

Semantic decisions in adolescents with autism spectrum disorder – functional magnetic resonance imaging study

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Summary

Aim. The aim of this article is to assess fMRI activation during semantic tasks in adolescents with ASD.

Material. 44 right-handed male adolescents aged 12–19 (mean 14.3 ± 2.0), 31 with autism spectrum disorder who met DSM–IV–TR criteria for Asperger syndrome and 13 neurotypical adolescents matched according to age and handedness.

Method. Functional testing (fMRI) was performed during semantic decisions tasks and control phonological decisions in three categories of tasks: concrete nouns, verbs with multiple meanings, words describing states of mind, as a control condition. Statistical analyzes were performed at the level of $p < 0.05$ with FWE (family-wise error) correction and $p < 0.001$.

Results. In the ASD group, lower BOLD signal was demonstrated in many brain areas (including the precuneus, the posterior cingulate gyrus, the angular gyrus, the parahippocampal gyrus) regardless of task category and processing method. The smallest differences in semantic processing were found for concrete nouns and the greatest ones for words describing states of mind.

Conclusions. The presence of different activation patterns in the ASD group suggests that far more than just the areas of the CNS traditionally attributed to language processing are involved in semantic deficits in ASD.

Key words: autism spectrum disorder, functional magnetic resonance imaging, semantic processing

Introduction

Autism spectrum disorders (ASD) are characterized by deficits in social communication and by limited, repetitive patterns of behavior [1]. They form a group of neurodevelopmental disorders, currently considered to be among the most common

psychiatric problems in children and adolescents, with a prevalence of about 1% [2]. Results of neurofunctional research [3], including functional magnetic resonance imaging (fMRI), indicate altered connectivity within and between brain networks in ASD. Under-connectivity of neural networks involved in various tasks, such as speech and language processing, theory of mind processing, executive functions, working memory, and visual-spatial processing has been observed [5–8]. However, other studies [9] show that the problem is more complex and includes not only reduced connectivity, but also functional over-connectivity while performing tasks, also observed in resting state fMRI paradigms, without an external task. Some researchers postulate [10] reduced connectivity between distant regions, and increased local connectivity. There is an increasing number of studies [11] that allow us to assume that in ASD we are dealing with ineffective organization of neural networks resulting from poor functional differentiation and integration.

The presence of communication deficits in ASD, including semantic ones, often of very different intensity, justifies functional research on speech and language processing. The results of fMRI studies [4, 12–18] revealed decreased synchronization between brain regions involved in language processing, differential lateralization patterns (i.e., reduced left lateralization) as well as the involvement of brain regions that do not typically process speech. The findings also revealed atypical semantic processing patterns – i.e., substantially reduced [19, 20] or stronger [21] activation in Broca's area.

The aim of our study was to evaluate fMRI brain activation patterns in adolescents with ASD during semantic decision tasks. Most likely, the semantic deficits in autism spectrum disorder are associated with abnormal functional organization of not only cortical linguistic areas but also other regions involved in processing of meanings. Based on current functional studies [22], it can be assumed that phonological processing of speech sounds is related to the left superior temporal cortex, left inferior frontal gyrus and left inferior parietal cortex around the supramarginal gyrus. Activation from Heschl's gyri extends in multiple directions, including the middle and inferior temporal gyri, also the medial temporal cortex (fusiform gyrus and parahippocampal gyrus). A pattern of gradual activation in these structures was observed in the process of specific semantic associations formation. The integration of semantic meanings is related to the activation of the medial and lower parietal cortex (angular gyrus, precuneus and posterior cingulate cortex), and the selection of meanings is related to the activation of the superior, middle and inferior frontal gyrus. The involvement of the right cerebellum and the homologous areas of the right hemisphere, participating in the integration of semantic concepts and executive processing, is also emphasized.

Aim of the study: To identify the fMRI activation patterns in a group of adolescents with ASD during semantic decision tasks in three categories (concrete nouns, verbs describing activities with context dependent meaning and words describing states of the mind).

Material

The evaluated group consisted of 63 Polish-speaking, right-handed male adolescents aged 12 to 19 years – 42 adolescents with ASD and 21 adolescents in the control group (HC). Subjects who experienced excessive head movements during functional scanning (6 adolescents with ASD and 5 from the HC group) and those who had massive motor artifacts due to the inability to lie down for a long time (5 adolescents with ASD and 3 from the HC group) were excluded. 44 subjects were included in the final analyses. ASD sample consisted of 31 adolescents (ASD group) who met DSM-IV-TR [23] criteria for Asperger's syndrome – the diagnosis was confirmed by experienced clinicians (the assessment included the analysis of the Childhood Asperger's Syndrome Test – CAST results [24], developmental history with particular emphasis on data pertaining to specific aspects of social, linguistic, cognitive, and motor competences, qualitative interest analysis, psychiatric and behavioral observation). The control group included 13 typically developing adolescents matched according to age and handedness (HC group). No significant differences were observed in terms of age between ASD and HC group (14.3 years \pm 2 vs. 14.4 years \pm 2).

All participants were right-handed – the handedness was evaluated according to the writing hand, self-report and the Edinburgh Handedness Inventory [25]. Intellectual functioning, as measured with the Wechsler Intelligence Scale for Children – Revised (WISC-R) or Wechsler Adult Intelligence Scale – Revised (WAIS-R) was normal in both ASD (full scale IQ = 106 points \pm 17, range 77–135 points; verbal IQ = 107 points \pm 18, range 85–146 points; non-verbal IQ = 102 points \pm 17, range 70–141 points) and control group (full scale IQ = 128 points \pm 13, range 95–144 points; verbal IQ = 125 points \pm 14, range 93–145 points; non-verbal IQ = 126 points \pm 13, range 97–142 points). The selection to study groups did not take into account the criterion of homogeneity of IQ results.

Exclusion criteria involved: diagnosed genetic disorder, CNS damage or seizures within the period of three years prior to the study, ferromagnetic metal implants for both groups and the history of DSM-IV-TR Axis I psychiatric disorder in control subjects. All participants signed an informed consent form. For subjects younger than 18, a written consent was also signed by caregivers. The study was approved by the Bioethics Committee at the Medical University of Warsaw.

Method

To activate the regions responsible for semantic processing we used juxtaposition of semantic tasks (questioning about the meaning of words or phrases) and control perceptual tasks (phonological). The study paradigm involved questions about the meaning of three different categories of stimuli, ordered according to semantic processing difficulties: 1. concrete nouns, 2. verbs describing activities with context depend-

ent meaning (idioms) and 3. words referring to the theory of mind (ToM) describing states of the mind.

Paradigm

The activating stimuli were presented auditorily, binaurally via MRI-compatible headphones, answers provided by the respondents were registered by cordless response pads dedicated to MRI use.

Each subject participated in three consecutive functional scan sessions (a single session included questions from one stimulus category). Each session included 3 consecutive tasks: semantic decision, phonological decision and motor control, preceded by instruction presentation, repeated in block design. Each semantic decision task and phonological decision task consisted of pairs of words/expressions while a single word was presented in motor tasks.

The stimuli in the semantic decision tasks, phonological decision tasks and the motor control task were presented with 6-second intervals, while in each block the stimuli were presented 7 times. Within each session, each task was repeated four times. A single task block was 42 s long and an instruction block was 20 s long. The total duration of each block was 3 min 6 s, and the duration of each session was 12 min and 24 s.

During semantic decisions task, subjects were asked to assess whether the presented pairs of words had the same meaning ('do they mean the same?'), and whether the given pairs of phrases described the same activity. In the control phonological decisions tasks, the subjects were asked to judge whether the presented word pairs began with the same letter or whether subsequent words in the given phrases began with the same letter. During the motor control tasks, subjects were asked to press the right or left response pad button as instructed. In the first session, the subjects performed tasks from the concrete noun category (i.e., 'a stick' and 'a twig'), during the second session they made decisions about context-dependent plural meanings – the category of idioms (i.e., 'to kick a colleague' and 'to kick a habit'), and during the third session, decisions about words describing mental states – the category of ToM words (i.e., 'fear' and 'anxiety'). Before scanner examination, each participant was acquainted with the task and had three practice sessions.

fMRI activation parameters

Functional testing were performed using a 3T Magnetom TRIO TIM Siemens scanner (ver. VB17A) and 12-channel Matrix Head Coil. For acoustic stimulation Nordic Neuro Lab electrostatic headphones dedicated for use in an MRI scanner were used at 90 dB. To evaluate and exclude subjects with brain pathology, standard T1 and T2 sequences were applied. For functional imaging a T2* SingleShot Echo-Planar Imaging (EPI) and for anatomical reference a 3D high-resolution T1 sequence were

used. No contrast agent was administered. The parameters of the sequences were as follows:

- a. T1 MPR (Multi Planar Reconstruction) high-resolution sequence: 208 sagittal slices with isotropic resolution 0.9 x 0.9 x 0.9 mm; TR = 1900 ms; TE = 2.21ms; TI = 900 ms; FA = 9.0; FOV = 260 x 288 mm; matrix = 320 x 290; Pixel bandwidth = 200 Hz/pix; iPAT = 2; TA = 5min;
- b. T2* SingleShot EPI sequence: 49 axial slices with isotropic resolution 3 x 3 x 3 mm; TR = 3000 ms; TE = 30 ms; FA = 90.0; FOV = 192 x 192mm; matrix = 64 x 64; Pixel bandwidth = 2230 Hz/pix, iPAT = 1; 248 volumes in series; TA=12 min 24 s.

Data processing and analysis

Subjects with head movements exceeding 1.5 mm were excluded from the analyses (6 participants from the ASD group and 5 from participants from the HC group). Data analysis was performed using the SPM8 package (Wellcome Department of Imaging Neuroscience, London, www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks Inc., Sherborn, MA, USA). Single-subject pre-processing was done using standard procedures. Functional scans from all series were realigned to the first image of the time series, normalized to a standard brain atlas EPI template SPM8 MNI space and smoothed using a 6 mm FWHM Gaussian kernel. Next, a general linear model (GLM) and a standard hemodynamic response function (HRF) were fitted to the data. Motion parameters were used as regressors in GLM. Time-series for each voxel were high-pass filtered (1/128 Hz) to remove low-frequency noise and signal drift. Due to some respondents' excessive movements, some particular scans were omitted in the analysis (when the relative movement exceeded 1mm). A special script written in MATLAB was used to verify the correctness of the realignment algorithm.

In second-level statistical analysis, full-factorial design was applied with the following factors: (1) group (HC group vs. ASD group), (2) material (concrete nouns vs. verbs with multiple meanings (idioms) vs. words describing states of mind (ToM words)), (3) cognitive processing (semantic decision vs. phonological decision). Two sample T-test as well as full factorial (ANOVA) analysis were used to compare means and variations of activations. Firstly, the hot spot analyses were performed on individual and group data. The aim of hot spot analysis was to show which regions of the brain are involved in test performance and to show a group effect. In first-level analyses, two contrasts were calculated: phonological decision vs. motor control and semantic decision vs. motor control. These two contrasts were taken to the second-level analyses. All analyses were tested both on $p < 0.001$ without family-wise error (FWE) correction and $p < 0.05$ with FWE correction.

Results

The majority of the simple and complex comparisons were statistically insignificant after the FWE correction although the localization of activations in those comparisons reflected the ones observed in the main effects of the full factorial analysis (Table 1). In the full factorial analysis, no significant interactions were found between the specified factors, i.e., between (1) the group x material x cognitive processing factor, (2) the group x material factor, (3) the group x cognitive processing factor, and (4) the material x cognitive processing factor; therefore, the main effects are interpretable.

The following tables present the activation results for the main effects in the full factor analysis (contrast HC group vs. ASD group; Table 1), for simple within-group comparisons (semantic decisions > motor control, phonological decisions > motor control, semantic decisions > phonological control, phonological control > semantic decisions; Table 2) and for intergroup and within-group complex comparisons (semantic decisions made in various task categories by subjects from the ASD group and subjects from the HC group; Table 3 and Table 4). In the tables, the anatomical locations are described using the abbreviations of English names, the expansion of which is given below Table 4.

Table 1. **Regions of activations for main effects (full factorial analysis)**

	p <0.001	p <0.05 with FWE
HC group vs. ASD group	bIFG, bMFG, bACC, bCN, bPC, rPL, bCereb	bACC, ICN, bPCN, rSMG, rCereb
Concrete nouns vs. idioms vs. ToM words	IMFG, bACC, bPCC, IFG	bACC, IPCC, IFG
Semantic decisions vs. phonological decisions	lIFG, bSTG, bPCN, bSPL, bPCC, rCereb	-

Table 2. **Regions of activations for simple within-group comparisons**

	ASD group					
	Concrete nouns		Idioms		ToM words	
	p <0.001	p <0.05 with FWE	p <0.001	p <0.05 with FWE	p <0.001	p <0.05 with FWE
Sem > Motor	lIFG, IMFG, bSTG, IMTG, lflNS	bSTG	lIFG, IMFG, lSTG, IMTG, bflNS, rCereb	lIFG, lSTG, IMTG	lIFG, IMFG, bSTG, rTP, bflNS, rCereb	lIFG, bSTG

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Phon > Motor	IMFG, bSTG, IMTG, bACC, rCereb	-	IMFG, bSTG, bSPL, bACC, rCereb	IMFG, bSTG,	IIFG, bMFG, bSTG, bMTG, bfINS, bIPL	bSTG
Sem > Phon	pTP	-	IMFG, ISTG, bCereb	-	bCereb	-
Phon > Sem	pPCC, pfINS	-	bSTG, IPCN, IIPL, bACC, bPCC	rSTG	IMFG, bACC, bPCN	-
HC group						
	Concrete nouns		Idioms		ToM words	
	p <0.001	p <0.05 with FWE	p <0.001	p <0.05 with FWE	p <0.001	p <0.05 with FWE
Sem > Motor	IIFG, ISFG, IMTG, bfINS, rCereb	-	IIFG, bSTG, bMTG, bfINS, bACC, bPCC, bCereb	IIFG	IIFG, IMFG, ISTG, IMTG, fINS, rCereb	ISTG
Phon > Motor	IIFG	IIFG	IIFG, IMFG, bSTG, bMTG, fINS, bIPL, bCereb	ISTG, rCereb	IMFG, ISTG	ISTG
Sem > Phon	-	-	bMFG, ISTG, bACC bPCC	-	IMFG, fINS, IMTG, rCereb	-
Phon > Sem	IPCN	-	IIFG, rSTG, bIPL, bSPL	IIPL	bPCN, bPCC	-

Sem – semantic decisions; Phon – phonological decisions; Motor – motor control

Table 3. Regions of activations for complex intergroup comparisons (semantic decisions)

p <0.001	ASD group > HC group	HC group > ASD group
Concrete nouns	-	bPCN
Idioms	IMTG	bACC, IPCC, rFC
ToM words	bSTG, rMTG, rIPL	IIPL, rCN, rACC, rPCC

Table 4. Regions of activations for complex within-group comparisons (semantic decisions)

p <0.001	ASD group	HC group
Concrete nouns > idioms	bACC, bPCN	-
Idioms > concrete nouns	IMTG	-
Concrete nouns > ToM words	bACC, bPCN	bACC, bPCC
ToM words > concrete nouns	bMTG, bIPL	-

table continued on the next page

Idioms > ToM words	IPHG	IPCC, IMFG
ToM words > idioms	rMTG	ISFG

IFG – inferior frontal gyrus; MFG – middle frontal gyrus; FC – frontal cortex; STG – superior temporal gyrus; MTG – middle temporal gyrus; TP – temporal pole; FG – fusiform gyrus; fINS – frontal insula; ACC – anterior cingulate cortex; PCC – posterior cingulate cortex; CN – cuneus; PCN – precuneus; SPL – superior parietal lobule; IPL – inferior parietal lobule; PHG – parahippocampal gyrus; SMG – supramarginal gyrus; Cereb – cerebellum; r – right; l – left; b – bilateral.

Discussion

A combination of semantic and perceptual tasks, which is one of the most frequently used methods of the Broca's area activation, was used to activate the areas responsible for the semantic processing. Activating stimuli were presented auditorily, the goal of which was to improve cooperation. However, the visual presentation of the stimuli can be justified, as it enables better differentiation of the obtained activations (activation in the fronto-temporal areas for semantic tasks vs. activation in the occipital areas for control visual perceptual tasks). Auditory presentation of the stimuli did not make it impossible to differentiate between activations obtained in semantic tasks and perceptual-phonological control tasks (inferior left prefrontal cortex activation in semantic tasks vs. superior left prefrontal cortex activation in phonological tasks) [26].

As expected, significantly higher BOLD signal was observed in both groups in both semantic and phonological tasks, mostly in the areas associated with auditory (temporal cortex) or language processing (superior and middle temporal gyrus, inferior frontal gyrus), with left lateralization of functions (results of the simple within-group comparisons – semantic decisions > motor control as well as phonological decisions > motor control contrasts; Table 2). Although some studies [12, 27] revealed atypical language laterality (reduced left or reversed – right greater than left) in the ASD group, we failed to replicate this finding.

The main effect of the cognitive processing factor (semantic decisions vs. phonological decisions contrast; Table 1) indicates that the left inferior frontal gyrus, the right and left superior temporal gyrus, the superior and medial parietal cortex, the cingulate cortex, and the cerebellum were involved in different types of language processing. Significant differences were most notable in the idioms and ToM words category (results of the simple within-group comparisons: semantic decisions > phonological decisions or phonological decisions > semantic decisions contrasts; Table 2). The left superior temporal gyrus and the right cerebellum were activated strongly during semantic decisions in both groups as well as the left medial frontal gyrus in the ASD group and the bilateral medial frontal gyrus in the HC group. Furthermore, the left frontal part of the insula, the left middle temporal gyrus, and medial structures of the prefrontal cortex (anterior cingulate cortex) and the parietal cortex (posterior cingulate cortex)

were involved in semantic processing of the stimuli in the HC group, but not in the ASD group. Taking all this into account, we can assume that many more structures were involved in the semantic processing in the HC group than in the ASD group. In turn, phonological processing in both groups was bilaterally related to a higher BOLD signal in the superior temporal cortex but also the inferior and medial parietal cortex (inferior parietal lobuli, precuneus and posterior cingulate cortex). The superior parietal lobuli and the left inferior frontal gyrus were strongly activated during phonological decisions in the HC group, while in the ASD group stronger activations were additionally observed in the middle or medial frontal cortex (left middle frontal gyrus, anterior cingulate cortex) and the right frontal part of the insula.

The most interesting finding was obtained for the main effects and concerns the group factor (HC group vs. ASD group contrast; Table 1). Significantly lower BOLD signal in the ASD group was observed bilaterally in several regions irrespective of the material and the processing type (concrete nouns, idioms or ToM words; semantic decisions or phonological decisions). These regions included: the frontal cortex (inferior frontal gyrus, middle frontal gyrus), medial prefrontal cortex (anterior cingulate cortex), parietal cortex (precuneus, inferior parietal lobule around the supramarginal gyrus), occipital cortex (cuneus), and the cerebellum. The activations illustrating these intergroup differences partly overlap with the brain areas included in the default mode network (DMN). This network includes the middle frontal regions (the middle prefrontal cortex, including the superior frontal gyrus and the anterior cingulate cortex), the middle parietal regions (precuneus and posterior cingulate cortex), lateral parietal regions (right and left angular gyrus, right and left inferior parietal lobuli) and medial temporal regions (parahippocampal gyrus), which are mostly activated in resting state (no task) [28] but also during ToM-related tasks. These areas are significantly less activated in subjects with ASD as a consequence of poorly developed introspective and auto-reflective thinking.

The results of complex intergroup comparisons provide further insight into differences in semantic processing (Table 3). The HC group showed significantly higher BOLD signal in the anterior and posterior part of the cingulate cortex, bilateral precuneus and cuneus, while the ASD group showed a higher signal mainly in the areas involved in the perceptual stimuli analysis or attention processing, i.e., superior and middle temporal gyrus and the right inferior parietal lobule. It seems that the number of areas with significant intergroup differences depended on the task category. The smallest group differences occurred in the concrete nouns category while the greatest group differences were observed in the category of words describing states of mind (ToM words category). Therefore, it can be assumed that the more difficult the task was (i.e., it required a more complicated and complex processing), the greater intergroup differences were observed.

Another result revealed differences between the semantic processing of different categories of tasks. The main effect of the material factor (concrete nouns vs. idioms vs. ToM words contrast) showed differences in the left middle frontal gyrus, anterior and posterior cingulate cortex and left fusiform gyrus (Table 1). Furthermore, in the ASD group, the differences were observed in all comparisons of semantic decisions in different task categories (the complex within-group comparisons for semantic decisions; Table 4). Semantic decisions in the category of concrete nouns was associated with a stronger activation of the anterior cingulate cortex and precuneus compared to idioms or ToM words categories in the ASD group (concrete nouns > idioms and concrete nouns > ToM words contrast). In opposite comparisons (idioms > concrete nouns and ToM words > concrete nouns) differences in the ASD group were related to the middle temporal gyrus or inferior parietal lobule. In the HC group, significant differences were found for a much smaller number of comparisons, including concrete nouns > ToM words comparison (the area of the anterior and posterior cingulate cortex) and contrasts concerning the semantic processing of idioms and ToM words (differences in the posterior cingulate cortex and frontal cortex, including left superior or middle frontal gyrus). Importantly, in the ASD group, the smallest differences were observed for the comparisons of the semantic idioms and ToM words processing (differences in the BOLD signal in the areas of auditory processing – middle temporal gyrus and parahippocampal gyrus). It may be concluded that during the semantic processing of potentially difficult tasks (i.e., idioms or ToM words), which require wide networks arousal and integration, the ASD group tended to activate perceptual processes, more focused on the perception of stimuli (temporal cortex) or attention processes (right inferior parietal lobule), whereas the healthy controls relied more on their own knowledge and experience (more focused on the understanding of stimuli).

The observed differences may be related to diverse cognitive strategies used in semantic processing by ASD and neurotypical subjects, which is confirmed by the results of neuroimaging studies (according to Gaffrey et al. [19] subjects with ASD activate areas related to stimulus visualization processes when performing semantic tasks, while Harris et al. [20] found less pronounced differences in activation patterns for semantic tasks processing and visual perceptual tasks processing in ASD). The observations indicate that the subjects with ASD primarily use visual-spatial strategies during linguistic processing, even when performing advanced cognitive tasks. This may be due to a deficit in the neural networks development in the fronto-temporal language areas, and, to the over-connectivity in the occipital-parietal regions [29]. Based on our results, the possibility of compensatory auditory strategies intensification in ASD, challenged by difficult verbal stimuli should be considered.

Study limitations

1. The relatively small sample size is a major limitation of the study. Initially, the experimental group consisted of 63 subjects (42 adolescents with ASD, 21 adolescents in HC group). However the final, individual and group analysis of fMRI activation was based on the results of 31 subjects with ASD and 13 subjects in the HC group. The exclusion of some of the obtained activations was mainly due to the excessive head movements during functional scanning and the inability to lie down for a long time (massive motor artifacts). Proper execution of fMRI paradigms very often encounters difficulties, mainly related to the need to lie still in the scanner, which is difficult to achieve especially in the case of pediatric patients and people with conditions which limit cooperation.
2. The diagnosis of ASD was not verified with the ADOS-2 (Autism Diagnostic Observation Schedule) [30] and ADI-R (Autism Diagnostic Interview Revised) [31] – at the time of recruitment for the study the center did not have the above-mentioned tools, and did not employ people trained in this field.
3. The study groups were selected only on the basis of age and handedness. Due to varied language deficits presented by subjects with ASD, it was difficult to apply a selection method that would take into account the criterion of verbal functioning. Increasing the homogeneity of the group in terms of verbal competences would be possible thanks to a more accurate assessment of language skills, which, however, was not possible due to the lack of standardized, Polish-language tools, in particular adapted to the study of subjects with ASD. Another important limitation includes significant differences in the intellectual functioning of ASD subjects and HC subjects
4. Boys aged 12–19 were examined. Studies on the influence of age on fMRI activation in language tasks patterns in normotypic samples indicate differences, although their results are not consistent [32].
5. The frequency of the occurrence of particular words and phrases in everyday life was not assessed due to the lack of appropriate tools. The assessment of this parameter is justified because, as shown in the studies by Chee et al. [33], the frequency of using a given term has an impact on the amount of fMRI activation in the left prefrontal cortex.

Conclusions

Our results (different patterns of fMRI activation within brain structures, including those building the DMN – precuneus, posterior cingulate cortex, angular gyrus, parahippocampal gyrus, and no intergroup differences in areas related to language functions – Broca's area and Wernicke's area) emphasize the role of abnormal functional organization of many regions of the CNS, far more than just the areas traditionally

attributed to language processing, in the development of semantic deficits in people with ASD.

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