resonance imaging and MRS were performed on a 3T Prisma Siemens scanner with a 64-channel head coil separately from the VST (MRS and VST visits occurred no longer than 3 months apart; average duration between visits was 17 days). To minimize movement, participants' heads were stabilized with foam padding and they were instructed to remain as still as possible and watch a video of their choice for the duration of the scan. A high-resolution T1-weighted image (MPRAGE, echo time [TE] = 4.91, repetition time [TR] = 2000, inversion time [TI] = 977, flip angle [FA] = 9) was taken for MRS voxel placement and tissue segmentation. GABA was acquired using MEGA-semi-LASER localization (TE = 68, TR = 2000, averages =128, acquisition time = 8:56) [Andreychenko, Boer, Arteaga De Castro, Luijten, & Klomp, 2012; Klomp, Bitz, Heerschap, & Scheenen, 2009]. Prior studies have shown that when performing spectral editing [Mescher, Merkle, Kirsch, Garwood, & Gruetter, 1998] (as is the case with MEGA-sLASER) some macromolecular signal contributes to the total GABA signal, therefore we refer to GABA as GABA+. To measure the neurochemicals Glx, NAA, mI, tCh, and tCr, ^{1}H-MRS was acquired using semi-LASER localization (TE = 35, TR = 2000, averages = 64, acquisition time = 2:28) [Marjańska et al., 2013]. Unsuppressed water acquisitions were acquired as reference scans both for phase and eddy-current corrections as well as for quantification (ratio of metabolite over water) for both semi-LASER and MEGA-sLASER. Parameters for the reference scans were the same as for water suppressed scans with the exception of only eight averages acquired. Total acquisition time was approximately 45 min.

Volumes of interest (VOI) were placed in the rFEF (20 × 30 × 25), rTPJ (30 × 20 × 30), and VIS (30 × 30 × 20) using anatomical landmarks (Fig. 2). The rFEF VOI was positioned at the junction of the precentral and superior frontal sulci and aligned with the cortical surface, while remaining anterior to the central sulcus [similar to Sumner et al., 2010]. The rTPJ VOI was centered and aligned to the sylvian fissure and included superior temporal gyrus, supramarginal gyrus, angular gyrus, and posterior superior temporal sulcus, while remaining posterior to postcentral gyrus. Similar to Evans, McGonigle, and Edden [2010] and Muthukumaraswamy, Edden, Jones, Swettenham, and Singh [2009], the VIS VOI was centered on the midline, aligned with the cerebellar tentorium, and positioned anterior to the sagittal sinus [Evans et al., 2010; Muthukumaraswamy et al., 2009]. Absolute quantification of GABA, Glx, NAA, tCr, tCho, and mI was performed on spectra from each VOI with LCModel V6.3-1B [Provencher, 1993]. Basis sets used in LCModel were generated using density matrix simulation and using GABA coupling constants from Kaiser, Young, and Matson [2007]. Results from LCModel for each neurochemical were in mM and only neurochemicals with Cramer–Rao lower bounds of <20% across all participants were used for subsequent analyses. Tissue segmentation to obtain percentages of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) was performed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). All metabolites were CSF-corrected with the exception of GABA, which was tissue-corrected using the method as described in Harris, Puts, Barker, and Edden [2015] using an $\alpha = 0.5$ [Harris, Puts, & Edden, 2015].

To determine repeatability of VOI placement, each participant's VOI was aligned to a standard spatial template, MNI 152 (http://nist.mni.mcgill.ca). First, each participant's T1-weighted image was registered to the standard volume with FSL's FLIRT using 6 degrees of freedom. The resulting registered image then underwent nonlinear transformation into standard space using FSL's FNIRT. The resulting transformations from both FLIRT and FNIRT were then applied to the VOI mask using ApplyXFM and ApplyWarp, respectively. The resulting masks were combined into one image which was used to assess the repeatability of VOI placement.

Data Analyses

Wilk–Shapiro tests were performed to assess normality for each variable. Most neurochemicals and VST measures were not normally distributed and were therefore transformed. MRS were log-transformed whereas, due to negative values, VST measures were transformed using $y = \log(x + \min(x) + 1)$, where y is the transformed measure and x is the original measure.
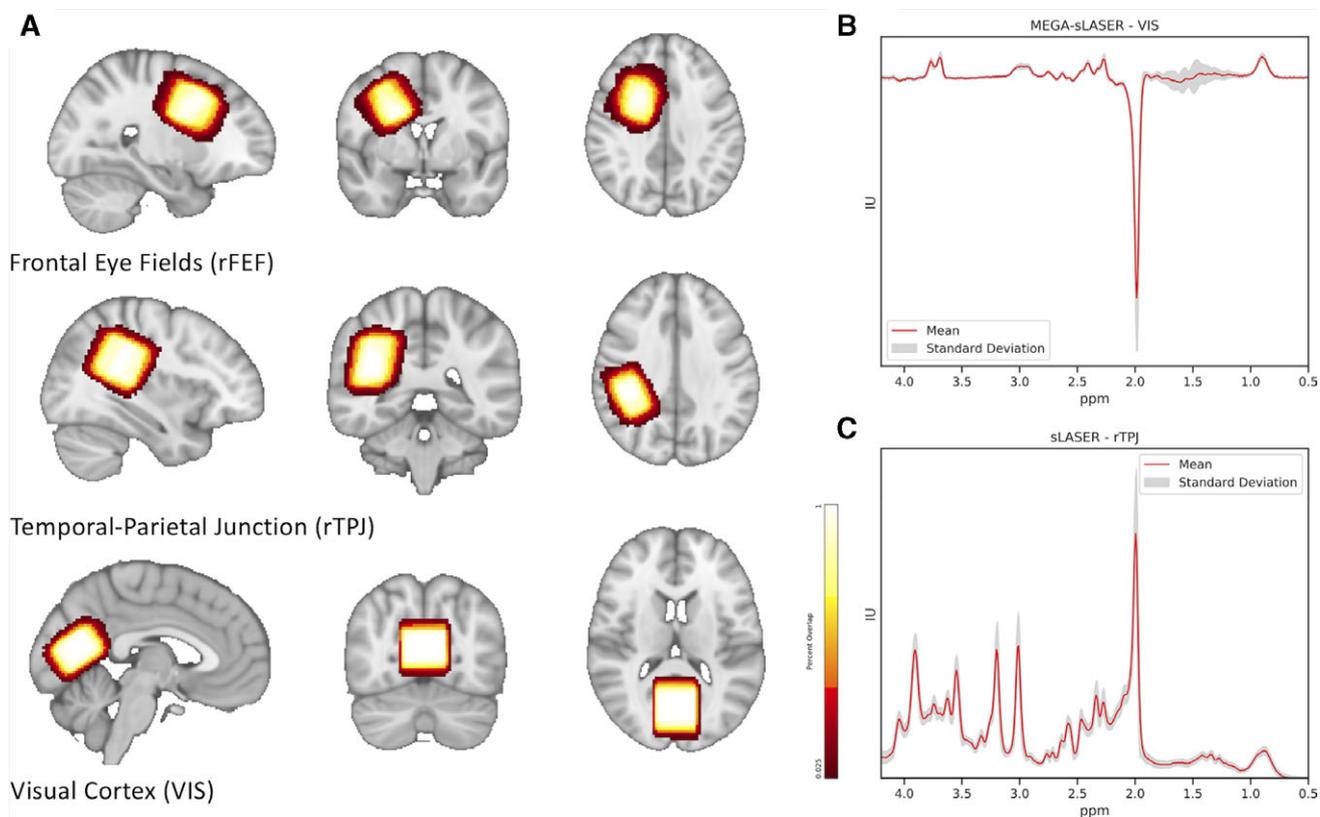
Figure 2. Volumes of interest (VOI) for magnetic resonance spectroscopy (MRS) acquisition. (A) Representative locations and the % overlap for repeatability of voxel placement in volumes of interest (VOIs): right frontal eye fields (rFEF, 78.8% overlap), right temporal–parietal junction (rTPJ, 84% overlap), and visual cortex (VIS, 82.3% overlap). Shown in radiological orientation. (B) Mean (standard deviation in gray) VIS difference spectrum acquired using MEGA-semi-LASER (MEGA-sLASER) with a TE of 68 msec, TR of 2000 msec, and 128 averages. (C) Mean rTPJ ^{1}H spectrum acquired using semi-LASER (sLASER) with an echo time (TE) of 35 mses, repetition time (TR) of 2000 msec, and 64 averages.

For assessing VST RT and accuracy, a mixed-model repeated measures analysis of variance (ANOVA) with between-subjects factor group (ASD, TD) and within-subjects factors of set size (18, 24, and 36) and target presence (present, absent). Other VST metrics (i.e., slope and y-intercept) were assessed using similar repeated measures ANOVA with between-subjects factor group (ASD, TD) and within-subjects factor target presence (present, absent). Post hoc analysis was performed using Tukey's honestly significant difference test.

To assess the effect of group (ASD, TD) on neurochemical (GABA+, Glx, NAA, mI, tCr, and tCh) concentration in each VOI (rFEF, rTPJ, and VIS), multivariate ANOVA (MANOVA) was performed followed by post hoc analysis using one-way ANOVA, correcting for multiple comparisons using false discovery rate (FDR). Due to collinearity of neurochemicals within each VOI, principle component analysis was used to transform data into principle components (PCs) for input into each MANOVA model. A number of PCs were used equal to 90% of total variance explained. Student t-tests were used to assess differences between groups in MRS quality assurance parameters.

Finally, to assess the relationships between neurochemicals and the VST metrics (RT, slope, and y-intercept), partial Pearson's product–moment correlation tests were used. While groups were matched for age, behavioral and MRS measures vary across the ages tested, therefore we corrected for age. P-values were corrected for multiple comparisons using FDR. An alpha of 0.05 was used to determine statistical significance for both uncorrected and corrected values.

Analyses were performed in the R environment [R Core Team, 2019]. Specific packages used included micompr [MANOVA, Fachada, Rodrigues, Lopes, Martins, & AC, 2016], emmeans [repeated measures ANOVA, Lenth, 2019], ppcor [partial correlations, Kim, 2015], and ggplot2 [figures, Wickham, 2016].

Results
Visual Search Task

Four children with ASD and one TD child were excluded from VST analyses due to accuracy rates below 60%. VST performance is summarized in Figure 3.
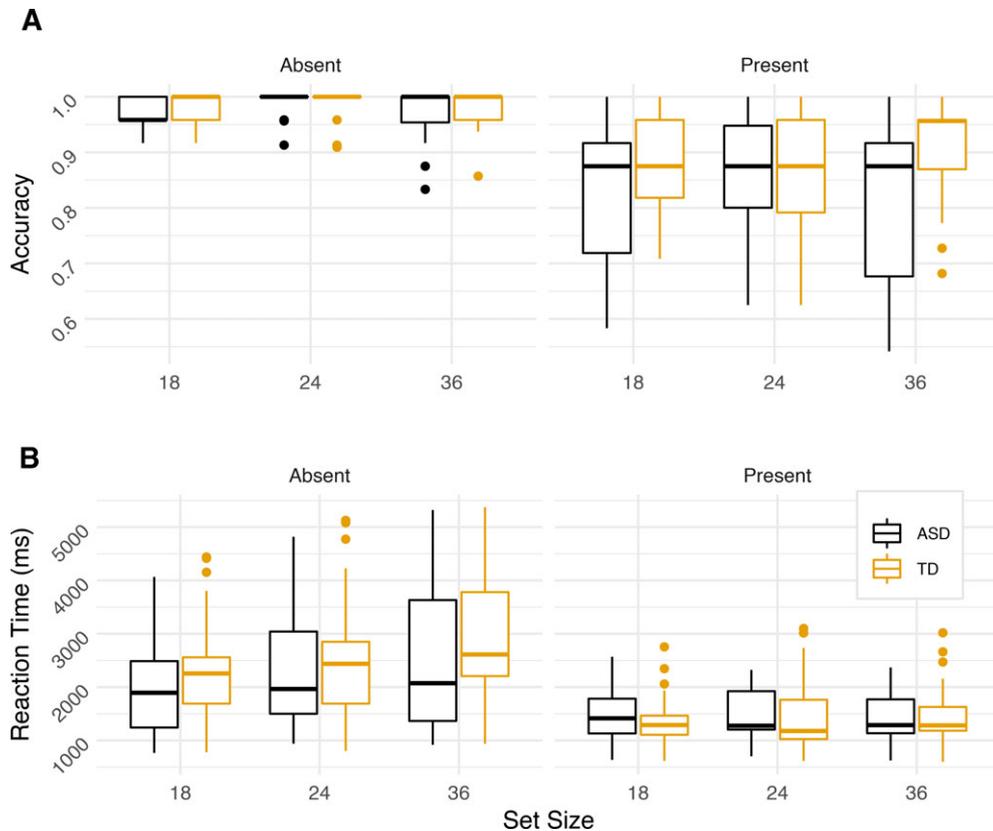
Figure 3. Visual search task performance. (A) Accuracy is shown for target absent and target present conditions in the VST across set sizes of 18, 24, and 36. (B) RT for the target absent and target present conditions are shown.

Accuracy. There was a significant main effect of target presence, $F(1, 37) = 65.459$, $P < 0.0001$, $\eta_p^2 = 0.64$, with greater accuracy for target present ($M = 0.98$; $SD = 0.02$) compared to target absent condition ($M = 0.86$; $SD = 0.10$) (Fig. 3A). There was no significant main effect for group, $F(1, 37) = 2.64$, $P = 0.11$, or set size, $F(2, 74) = 0.54$, $P = 0.59$, nor were there statistically significant interactions between group, target presence, or set size (all $P > 0.05$).

Reaction time. There were significant main effects of target presence, $F(1, 37) = 70.92$, $P < 0.0001$, $\eta_p^2 = 0.66$ and set size, $F(2, 74) = 30.29$, $P < 0.0001$, $\eta_p^2 = 0.45$. Post hoc analyses showed that RT was faster for present compared to absent ($P < 0.0001$) and increased at larger set sizes ($P < 0.0001$). Additionally, there was a significant interaction between target presence and set size, $F(2, 74) = 35.07$, $P < 0.0001$, $\eta_p^2 = 0.49$, as there was no difference in RT in the present condition across set size ($P = 1$), but RT did increase across set sizes in the absent condition ($P < 0.0001$) (Fig. 3B). However, there was no main effect of group, $F(1, 37) = 0.52$, $P = 0.48$, nor an interaction between group and target presence,

$F(1, 37) = 2.63$, $P = 0.11$, or set size, $F(2, 74) = 1.95$, $P = 0.17$.

Slope and γ-Intercept. For slope of the RT × set size function, there was a significant main effect of target presence, $F(1, 37) = 33.791$, $P < 0.0001$, $\eta_p^2 = 0.48$, as search was more efficient in target present compared to target absent trials (i.e., lower slope in present compared to absent). However, there was no significant difference for ASD and TD groups, $F(1, 37) = 2.17$, $P = 0.15$, nor was there an interaction between target presence and group, $F(1, 37) = 0.17$, $P = 0.68$. Likewise, for γ-intercept there was a significant main effect of target presence, $F(1, 37) = 5.82$, $P = 0.02$, $\eta_p^2 = 0.14$, but no significant main effect of group, $F(1, 37) = 0.01$, $P = 0.92$, nor an interaction between group and target presence, $F(1, 37) = 1.73$, $P = 0.20$.

Magnetic Resonance Spectroscopy

Quality assurance. Measures of quality assurance can be found in Table 2. Group differences between shims and spectral SNR were present. The TD group had larger shim values, as obtained from the Siemens preparation scans, than the ASD group in the rFEF (13.1 vs. 12.0 Hz,

Table 2. MR Spectroscopy Quality Assurance

	Shim (Hz)		
	rTPJ	rFEF	VIS
ASD	12.8 (1.4)	12.0 (0.7)	12.8 (0.7)
TD	14.2* (1.6)	13.1* (1.8)	13.2 (0.9)

	Segmentation (GM, WM, and CSF fractions)								
	rTPJ			rFEF			VIS		
	fGM	fWM	fCSF	fGM	fWM	fCSF	fGM	fWM	fCSF
ASD	0.35 (0.14)	0.62 (0.14)	0.03 (0.04)	0.28 (0.09)	0.70 (0.1)	0.02 (0.02)	0.72 (0.04)	0.22 (0.04)	0.07 (0.03)
TD	0.41 (0.07)	0.58 (0.07)	0.02 (0.01)	0.29 (0.05)	0.70 (0.05)	0.01 (0.004)	0.73 (0.04)	0.21 (0.04)	0.06 (0.02)

	FWHM (Hz)					
	rTPJ		rFEF		VIS	
	GABA	SVS	GABA	SVS	GABA	SVS
ASD	0.03 (0.009)	0.03 (0.004)	0.03 (0.003)	0.03 (0.008)	0.03 (0.006)	0.03 (0.004)
TD	0.03 (0.008)	0.03 (0.008)	0.03 (0.006)	0.02 (0.004)	0.03 (0.01)	0.03 (0.005)

	SNR					
	rTPJ		rFEF		VIS	
	GABA	SVS	GABA	SVS	GABA	SVS
ASD	46.2 (13.7)	69.5 (14.9)	43.9 (10.1)	56.2 (9.1)	53.3 (13.0)	91.8 (10.3)
TD	58.5* (12.5)	78.7* (9.9)	50.2 (14.0)	64.6** (5.9)	55.4 (15.2)	92.2 (7.0)

Note. The values are represented as mean (SD).

Abbreviations: fCSF, fractional cerebrospinal fluid; fGM, fractional gray matter; fWM, fractional white matter; GABA, gamma-aminobutyric acid, as acquired with MEGA-semi-LASER; rFEF, right frontal eye fields; SVS, single-voxel spectroscopy, as acquired with semi-LASER; rTPJ, right temporal–parietal junction; VIS, visual cortex.

Student's T-tests between ASD and TD: *$P < 0.05$; **$P < 0.01$.

$P = 0.02$) and the rTPJ (14.2 vs. 12.8 Hz, $P = 0.01$). However, it should be noted that all of these shim values represent good shims and produced high quality spectra. SNR was also higher in the TD group for MEGA-sLASER spectra in the rTPJ (58.5 vs. 46.2, $P = 0.01$). Semi-LASER spectra had higher SNR in the TD group for rTPJ spectra (78.7 vs. 69.5, $P = 0.01$) and rFEF spectra (64.6 vs. 56.2, $P = 0.003$). However, again, SNR is still considered high for all groups in this cohort. Linewidth (full width at half maximum; FWHM), obtained from LCModel analysis, was consistent across groups as was tissue segmentation in fractional GM (fGM), fractional WM (fWM), and fractional CSF (fCSF). Repeatability of VOI placement is shown in Figure 2. Combined with the consistent tissue fractions, the VOI placement was reasonably consistent across all participants with 78.8% overlap in the rFEF, 84% overlap in the rTPJ, and 82.3% overlap in the VIS.

Neurochemistry. No significant differences in GABA+ were found between TD and ASD (Fig. 4A). There were no significant differences in other neurochemicals for the rFEF or VIS VOI; however, groups did differ in the rTPJ VOI, Pillai's trace = 0.42, $F(1, 33) = 3.38$, $P = 0.01$. Post hoc analysis showed significant differences between TD and ASD in NAA, $F(1, 34) = 7.17$, $P = 0.02$, adj. $P = 0.03$, $\eta_p^2 = 0.17$ (Fig. 4B), tCr, $F(1, 34) = 7.70$, $P = 0.02$, adj. $P = 0.03$, $\eta_p^2 = 0.18$ (Fig. 4C), and Glx, $F(1, 34) = 16.3$, $P = 0.008$, adj. $P = 0.03$, $\eta_p^2 = 0.32$ (Fig. 4D). Due to differences in Glx between ASD and TD, there was a significant difference in GABA/Glx, $F(1, 34) = 7.69$, $P = 0.009$, adj. $P = 0.03$, $\eta_p^2 = 0.18$. Internal neurochemical ratios were not used because of significant differences in NAA and tCr, instead absolute values for neurochemicals were used.

Correlations Between VST, MRS, and ASD Symptomatology

As illustrated in Figure 5A, there was a significant association between VIS GABA+ and slope in the absent condition, $r(15) = -0.71$, $P = 0.0001$, adj. $P = 0.005$, for the ASD group, but not for TD group ($r = -0.12$). These two
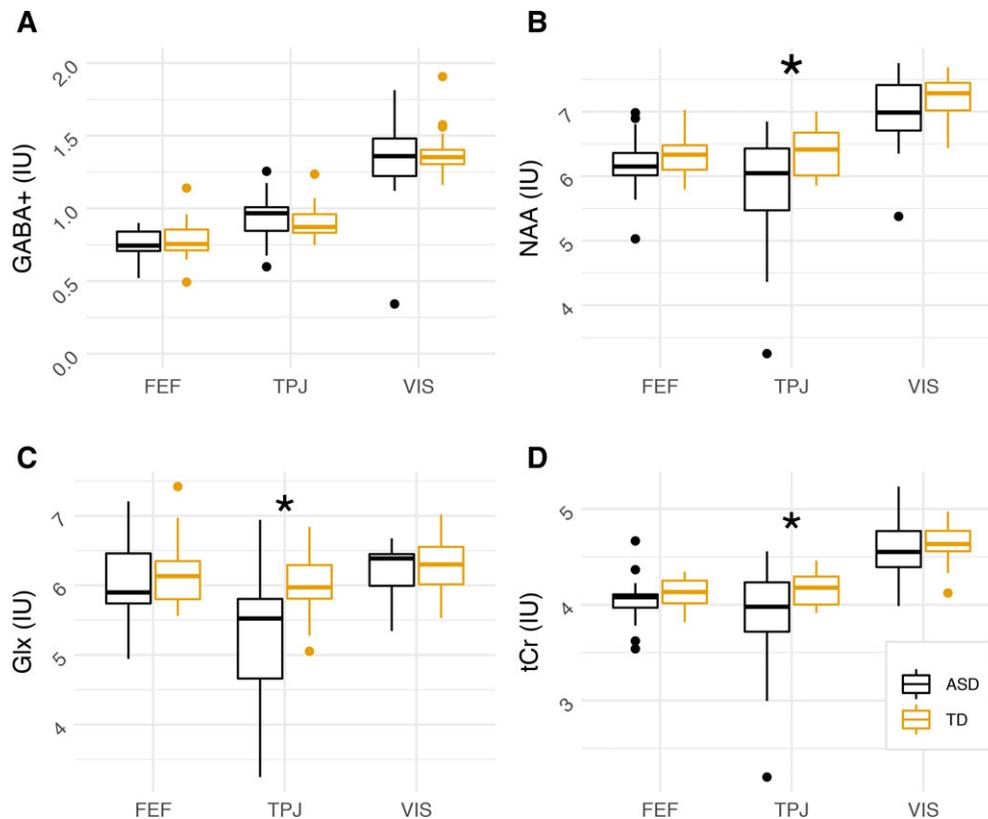
Figure 4. Box plots of metabolite concentrations for ASD and TD children. Distributions for neurochemicals in all three regions (rFEF, rTPJ, and VIS) are shown in (A) GABA+, (B) NAA, (C) Glx, and (D) tCr. Post hoc analysis showed there were significant differences in NAA, Glx, and tCr between ASD and TD in the TPJ. *Statistical significance where $P < 0.05$.

correlations were significantly different from one another (Fisher's $z = -2.209$, $P = 0.03$). Additionally, the SRS-2 Social Communication and Interaction (SCI) t-score was significantly correlated with VIS GABA+, $r(15) = -0.52$, $P = 0.02$, adj. $P = 0.26$), as was the SRS total t-score, $r(15) = -0.50$, $P = 0.02$, adj. $p = 0.26$, in ASD (but neither survived multiple comparison adjustment; Fig. 5B). There was no significant relationship between ADOS-2 Comparison score and GABA+ levels. Additionally, despite differences between ASD and TD for NAA, tCR, and Glx in the rTPJ, there were no significant correlations between any rTPJ neurochemical and ASD symptoms or VST performance.

Discussion

The objective of the present report was to investigate whether region-specific GABA concentrations may underlie superior search in children with ASD. Across all three VOI, GABA+ levels did not differ between groups; however, for children with ASD (but not TD), GABA+ concentration in the VIS was associated with more efficient visual search abilities. In addition, reduced VIS GABA+ values were related to increased ASD symptomatology.

Finally, significantly lower NAA, tCr, and Glx in the rTPJ provide further evidence of regional neurochemistry differences in ASD. Each will be discussed in turn.

No Evidence of Reduced GABA Concentrations

Contrary to our original hypothesis, we did not find any differences in GABA+ concentrations between ASD and TD. Other studies have investigated differences in GABA and showed no differences in the VIS [Gaetz et al., 2014; Robertson et al., 2016], striatum [Harada et al., 2011; Horder et al., 2018], and medial prefrontal cortex [Horder et al., 2018]. However, other studies have reported lower GABA levels in other areas, such as the sensorimotor cortex [Puts et al., 2017; Sapey-Triomphe et al., 2019], frontal lobe [Harada et al., 2011; Kubas et al., 2012], and auditory cortex [Gaetz et al., 2014; Port et al., 2017; Rojas et al., 2014].

Although these mixed results may result from region-specific group differences, methodological variability across studies may also contribute to these inconsistent findings. We used a measure for GABA that included the co-edited macromolecule signal (GABA+) and corrected for GM, WM, and CSF composition of the VOI [Harris,
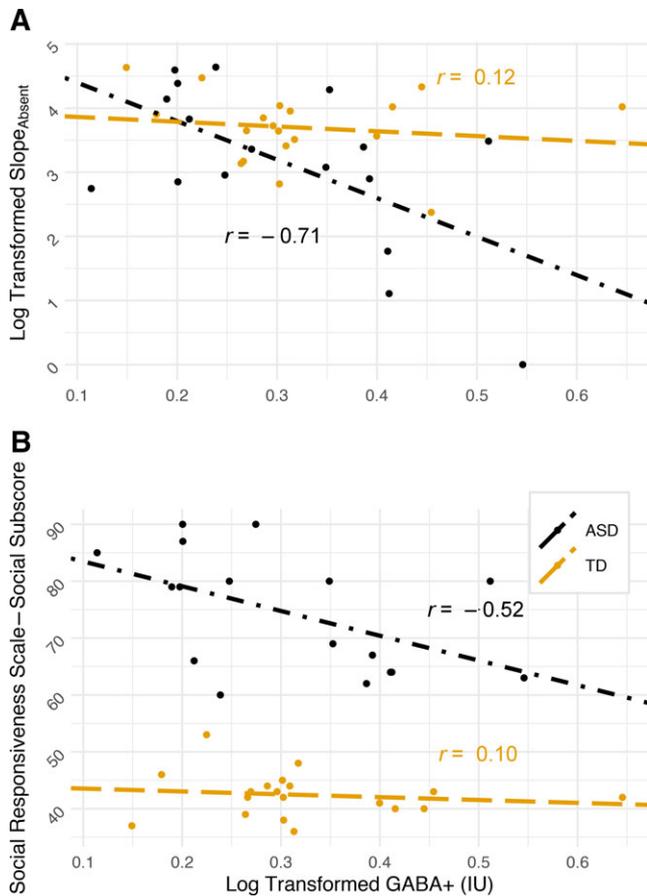
Figure 5. Correlations between GABA and VST performance and ASD symptomatology in the visual cortex (VIS). (A) Scatterplot of VIS VOI GABA+ values and RT × set size slope for the absent condition. (B) Scatterplot of VIS VOI GABA+ values and Social Responsiveness Scale (SRS) Social Communication and Interaction (SCI) scale.

Puts, Barker, et al., 2015]. A majority of the studies listed above that found decreases in GABA used internal metabolite references, such as GABA/tCr [Gaetz et al., 2014; Kubas et al., 2012; Port et al., 2017; Rojas et al., 2014] or GABA/NAA [Harada et al., 2011]. Additionally, we used an advanced method of voxel localization, semi-LASER, that minimizes the chemical shift displacement artifact (CSDA), which allows unwanted contributions of neurochemicals from outside the VOI to contribute to the signal. CSDA is a known complication in point-resolved spectroscopy (PRESS), which most previous studies used, and therefore consensus papers have suggested to cease using this sequence in research [Wilson et al., 2019]. Therefore, comparisons between prior and future studies that report GABA levels should be done mindful of these differences in methodology, especially in cases where internal references or PRESS were used. Nevertheless, our results provide further evidence that group differences in GABA+ concentrations are limited, and if present are likely to be region specific.

Relationship Between GABA and VST Performance

Our study provides further evidence of potential atypical GABA signaling in the VIS of individuals with ASD. Similar to reported deficits in binocular rivalry proportionate to lower GABA+ in children with ASD [Robertson et al., 2016] without differences in GABA+ between groups, findings from the present report show a strong negative relationship between VIS GABA+ and VST performance in children with ASD, but not in TD children (absent a difference in GABA+ in the VIS between ASD and TD). Children with ASD who had greater GABA+ concentrations demonstrated more efficient search performance.

In the present study target identification required orientation discrimination, which has shown to be enhanced or altered in ASD. For example, Dickinson et al. [2016] showed that individuals with ASD observed differences in orientation earlier than neurotypical individuals, suggesting improved orientation discrimination. This was accompanied with increased gamma-band response, further suggestive of increased neural inhibition in the VIS [Dickinson, Bruyns-Haylett, Smith, Jones, & Milne, 2016]. Using contextual illusions, Song et al. [2017] identified a significant positive correlation between occipital GABA+/tCr and orientation magnitude, whereas they found a significant positive correlation between parietal GABA+/tCr and size magnitude. Together, these results suggest that GABA levels in different cortical regions have an influence on different visual features [Song et al., 2017]. Therefore, it is possible that enhanced visual perception, in the form of improved orientation discrimination, might be the underlying cause of improved VST performance with higher GABA+, perhaps due to greater inhibition, in ASD.

In contrast to the findings from the present study, it should be noted, that others have reported region-specific reductions in GABA linked to poorer nonvisual discrimination abilities. For example, Puts et al. [2017] showed decreased somatosensory GABA levels in ASD, which were associated with higher tactile discrimination thresholds [Puts et al., 2017]. Similarly, reduced GABA in the auditory cortex and atypical gamma-band response to tones has been shown in ASD [Port et al., 2017]. Thus, while our findings are consistent with previous psychophysics and electrophysiology findings related to visual perception, these may differ from other sensory modalities.

GABA and ASD Symptomatology

Correlational analyses also suggested that there was an association between GABA+ and ASD symptomology. Specifically, higher SRS-2 scores (indicative of greater ASD symptomatology) were associated with reduced concentrations of GABA+ in the VIS. This finding is consistent with previous findings linking reductions in GABA to increases in ASD symptoms [Brix et al., 2015; Carvalho

Pereira et al., 2018]. However, in light of the inverse relationship between VIS GABA+ and VST performance, this result appears to be conflicting, especially given that prior reports have shown that faster, more efficient search is related to ASD symptom severity [Joseph et al., 2009; Keehn et al., 2013]. Due to these conflicts, as well as the result not surviving correction for multiple corrections, this finding should be interpreted with caution.

Differences in Neurochemical Concentrations in the rTPJ

While GABA+ levels did not differ between groups, results from the present study did show significant differences in other neurochemical concentrations (NAA, tCr, and Glx) between ASD and TD in the rTPJ. In children with ASD, NAA has been found to be lower in various regions of the cortex [Carvalho Pereira et al., 2018; Harada et al., 2011; Kleinhans, Schweinsburg, Cohen, Müller, & Courchesne, 2007; Kubas et al., 2012]. NAA is a neuronal marker representing neurodysfunction or neuronal loss [de Graaf, 2018]. Kubas et al. [2012] also found lower NAA/Cr and Glx/Cr in the frontal cortex, with no changes in Cr. The combined term of phosphocreatine and creatine, tCr, is a marker for energy metabolism where it functions as an energy buffer and shuttle. Decreases in tCr have been found in the occipital [DeVito et al., 2007; Levitt et al., 2003], temporal [DeVito et al., 2007], frontal [Friedman et al., 2006], and parietal lobes [Friedman et al., 2003], as well as the thalamus [Friedman et al., 2003; Hardan et al., 2008]. Glx findings appear to be regionally specific as well, with prior studies showing both elevated [Bejjani et al., 2012] and decreased Glx levels [Corrigan et al., 2013; DeVito et al., 2007]. Combined, these results suggest dysfunction in the rTPJ that may be associated with decreased Glx, and thus resulting in an excitatory/inhibitory destabilization, perhaps in regions projecting from the rTPJ.

The rTPJ is a supramodal association area, which plays a role in both social and non-social cognitive abilities [Carter & Huettel, 2013] and follows a unique developmental trajectory [Sowell, 2004]. Atypical activation, possibly due to neuronal dysfunction in the rTPJ, in individuals with ASD has been shown using a variety of paradigms, including social information processing paradigms, such as mentalizing tasks [e.g., Castelli, 2002; Lombardo et al., 2010], as well as non-social attention tasks [Gomot et al., 2006; Keehn, Nair, Lincoln, Townsend, & Müller, 2016]. Functional connectivity studies have also demonstrated that this region is a critical node in multiple functional brain networks [Jakobs et al., 2012], and that children with ASD exhibit atypical functional differentiation and the absence of typical age-related changes in specialization of rTPJ-linked cortical networks [Shih et al., 2011]. Collectively, these studies and our results suggest further exploration into differences between ASD and TD may be needed for further understanding the role of this area in the development of ASD.

Limitations

Children with ASD in the present study did not demonstrate faster, more efficient search. The ASD search advantage is greater for more difficult visual search paradigms. The present task may have been too easy to elicit significant differences in performance between ASD and TD. Nonetheless, we were able to identify differences between ASD and TD in terms of neurochemistry and their contribution to VST performance. Second, medication use was not an exclusionary criterion for the present study, and some children with ASD ($n = 10$) in the current study were prescribed psychotropic medication. Although these drugs did not specifically target the GABAergic or glutamatergic systems, our results should be interpreted with caution. Finally, MRS cannot determine the type of GABA measured, whether within a neurotransmitter or metabolite pool. Therefore, while GABA is the major inhibitory neurotransmitter in the CNS, we are unable to identify whether concentration differences are present in the synapse versus storage vesicles. Future research employing more advanced techniques, specifically diffusion-weighted MRS [Ligneul et al., 2019; Ronen, Ercan, & Webb, 2013], may be able to determine what type of GABA contributes to the measured GABA signal.

Conclusions

Together, our findings are in agreement with prior reports that show equivalent GABA levels in ASD and TD children [Gaetz et al., 2014; Harada et al., 2011; Horder et al., 2018; Robertson et al., 2016]; however, correlational findings indicate that visual search superiority in individuals with ASD may be associated with GABA signaling in the VIS, and suggest that more efficient visual search is achieved via enhanced visual discrimination. Additionally, children with ASD showed decreased NAA, tCr, and Glx in the rTPJ compared to their TD peers. Evidence of neurochemical differences in the rTPJ along with prior findings of atypical activation and connectivity suggest this region, which plays a key role in sensory integration and social and nonsocial cognition, may be disrupted in ASD.

Acknowledgments

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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