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Mapping access to meaning in adolescents with autism: Atypical lateralization and spatiotemporal patterns as a function of language ability

Yuqi You [a,b], Angeles Correas [a], David R. White [a], Laura C. Wagner [a], R.Joanne Jao Keehn [a], Burke Q. Rosen [a,c], Kalekirstos Alemu [a], Ralph-Axel Müller [a,d], Ksenija Marinkovic [a,d,e,*]

[a] Department of Psychology, San Diego State University, San Diego, CA, United States
[b] Department of Psychology and Behavioral Sciences, Zhejiang University, Hangzhou, China
[c] Department of Neurosciences, University of California San Diego, San Diego, CA, United States
[d] Joint Doctoral Program in Clinical Psychology, San Diego State University and University of California San Diego, San Diego, CA, United States
[e] Department of Radiology, University of California San Diego, San Diego, CA, United States

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ABSTRACT

Individuals with autism spectrum disorders (ASD) vary in their language abilities, associated with atypical patterns of brain activity. However, few studies have examined the spatiotemporal profiles of lexico-semantic processing in ASD, particularly as a function of language heterogeneity. Thirty-nine high-functioning adolescents with ASD and 21 typically developing (TD) peers took part in a lexical decision task that combined semantic access with demands on cognitive control. Spatiotemporal characteristics of the processing stages were examined with a multimodal anatomically-constrained magnetoencephalography (aMEG) approach, which integrates MEG with structural MRI. Additional EEG data were acquired from a limited montage simultaneously with MEG. TD adolescents showed the canonical left-dominant activity in frontotemporal regions during both early (N250m) and late (N400m) stages of lexical access and semantic integration. In contrast, the ASD participants showed bilateral engagement of the frontotemporal language network, indicative of compensatory recruitment of the right hemisphere. The left temporal N400m was prominent in both groups, confirming preserved attempts to access meaning. In contrast, the left prefrontal N400m was reduced in ASD participants, consistent with impaired semantic/contextual integration and inhibitory control. To further investigate the impact of language proficiency, the ASD sample was stratified into high- and low-performing (H-ASD and L-ASD) subgroups based on their task accuracy. The H-ASD subgroup performed on par with the TD group and showed greater activity in the right prefrontal and bilateral temporal cortices relative to the L-ASD subgroup, suggesting compensatory engagement. The L-ASD subgroup additionally showed reduced and delayed left prefrontal N400m, consistent with more profound semantic and executive impairments in this subgroup. These distinct spatiotemporal activity profiles reveal the neural underpinnings of the ASD-specific access to meaning and provide insight into the phenotypic heterogeneity of language in ASD, which may be a result of different neurodevelopmental trajectories and adoption of compensatory strategies.

1. Introduction

Autism spectrum disorders (ASD) are a group of complex neurodevelopmental disorders defined by core features including social communication deficits, restricted interests, and repetitive behaviors (American Psychiatric Association, 2013), with considerable variability in phenotypic presentation, etiology, and outcomes (Amaral et al., 2008; Betancur, 2011; Georgiades et al., 2013; Geschwind and Levitt, 2007; Waterhouse, 2013). Language impairment is no longer considered a core diagnostic criterion, largely due to wide heterogeneity in both early language development and current language skills among individuals with ASD (Anderson et al., 2007; Boucher, 2012; Groen et al., 2008; Kjelgaard and Tager-Flusberg, 2001; Pickles et al., 2014; Tager-Flusberg, 2006; Tek et al., 2014). While some individuals with ASD remain minimally verbal and never acquire functional spoken language (Sigman and McGovern, 2005; Tager-Flusberg and Kasari, 2013), others demonstrate language ability within the range of their typically-developing (TD) peers (Fein et al., 2013; Tager-Flusberg, 2006),

* Corresponding author at: 6505 Alvarado Rd. #202, San Diego, CA 92120, United States.
E-mail address: kmarinkovic@sdsu.edu (K. Marinkovic).

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despite subtle deficits in pragmatics and discourse (Eigsti et al., 2011; Kelley et al., 2006).

A better understanding of the phenotypic heterogeneity of verbal functions in ASD can be gained by mapping the neural underpinnings of word processing in terms of their spatial activation pattern, as well as temporal stages of processing. Evidence from neurotypical adults indicates that visual word processing starts in the visual cortex at ~ 100 ms and proceeds anteriorly along the ventral visual stream. Activity reaches the left temporal cortex at ~ 250 ms for initial orthographic analysis and lexical access (Grainger and Holcomb, 2009; Marinkovic et al., 2003; Marinkovic et al., 2014b; Martin-Loeches et al., 2001), followed by engagement of the left-dominant frontotemporal language network during lexico-semantic retrieval at ~ 400 ms (Halgren et al., 2002; Lau et al., 2008; Maess et al., 2006; Marinkovic et al., 2003; Pulvermüller, 2007; Pylkkänen et al., 2009; Service et al., 2007; Van Petten and Luka, 2006). At this latency, a negative event-related potential (ERP) termed the N400 is measured on the scalp (Kutas and Federmeier, 2011). Intracranial electroencephalography (EEG) studies have confirmed its distributed generators in the anterior temporal and ventrolateral prefrontal regions (Halgren et al., 1994a; Halgren et al., 1994b; Nobre and McCarthy, 1995). The N400 is sensitive to orthographic, semantic, and contextual factors, and is evoked by a wide range of verbal (e.g., single words, sentences, discourse-level text) and nonverbal, but potentially meaningful stimuli (Hagoort and van Berkum, 2007; Kutas and Federmeier, 2000). The N400 amplitude decreases with ease of semantic processing (Hagoort, 2003; Kutas and Federmeier, 2011). Because it is larger to pseudowords (i.e., orthographically and phonologically legal, pronounceable nonwords) than regular words (Bentin et al., 1985; Holcomb, 1993; Holcomb et al., 2002), it has been proposed that the N400 reflects attempts to access semantic networks and integrate meaning within the current context (Deacon et al., 2004; Halgren, 1990; Ziegler et al., 1997).

A few EEG studies have investigated temporal dynamics of language processing in ASD. The N400 is reported to be absent or attenuated in children (Cantiani et al., 2016; Dunn and Bates, 2005; Dunn et al., 1999; Manfredi et al., 2020; McCleery et al., 2010; Ribeiro et al., 2013) and adults (Coderre et al., 2018; Fishman et al., 2011; Pijnacker et al., 2010) with ASD, suggesting lexico-semantic impairments. Moreover, even though the timing of the N400 is remarkably stable across experimental manipulations in neurotypical individuals (Federmeier and Laszlo, 2009), there is evidence of delayed N400 responses in children with ASD (DiStefano et al., 2019; Valdizan et al., 2003). Magnetoencephalography (MEG) shares excellent (ms) temporal resolution with EEG, but it additionally offers insight into spatial patterns of activity across time, based on inverse modeling of signal generation (Ahlfors and Mody, 2019; Baillet, 2017). Even though MEG evidence on the N400m (the magnetic equivalent of N400) in ASD is scarce, the overall findings suggest weaker N400 and right lateralized activity (Ahtam et al., 2020; Braeutigam et al., 2008; Ogawa et al., 2019).

Functional neuroimaging studies have revealed altered lateralization during language-related tasks in children and adults with ASD (for reviews, see; Herringshaw et al., 2016; Lindell and Hudry, 2013). The typical left hemisphere dominance is often reduced or reversed in ASD (Boddaert et al., 2003; Gaffrey et al., 2007; Gendry Meresse et al., 2005; Just et al., 2004; Kana et al., 2006; Lepistö et al., 2005), with some studies reporting increased rightward asymmetry (Boddaert et al., 2003; Coffey-Corina et al., 2008; Dawson et al., 1986; Dawson et al., 1989; Eyler et al., 2012; Flagg et al., 2005; Frye and Beauchamp, 2009; Kleinhans et al., 2008; Mason et al., 2008; Müller et al., 1999; Redcay and Courchesne, 2008; Takeuchi et al., 2004; Wang et al., 2006).

When these complementary lines of evidence are considered together, studies using temporally sensitive methods such as EEG and MEG have revealed reduced amplitude and delayed latency of the N400 or N400m in ASD, whereas fMRI studies have identified atypical hemispheric asymmetry in a network of core language areas. To address both, the temporal and spatial aspects of language processing, we employed a multimodal, anatomically-constrained MEG approach. This method combines distributed source modeling of the high-density MEG signal with structural MRI and generates dynamic statistical parametric maps (dSPMs) of estimated cortical activity as it unfolds in time (Dale et al., 2000; Marinkovic et al., 2003; Marinkovic et al., 2014b). To provide insight into the anatomical distribution and functional engagement of language networks, the present study examined lexico-semantic processing in individuals with ASD and matched TD peers. Scalp EEG was recorded simultaneously with MEG from a limited montage and analyzed as ERPs for comparison purposes. Furthermore, the spatiotemporal activity profiles of adolescents with ASD were analyzed as a function of language proficiency. Although the collection of high-quality task-based neuroimaging data necessitates recruitment of relatively high-functioning individuals, language heterogeneity nevertheless persists even within this subpopulation (Gao et al., 2019; McIntyre et al., 2017; Tager-Flusberg, 2006). Despite recent reports of the link between language ability and fMRI activity patterns in young children with ASD (Lombardo et al., 2015), evidence associated with heterogenous language processing in high-functioning adolescents with ASD is lacking. To address this gap, the present study divided high-functioning adolescents with ASD into high- (H-ASD) and low-performing (L-ASD) groups based on their accuracy in a double-duty lexical decision task (Marinkovic et al., 2012; You et al., 2021), and compared both groups with typically developing (TD) peers.

2. Materials and methods

2.1. Participants

A total of sixty adolescents participated in this study, which comprised typically developing adolescents (TD, N = 21) and those with ASD (N = 39). The ASD group was further divided into two subgroups based on the median split of their performance in the lexical decision task described below. The ASD participants whose overall accuracy on the verbal task was 80% or higher (N = 20) comprised the high-performing (H-ASD) group, whereas those who scored below 80% (N = 19) were assigned to the low-performing (L-ASD) group. Diagnoses of ASD were established using the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2; Lord et al., 2012), the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al., 2003), and expert clinical judgment based on DSM-5 criteria (American Psychiatric Association, 2013). None of the TD or ASD participants had a history of neurological disorders (e.g. epilepsy), or inherited medical conditions associated with autism (e.g., Fragile-X syndrome, tuberous sclerosis). Among all thirty-nine ASD participants, twelve (L-ASD: 7, H-ASD: 5) reported taking psychoactive medications, seventeen (L-ASD: 9, H-ASD: 8) reported co-occurring attention-deficit/hyperactivity (L-ASD: 3, H-ASD: 3), depression (L-ASD: 2, H-ASD: 3), and anxiety (L-ASD: 4, H-ASD: 5), and three (L-ASD: 0, H-ASD: 3) reported more than one comorbid condition. Given the high prevalence of medication use and comorbidity in ASD, these participants were not excluded. However, as indicated above, the prevalence was matched approximately between two ASD groups. TD participants were free of a personal or family history of autism, or other developmental, neurological or psychiatric conditions. The ASD and TD groups did not differ on sex, handedness, age, or non-verbal IQ (Table 1). Moreover, the L-ASD group had lower scores on measures of language function in comparison to the TD group. Informed consent was obtained from all participants and their caregivers in accordance with the University of California, San Diego (UCSD) and the San Diego State University (SDSU) Institutional Review Boards.

2.2. Experimental procedure

During an initial familiarization session, a battery of neuropsychological tests and parent-report questionnaires was administered including the Wechsler Abbreviated Scale of Intelligence–2nd ed.

Table 1
Participant characteristics.

	TD (n = 21)	H-ASD (n = 20)	L-ASD (n = 19)	Group m.e.	TD vs H-ASD	TD vs L-ASD	H-ASD vs L-ASD
	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	χ^2 or F (p)	t (p)	t (p)	t (p)
Sex (M/F)[a]	16/5	15/5	16/3	0.57	–	–	–
	–	–	–	(0.75)	–	–	–
Handedness (R/L)[a]	18/3	19/1	17/2	0.99	–	–	–
	–	–	–	(0.61)	–	–	–
Age (y)	15.2 ± 1.8	15.9 ± 2.7	14.9 ± 1.9	1.05	-0.87	0.62	1.34
	(12.5–21.4)	(12.3–20.3)	(11.8–18.6)	(0.36)	(0.392)	(0.541)	(0.190)
Full Scale IQ	114.8 ± 13.9	110.6 ± 18.6	101.9 ± 15.1	3.3	0.82	2.80	1.58
	(88–140)	(59–136)	(83–136)	**(0.04)**	(0.415)	**(0.008)**	(0.123)
Verbal IQ	115.1 ± 11.8	110.8 ± 15.9	96.0 ± 13.4	10.36	1.00	4.80	3.12
	(98–135)	(68–134)	(76–123)	**(<0.001)**	(0.330)	**(<0.001)**	**(0.003)**
Nonverbal IQ	110.7 ± 14.9	110.4 ± 23.0	107.9 ± 18.4	0.12	0.05	0.53	0.37
	(80–138)	(54–156)	(80–156)	(0.88)	(0.959)	(0.603)	(0.716)
ADOS-2							
Total	–	12.0 ± 4.0	10.2 ± 3.6	–	–	–	1.43
	–	(6–20)	(6–20)	–	–	–	(0.161)
Social Affect	–	9.9 ± 4.1	7.7 ± 3.1	–	–	–	1.85
	–	(3–19)	(3–14)	–	–	–	(0.073)
Repetitive Behaviors	–	2.2 ± 1.4	3.1 ± 2.2	–	–	–	−1.53
	–	(0–5)	(0–9)	–	–	–	(0.135)
ADI-R							
Social Interaction	–	16.9 ± 4.3	19.2 ± 4.2	–	–	–	−1.74
	–	(10–24)	(9–25)	–	–	–	(0.097)
Communication	–	12.9 ± 3.4	14.5 ± 4.6	–	–	–	−1.26
	–	(8–20)	(4–21)	–	–	–	(0.216)
Repetitive Behaviors	–	5.2 ± 2.2	6.7 ± 1.8	–	–	–	−2.39
	–	(1–8)	(4–9)	–	–	–	**(0.022)**
WIAT-III Word Reading	111.1 ± 8.4	110.8 ± 13.8	98.1 ± 15.7	6.51	0.11	3.23	2.69
	(97–129)	(80–133)	(72–128)	**(0.003)**	(0.912)	**(0.003)**	**(0.011)**
CELF-5 Core Language	112.2 ± 13.3	111.2 ± 18.6	91.7 ± 13.7	10.78	0.15	4.72	3.59
	(89–135)	(62–140)	(67–117)	**(<0.001)**	(0.878)	**(<0.001)**	**(0.001)**
SRS-2 Total	45.2 ± 6.5	74.1 ± 10.9	72.3 ± 11.1	57.02	−9.85	−9.57	0.48
	(38–63)	(47–90)	(52–103)	**(<0.001)**	**(<0.001)**	**(<0.001)**	(0.634)
SCQ	2.2 ± 2.3	15.3 ± 6.8	18.3 ± 6.4	49.33	−8.02	−10.31	−1.37
	(0–10)	(3–21)	(7–35)	**(<0.001)**	**(<0.001)**	**(<0.001)**	(0.179)

Group comparisons were conducted with independent samples t-tests, except for categorical variables[a], which were performed using $\chi 2$ tests. SD, standard deviation; F = female; M = male; L = left; R = right; Values for IQ (WASI-II), WIAT-III, and CELF-5 are standard scores with a normative mean of 100 and SD of 15; values for SRS-2 are T-scores with a mean of 50 and SD of 10. Significant p values (< 0.05) are marked in bold font.

(WASI-II; Wechsler, 1999), the Clinical Evaluation of Language Fundamentals–5th ed. (CELF-5; Semel et al., 2013), the Edinburgh Handedness Inventory (Oldfield, 1971), the Social Responsiveness Scale–2nd ed. (SRS-2; Constantino and Gruber, 2012), and the Social Communication Questionnaire (SCQ; Berument et al., 1999). The Word Reading subtest of the Wechsler Individual Achievement Test, 3rd ed. (WIAT-III; Wechsler, 2009) was used as a screener to ensure that all participants were able to read at a 6th grade (i.e., 12-year-old) reading level. At this time, participants were acclimated to the MRI environment in a mock MRI scanner and practiced the behavioral task, which included trial-by-trial feedback. The practice run was followed by a pretest without feedback. The participants whose overall task accuracy exceeded 60% were eligible for the MEG scan. None of the practice and pretest words were included in the stimulus lists used in the MEG experiment.

Participants then completed a MEG and a structural MRI scan in two separate sessions. During the MEG session, participants were given an additional set of practice trials in the MEG scanner prior to performing the experimental task. During structural MRI scans, participants were instructed to lie still and were allowed to watch a movie of their choice.

2.3. Experimental task

A double-duty lexical decision task (Marinkovic et al., 2014b; Marinkovic et al., 2012; You et al., 2021) included three conditions: real, standard words (SW), real words that referred to animals (AN), and pseudowords (PW), i.e., orthographically and phonologically legal letter strings with no meaning (e.g., "kligor"). Participants were instructed to respond to each standard word (SW) with their left index finger, but to use their left middle finger to respond to words denoting animals (AN) thereby eliciting response conflict. Responses were withheld on PW trials, which engaged inhibitory control. One hundred trials were presented and analyzed for each condition. A prepotent response tendency was established by presenting 180 additional SW fillers. The three conditions were well matched on lexical aspects. The number of letters did not differ between the three conditions (SW: 5.9 ± 1.5; AN: 6.0 ± 1.7; PW: 6.0 ± 1.5). SW and AN conditions did not differ in terms of the age of acquisition (SW: 6.5 ± 1.9 years; AN: 6.6 ± 1.7) (Kuperman et al., 2012), number of syllables (SW: 1.8 ± 0.7; AN: 1.9 ± 0.7), or frequency of occurrence (SW: 3.5 ± 0.6; AN: 3.4 ± 0.6) based on the Zipf scale (Brysbaert and New, 2009; van Heuven et al., 2014).

Stimuli were presented as white lower-case letter strings on a black background in a randomized order using the Presentation software (Neurobehavioral Systems Inc.). Each trial lasted 2.5 s, during which letter strings were centrally presented for 500 ms, preceded and followed by a fixation string (i.e., "xxxxxx") subtending a visual angle of 6.2° x 1.1°. The same stimulus list was used for all participants. Short breaks were given approximately every 4 min.

2.4. Data acquisition and analysis

2.4.1. MRI

Structural MRI images were acquired with a General Electric Discovery MR750 3.0 Tesla Scanner (GE Healthcare, Milwaukee, WI) at the UCSD Center for fMRI, using a Nova Medical 32 channel head coil. Whole-head structural images were acquired with a standard Fast Spoiled Gradient Recalled (FSPGR) T1-weighted sequence (TR = 8.136

ms; TE = 3.172 ms; flip angle = 8°; FOV = 25.6 cm; acquisition matrix = 256 × 256; voxel size = 1 mm^3; slices: 172; total duration: 5 min). Each participant's cortical surface was reconstructed from these images using Freesurfer (Dale et al., 1999; Fischl et al., 1999a) and served to constrain inverse solution estimates. For forward calculations, inner skull surface was derived from segmented MRI data and used for a boundary element model of the volume conductor. For group-wise analyses, the reconstructed individual surfaces were morphed into an average representation by aligning their sulcal-gyral patterns (Fischl et al., 1999b) and decimated, defining the solution space with 5124 free-rotating dipoles spaced ~ 7 mm apart.

2.4.2. MEG and EEG

High-density MEG signals were acquired from 204 planar gradiometers (102 pairs) with a whole-head Neuromag Vectorview system (Elekta AB, Stockholm, Sweden) in a magnetically and electrically shielded room at the UCSD Radiology Imaging Laboratory. The signals were recorded continuously with a 1000 Hz sampling rate and filtered with a band pass filter (0.1 to 300 Hz). The main fiducial points (the nasion and preauricular points), the position of head position indicator (HPI) coils, and a large array of random points covering the scalp were digitized with 3Space Isotrak II (Polhemus Inc., Colchester, VT) system for subsequent precise co-registration with structural MRI images. Head localization was checked before each acquisition run. To mitigate potential motion-related artifacts, we were exceedingly careful to ensure that participants were positioned correctly in the dewar, and applied a series of steps to minimize head motion (e.g. practicing sitting still in the dewar, securing the head position with foam padding and ensuring a snug fit, while maintaining comfort). EEG data were recorded simultaneously with the MEG signal from a limited montage, with the nose serving as the reference. Electrooculogram was recorded with bipolarly referred electrodes attached above and below the left eye. Electrode impedance was kept well below 5 kΩ. Data from 6 participants (TD: 1, H-ASD: 2, L-ASD: 3) were excluded due to excessive noise and technical difficulties.

MEG and EEG data were analyzed in time domain (Dhond et al., 2001; Marinkovic et al., 2003; Marinkovic et al., 2011; Marinkovic et al., 2014a) with custom MATLAB routines (Beaton et al., 2018; Correas et al., 2019; Marinkovic et al., 2011; Marinkovic et al., 2014b), which partly incorporate publicly available packages including Fieldtrip (Oostenveld et al., 2011), EEGLab (Delorme and Makeig, 2004) and MNE (Gramfort et al., 2014). Continuous MEG/EEG signals were downsampled to 250 Hz, bandpass filtered from 0.1 to 30 Hz, epoched from −300 to 1000 ms relative to stimulus onset, and baseline-corrected using the 300 ms pre-stimulus period. Raw data were carefully inspected for motion-related artifacts, which were removed during preprocessing. Independent component analysis was used to remove eye-blinks and heartbeat artifacts (Delorme and Makeig, 2004). Any remaining artifacts were removed by subsequent careful visual inspection (Oostenveld et al., 2011). Only artifact-free trials with correct responses were included in the final analysis. To mitigate potential statistical bias due to unequal number of trials per condition, for each participant, trials were equated across conditions with an automated script that excluded randomly selected superfluous trials (Marinkovic et al., 2019).

An anatomically-constrained MEG (aMEG) method combines distributed source modeling of the MEG signal with structural MRI to compute cortically constrained noise-normalized minimum-norm estimates (Dale et al., 2000; Marinkovic, 2004; Marinkovic et al., 2011; Marinkovic et al., 2003; Marinkovic et al., 2014b). The aMEG method assumes that the synaptic currents giving rise to magnetic fields are generated in the cortical mantle, which is reconstructed from each individual's anatomical MRI and is used to constrain inverse estimates. The noise covariance matrix was computed from the pre-stimulus periods across data epochs and used for inverse calculation, resulting in dSPMs of cortical current dipoles (Dale et al., 2003; Marinkovic et al., 2003; Marinkovic, 2004). The source estimates were expressed as the square root of an *F*-statistic, indicating the likelihood that a particular dipole (cortical patch) is more active than pre-stimulus baseline at a given time point. For a group-level analysis, each participant's reconstructed surface was inflated and mapped onto a sphere using a maximally isometric transformation (Fischl et al., 1999a), followed by alignment of the cortical sulcal-gyral pattern with an average folding pattern of a canonical surface (Fischl et al., 1999b). After transformation into a unified surface-based coordinate system, group averages were created by averaging individual dSPMs.

Region-of-interest (ROI) analysis of the dSPM time courses was conducted to examine possible interactions of Group, Condition (i.e., letter string type), and Laterality factors. We first generated and visually inspected source estimate time courses averaged across all participants and conditions (grand averages). Given that potential group differences are orthogonal to their average, the selected ROIs were unbiased and comprised dipole locations along the cortical surface where group-level peaks were the most prominent. The same set of ROIs was used for all participants in a manner blind to their individual activations. These ROIs were applied to each subject's reconstructed surface thanks to intersubject averaging, which is accomplished by morphing each subject's reconstructed surface into an average representation by optimally aligning sulcal and gyral features. This averaging procedure reduces anatomical and functional variability across subjects (compared to volume-based normalization), and is a standard feature of the FreeSurfer pipeline (Dale et al., 1999; Fischl et al., 1999a; Fischl et al., 1999b). It is important to note that this approach is rather conservative since it does not allow for idiosyncrasies in terms of either spatial distribution or latency between subjects. As a result, only those activity areas that overlap very highly in both time and cortical space across participants and conditions have a chance of being selected for further analysis. We then proceeded by testing null hypotheses (i.e., all groups and word conditions were equivalent) within each ROI. ROIs encompassed the frontotemporal network associated with language processing and cognitive functions more broadly. The bilateral ROIs included the lateral temporal cortex (LTC), intraparietal cortex (IPC), anteroventral prefrontal cortex (aPFC), and posterolateral prefrontal cortex (pPFC) (see Figs. 2, 3) (Marinković, 2004; You et al., 2021).

2.5. Statistical analysis

Source estimates obtained with the aMEG method were analyzed with a mixed model analysis of variance (ANOVA) with the between-subject factor of Group (TD, H-ASD, L-ASD), and within-subject factors of Condition (SW, AN, PW), and Laterality (Left, Right). Greenhouse-Geisser corrections were applied. For each ROI, ANOVAs were performed on source estimate time courses averaged over time points in the time windows critical for language processing, which comprised early lexical access, N250m (210–260 ms), and lexico-semantic retrieval, N400m (350–550 ms for LTC, 400–600 ms for pPFC). These latency windows were chosen to capture prominent peaks in the grand-averaged source estimates time course across all participants and conditions. Group and Condition follow-up contrasts were computed with independent samples and two-tailed paired-sample *t*-tests respectively. To examine hemispheric dominance directly, a laterality index (LI) of estimated cortical activity for a given ROI was computed as (L – R)/0.5*(L + R), with positive and negative numbers indicating left- and right-lateralization, respectively. Based on each individual's dSPM time courses averaged across conditions and with the assistance of an automatic algorithm, the N400m onset latency was defined as the latency of a local minimum immediately before the N400m peak reflected in a local maximum closest in time to 400 ms. Pearson correlations were computed between N250m/N400m laterality index, N400m onset latency and neuropsychological measures of language/communication skills (i.e., WASI-II verbal, WIAT-III word reading, CELF-5 core language) for TD and ASD groups (collapsed across language ability), respectively. However, none of the correlations

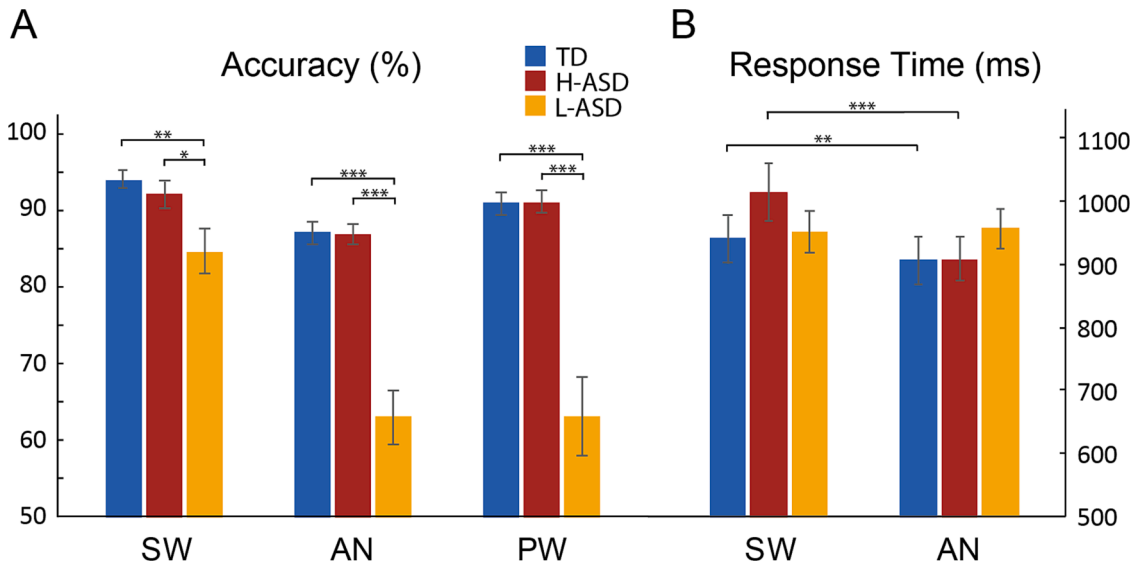

Fig. 1. Lexical decision task performance measured as accuracy (A) and response times (B) and shown as means ± standard errors for each group and word condition. SW: standard words; AN: animal words; PW: pseudowords. * p <.05, ** p <.01, *** p <.001.

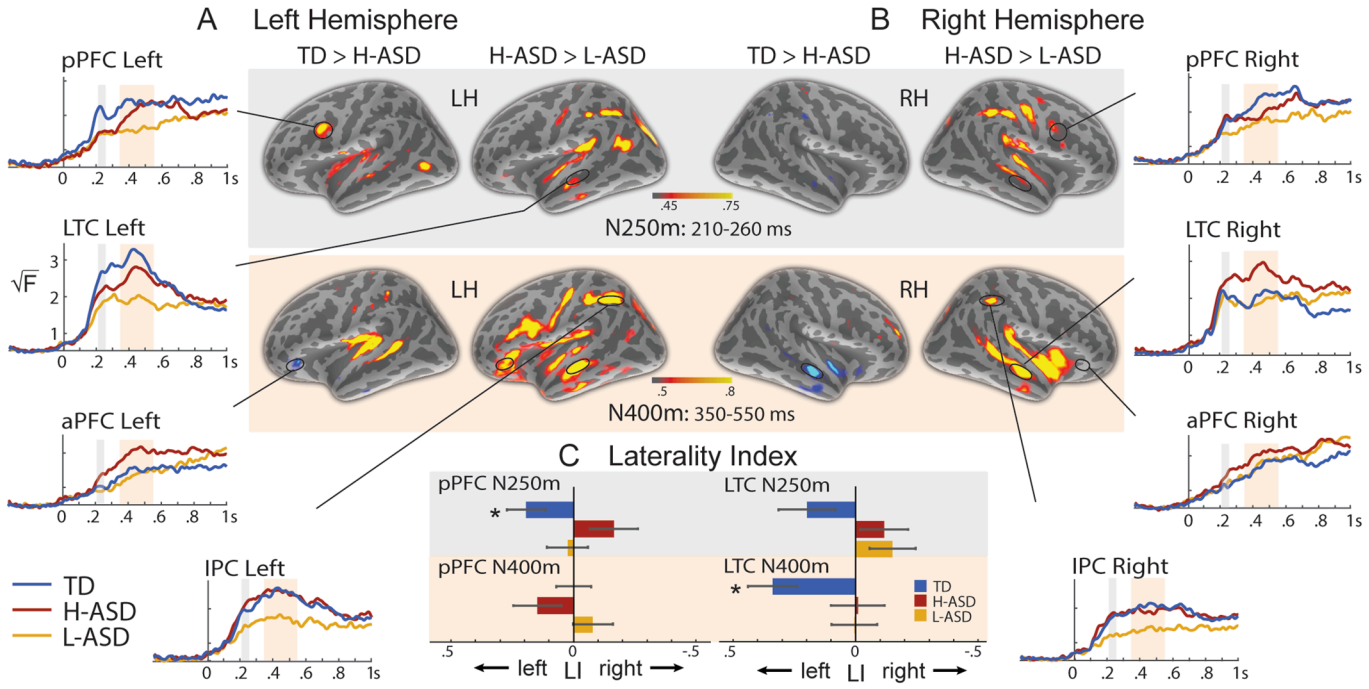

Fig. 2. Group average dSPMs and time courses of aMEG source estimates for selected ROIs (collapsed across conditions). Group-specific patterns of activity were observed in the left (A) and right (B) hemispheres, during the N250m and N400m time windows that are marked with gray- and peach-shaded bars respectively. (C) Laterality index (LI) for the pPFC and LTC is shown for both time windows. dSPM brain maps and time courses of the estimated source amplitudes are expressed as group averages ($\sqrt{F}$). pPFC: posterolateral prefrontal cortex; LTC: lateral temporal cortex; aPFC: anteroventral prefrontal cortex; IPC: intraparietal cortex. * p <.05. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

survived after correction for multiple testing by controlling the false discovery rate (Benjamini and Hochberg, 1995). The correlations were additionally computed for ADOS-2 social affect, ADI-R communication, and ADI-R age of 1st phrase for the two ASD groups only). Multiple comparisons were corrected with a false discovery rate (FDR)-based procedure (Benjamini and Hochberg, 1995). Behavioral data and ERP average amplitudes within the N400 (350–550 ms) time window were analyzed with mixed design ANOVAs that included Group and Condition factors.

3. Results

3.1. Task performance

As shown in Fig. 1A, there was a main effect of Group on overall performance accuracy, $F(2,57) = 62.39$, p <.001, with higher accuracy in H-ASD and TD compared to L-ASD participants (both comparisons p's < 0.001). The H-ASD and TD groups did not differ in performance accuracy [$t(39)$ = -0.42, p =.68]. A Group-by-Condition interaction [$F(3.3,93.6) = 5.67$, p =.001] indicated that H-ASD and TD participants

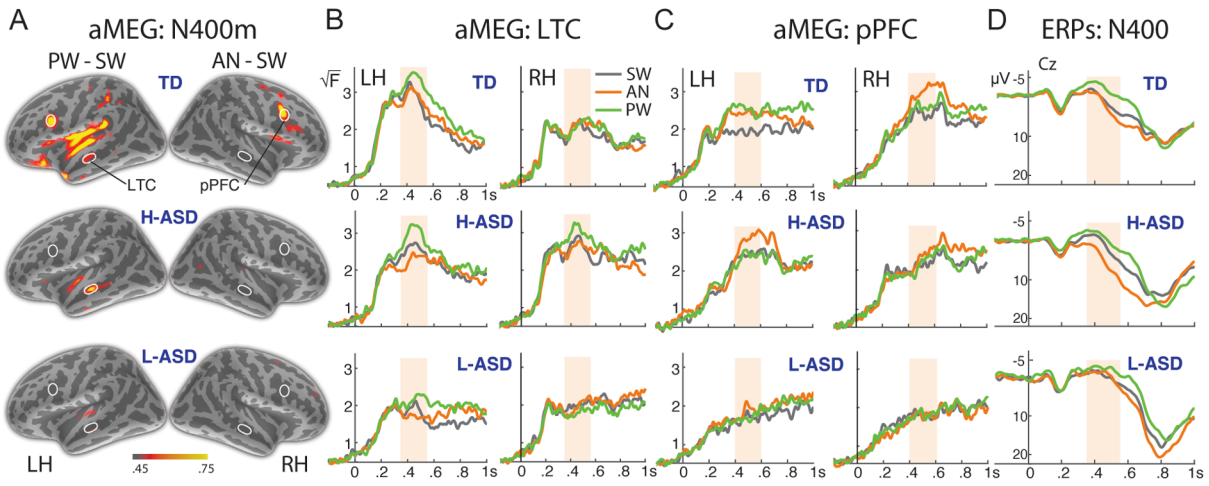

Fig. 3. Effects of word condition on aMEG source estimates and ERPs. (A) Group averaged dSPMs of estimated activity for the N400m time window. Time courses of activity estimated to the bilateral LTC (B) and pPFC (C). LH, RH: left and right hemisphere, respectively. The N400m time window is marked with peach-shaded bars. (D) Grand average ERPs at Cz to the three task conditions across all groups. Negative is up. LTC: lateral temporal cortex; pPFC: posterolateral prefrontal cortex. SW: standard words; AN: animal words; PW: pseudowords. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

had lower performance accuracy to AN relative to PW [H-ASD: $t(19)$ = -3.30, p =.004; TD: $t(20)$ = -2.01, p =.058] and SW [H-ASD: $t(19)$ = -2.71, p =.014; TD: $t(20)$ = -6.55, p <.001]. In contrast, in the L-ASD group, performance accuracy was comparably low to AN and PW [$t(18)$ = -0.01, p =.99], compared to SW (p's <=0.005).

Groups did not differ in response times (RTs) on correct AN and SW trials, $F(2,57) = 0.31$, $p = 0.74$, (Fig. 1B). A Group-by-Condition interaction [$F(2,57) = 14.2$, p <.001] was indicative of longer RTs to SW than AN in H-ASD, $t(19)$ = -5.45, p <.001 and TD groups, $t(20)$ = -3.22, p =.004. In contrast, RTs for the L-ASD group did not differ between the two conditions [$t(18) = 0.43$, p =.67].

3.2. Spatiotemporal aMEG estimates

Overall, the observed spatiotemporal pattern followed the canonical visual word processing stages, proceeding along the ventral visual stream and encompassing lexical access at ~ 250 ms (N250m), and left-dominant frontotemporal engagement of language networks at ~ 400 ms (N400m) after word onset (Dale et al., 2000; Dhond et al., 2001; Lau et al., 2008; Maess et al., 2006; Marinković, 2004; Marinkovic et al., 2003; Marinkovic et al., 2014b; Pulvermüller, 2007; Pylkkänen et al., 2009; Service et al., 2007; Van Petten and Luka, 2006). The earliest activity of the visual cortex as reflected in the N100m did not differentiate between TD and ASD groups, which is consistent with our previous findings in theta frequency (You et al., 2021). Group and Condition effects emerged for the subsequent deflections comprising the N250m and N400m time windows.

Group-specific patterns of activity lateralization were observed during both time windows (Fig. 2). Left lateralized activity was observed only in the TD but not ASD groups in the pPFC and LTC, while the H-ASD showed specifically enhanced N400m in the right LTC compared to other two groups. Word-specific N400m activity was similar across all groups in the left LTC in contrast to the left pPFC, which showed a Group × Condition interaction (Fig. 3). The L-ASD group showed the lowest activity overall, as well as delayed N400m onset latencies compared to other groups (Fig. 4). Group-specific engagement of aPFC and IPC were also noted (see Supplemental Information).

3.2.1. Group differences in hemispheric lateralization

Frontotemporal N250m is left-lateralized only in the TD group

As shown by contrast maps and group average time courses in Fig. 2, the earliest laterality differences between the TD and ASD groups emerged in the posterolateral prefrontal and lateral temporal cortices during the N250m (210–260 ms) time window. A Group-by-Laterality interaction [$F(2,57) = 3.96$, p =.01] was observed in the pPFC, with TD showing greater overall activity in the left compared to the right hemisphere, $t(20) = 2.43$, p =.025, in contrast to bilateral activity shown by ASD groups. When group effects were examined in the pPFC within each hemisphere, the TD group showed stronger activity in the left pPFC than both ASD groups [TD vs H-ASD: $t(39)$ = 2.35, p =.024; TD vs L-

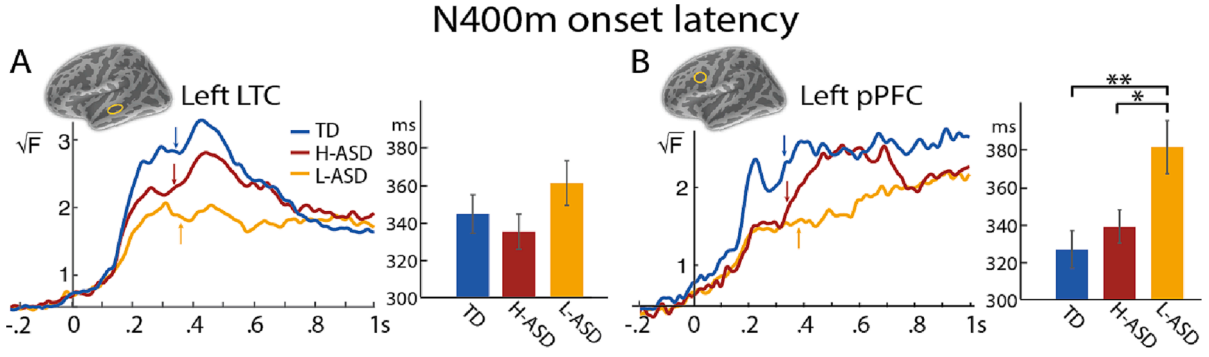

Fig. 4. Group average N400m onset latencies are indicated with colored arrows above the corresponding time courses estimated to the left LTC (A) and left pPFC (B). The averages are additionally shown with bar graphs. * p <.05, ** p <.01.

ASD: $t(38) = 2.65$, $p = .012$; Fig. 2A]. In the right pPFC, however, both TD and H-ASD groups showed stronger activity than the L-ASD group [TD vs L-ASD: $t(38) = 2.06$, p =.046; H-ASD vs L-ASD: $t(37) = 2.23$, $p = .035$; Fig. 2B]. In the LTC, there was a marginally significant Group-by-Laterality interaction for the N250m [$F(2,57) = 3.06$, $p = .055$] represented by greater activity in the left LTC in the TD than the L-ASD group [$t(29.9) = 2.28$, $p = .03$]. No group differences were observed in the right LTC (p's > 0.12).

To examine hemispheric dominance directly, a laterality index (LI) of estimated cortical activity was computed as (L – R)/0.5*(L + R), with positive and negative numbers indicating left- and right-lateralization, respectively (Fig. 2C). One-way ANOVA of the N250m LI indeed revealed a main effect of Group in the pPFC [$F(2,57) = 4.36$, $p = .017$], with more left-lateralized activity in the TD compared to H-ASD group [$t(39) = 2.87$, $p = .007$]. Follow-up t-tests indicated a positive LI (i.e., left dominance) for the TD [$t(20) = 2.48$, $p = .022$], and a non-significant LI (i.e., absence of asymmetry) for both ASD groups (p's > 0.11). A main effect of Group was also detected in the LTC [$F(2,57) = 3.48$, $p = .038$], reflecting a more left-lateralized LI in the TD compared to both ASD groups [TD vs. H-ASD: $t(39) = 2.06$, $p = .046$; TD vs. L-ASD: $t(38) = 2.30$, $p = .027$].

Temporal N400m is left-lateralized in the TD group, but is strongest in H-ASD in the right LTC.

Group-specific lateralization patterns continued during the subsequent N400m time window in the LTC, $F(2,57) = 6.04$, $p = .004$. Left > right pattern was only observed in the TD participants, evidenced by a positive LI [$t(20) = 3.36$, $p = .003$], which was greater than that of both ASD groups [TD vs. H-ASD: $t(39) = 2.35$, $p = .024$; TD vs. L-ASD: $t(38) = 2.41$, $p = .021$; Fig. 2C]. In contrast, the ASD groups showed bilateral LTC activity during the N400m interval (p's ≤ 0.65; Fig. 2C). In the left LTC, TD and H-ASD showed greater N400m activity than L-ASD group [TD vs L-ASD: $t(33.6) = 3.57$, $p = .001$; H-ASD vs L-ASD: $t(37) = 2.57$, $p = .014$; Fig. 2A]. In the right LTC, however, H-ASD participants showed stronger activity than both TD and L-ASD groups [H-ASD vs TD: $t(29) = 2.19$, $p = .036$; H-ASD vs L-ASD: $t(31.3) = 2.56$, $p = .015$; Fig. 2B]. In the pPFC, there was no Group-by-Laterality interaction for the N400m [$F(2,57) = 1.02$, $p = .37$].

To summarize, only the TD group showed the neurotypical left-hemisphere activity dominance across both time windows. In the right LTC, however, the H-ASD showed the greatest N400m in comparison to both TD and L-ASD groups, which suggests that highly successful lexicosemantic processing in ASD individuals relies on bilateral engagement of the frontotemporal areas.

3.2.2. N400m in the left temporo-frontal cortex is sensitive to word conditions

Consistent with a left-lateralized engagement during word reading, a Condition-by-Laterality interaction was observed for the N400m activity in LTC, $F(1.9, 107.2) = 8.36$, $p = .001$. As shown in Fig. 3A, a main effect of Condition was only observed in the left LTC, $F(1.9, 106.9) = 16.7$, $p < .001$, suggesting that it was differentially sensitive to word meaning. Specifically, the strongest activity was observed to PW relative to SW [$t(59) = 3.99$, $p < .001$] and AN [$t(59) = 5.21$, $p < .001$], with all three groups showing a comparable pattern. In contrast, a marginal Condition-by-Group interaction emerged in the right LTC [$F(4.0, 113.3) = 2.31$, $p = .069$], such that only the H-ASD group showed word Condition differences, with greater activity to PW than AN [$t(19) = 2.36$, $p = .029$], and marginally so than SW [$t(19) = 1.87$, $p = .077$]. No word effects were observed for TD and L-ASD groups in the right LTC (p's > 0.26).

The N400m activity estimated to the left posterior PFC showed a Group-by-Condition interaction [$F(3.8, 107.4) = 2.54$, $p = .047$] (Fig. 3B, C), but no such effects were observed in the right pPFC [$F(4.0, 112.7) = 1.18$, $p = .33$]. When the word condition effects were examined for the left pPFC for each group, TD participants showed word-specific differentiation, with stronger N400m activity to PW than SW [$t(20) = 3.12$, $p = .005$], and to AN than SW [$t(20) = 3.79$, $p = .001$]. The H-ASD group also demonstrated specifically enhanced N400m to AN relative to SW [$t(19) = 2.73$, $p = .013$], but the SW and PW did not differ [$t(19) = 0.26$, $p = .80$]. In contrast, the activity was undifferentiated for L-ASD participants (p's > 0.38). In the right pPFC, only the TD group showed greater activity to AN than SW [$t(20) = 2.41$, $p = .026$], with no word-specific differences for either of the ASD groups (p's > 0.32).

Taken together, all three groups demonstrated greater N400m activity to PW than SW in the left LTC, indicating preserved basic attempts to access meaning. In the left pPFC, however, only the TD group showed greater N400m to PW than SW, while enhanced N400m to AN compared to SW was observed in the TD and H-ASD groups. These results reveal specific neural correlates associated with impaired targeted semantic retrieval and cognitive control among ASD subgroups with varying language proficiency.

3.2.3. Group differences in the N400m onset latency

Based on prior evidence of delayed N400 latency in children with ASD (DiStefano et al., 2019), we examined the effect of Group on the N400m onset latency. No group differences were observed in the left [$F(2,56) = 1.49$, $p = .23$] or right LTC [$F(2,57) = 0.015$, $p = .99$] (Fig. 4A). In contrast, a main effect of Group emerged in the left pPFC, $F(2,57) = 6.53$, $p = .003$ (Fig. 4B), with shorter N400m onset latency in both TD and H-ASD groups compared to the L-ASD group [TD vs. L-ASD: $t(38) = -3.19$, $p = .003$; H-ASD vs. L-ASD: $t(37) = -2.55$, $p = .015$]. The TD and H-ASD groups did not differ [$t(39) = -0.91$, $p = .37$]. No group differences were detected in the right pPFC, $F(2,57) = 0.33$, $p = .72$.

To further characterize the relationship between the N400m onset latency and individual differences in language proficiency, we examined correlations between the N400m onset latency in the left pPFC and language-relevant neuropsychological measures within TD and ASD groups. Later N400m onset latency was associated with lower language ability as assessed by the CELF-5 Core Language score in both TD ($r = -0.596$, $p = .006$, FDR-corrected) and ASD groups ($r = -0.332$, $p = .045$, FDR-corrected). It was also associated with delayed age of 1st phrase acquisition ($r = 0.505$, $p = .002$, FDR-corrected) in ASD groups, indicating a potential neurodevelopmental origin of the shift of the N400 latency.

3.3. Scalp ERPs: The N400 is greatest to PW across all groups

As shown in Fig. 3D, grand average ERPs at Cz are characterized by clear negative-going potentials during the N400 time window. Similar to the N400m activity estimated to the left LTC (Fig. 3A), a main effect of Condition on the scalp N400 mean amplitude [$F(1.8, 91.1) = 29.90$, $p < .001$] revealed the largest negativity to PW, intermediate to SW, and the smallest negativity to AN overall [PW vs. SW: $t(53) = -5.81$, $p < .001$; SW vs. AN: $t(53) = -2.81$, $p = .007$]. An additional Group-by-Condition interaction [$F(3.6, 91.1) = 5.19$, $p = .001$] was indicative of differential condition effects across groups. While the N400 was greater to PW compared to SW in all three groups [TD: $t(19) = -4.72$, $p < .001$; H-ASD: $t(17) = -2.64$, $p = .017$; L-ASD: $t(15) = -2.62$, $p = .019$], only the H-ASD group showed larger N400 to SW than AN [$t(17) = -4.69$, $p < .001$].

4. Discussion

The current study used a multimodal imaging approach to examine spatiotemporal stages of neural activity during a lexical decision task in high-functioning adolescents with ASD and TD peers. To further explore the substantial heterogeneity of language abilities among ASD participants, they were divided into high- and low-performing (H-ASD and L-ASD) subgroups based on their task accuracy. While the H-ASD and TD groups performed equally well on the task, both groups outperformed the L-ASD group. Spatiotemporal aMEG estimates confirmed that lexicosemantic processing stages proceeded along the ventral visual stream, encompassing lexical access at ~ 250 ms (N250m), and semantic/

contextual integration at ~ 400 ms (N400m) after word onset. However, group comparisons revealed distinct spatiotemporal profiles, suggesting major differences in hemispheric laterality and sensitivity to word conditions, which can be summarized as follows: a. Only the TD group showed the canonical left-dominant activity in fronto-temporal areas during both stages of lexico-semantic processing. b. In contrast, both ASD groups showed a bilateral activity pattern, suggesting compensatory recruitment of the right hemisphere. c. In the left LTC, the N400m was greater to PW than SW across all three groups, reflecting robustly preserved attempts to access meaning. d. In the left pPFC, however, only the TD group showed N400m enhancement to PW (vs. SW), which is relevant to semantic access and inhibitory control. e. In addition, the N400m was greater to AN than SW in the H-ASD and TD groups in this region, indicating prefrontal engagement for cognitive control. f. In contrast, the L-ASD group generally showed lower and less differentiated activity between word conditions than the H-ASD and TD groups, especially in the pPFC. g. This was compounded with a delayed N400m onset latency in the L-ASD group in the same region, indicating more profound impairments in targeted semantic access and engagement of cognitive control.

Our findings suggest that spatiotemporal activity profiles during language processing differed as a function of ASD status and task accuracy rates. While the H-ASD participants performed equally well as their TD peers on the task, they relied on compensatory bilateral recruitment of the frontotemporal language circuit and right-dominant engagement of the temporal cortex. Compared to TD peers, both ASD subgroups demonstrated deficient prefrontal recruitment. This was especially prominent in the L-ASD group which showed lower activity and delayed engagement of the left pPFC compared to H-ASD and TD groups.

4.1. TD and H-ASD groups similarly outperformed the L-ASD group

Adolescents with ASD recruited for the present study were mostly high-functioning, necessitated by the demanding nature of the double-duty lexical decision task and multimodal neuroimaging requirements. All participants passed the WIAT-III screener, could read at 6th grade level, and exceeded the minimal performance requirement (60%) when pretested on the task. However, heterogeneity in language ability was still evident even within this selective ASD sample. Therefore, the sample was stratified into high- and low-performing ASD groups based on a median split of performance scores, resulting in a group (H-ASD) with performance at TD levels, and another (L-ASD) with performance significantly below TD levels. This functional division was consistent with neuropsychological test scores. The H-ASD and TD groups scored equivalently on all language-related measures, while the L-ASD group had lower scores than both H-ASD and TD on these measures (Table 1). This differentiation was specific to the language domain as the two ASD subgroups did not differ on nonverbal IQ or measures in social/communitive domains (Table 1). The only exception was the ADI-R Repetitive Behaviors score, which was higher in the L-ASD than H-ASD group. This difference was not surprising given the link between language impairments and restricted/repetitive behaviors which includes the repetitive use of language (Boucher, 2012). Specifically, task performance of the L-ASD group was compromised for AN and PW conditions that probed cognitive control (i.e., response switching) and response inhibition, respectively. This is suggestive of impaired targeted semantic retrieval, cognitive control, and inhibition of prepotent responses, and confirms prior reports of executive deficits among individuals with ASD (Boucher, 2012; Hill, 2004; Inokuchi and Kamio, 2013; Poljac and Bekkering, 2012; Solomon et al., 2008; Yeung et al., 2019).

4.2. Atypical bilateral frontotemporal engagement in ASD

In line with the left hemispheric dominance during language processing in neurotypical individuals (Binder et al., 2009; Marinković, 2004; Price, 2012; Pulvermüller, 2007; Van Petten and Luka, 2006), the TD group showed expected left-lateralized activity in frontotemporal language areas. Left-dominant activity was observed during both the N250m and the N400m time windows, which may represent lexical access and targeted semantic/contextual integration, respectively. In contrast, both ASD groups showed bilateral frontotemporal engagement during the N250m and N400m time windows. We further evaluated laterality effects statistically by means of the laterality index (LI). Our results confirmed left-lateralized frontotemporal activity in the TD group and no hemispheric dominance in either ASD subgroup, which aligns with previous reports in ASD (Floris et al., 2016; Joseph et al., 2014; Kleinhans et al., 2008).These results provide additional temporal precision and complement a growing number of functional neuroimaging studies revealing reduced left hemispheric activity (Boddaert et al., 2003; Gaffrey et al., 2007; Gendry Meresse et al., 2005; Just et al., 2004; Kana et al., 2006; Lepistö et al., 2005) or a trend towards rightward asymmetry in ASD (Boddaert et al., 2003; Coffey-Corina et al., 2008; Dawson et al., 1986; Dawson et al., 1989; Eyler et al., 2012; Flagg et al., 2005; Frye and Beauchamp, 2009; Kleinhans et al., 2008; Mason et al., 2008; Müller et al., 1999; Redcay and Courchesne, 2008; Takeuchi et al., 2004; Wang et al., 2006).

Neurotypical adults show neural sensitivity to words at ~ 250 ms in the left LTC, implicating its involvement in orthographic analysis and lexical access (Grainger and Holcomb, 2009; Helenius et al., 1998; Marinkovic et al., 2003; Marinkovic et al., 2014b; Martin-Loeches et al., 2001; Pylkkänen et al., 2002; Uusvuori et al., 2008; Wydell et al., 2003). In line with these reports, TD adolescents in the present study demonstrated a clear N250m peak in the left LTC and left-lateralized N250m activity in the pPFC (Fig. 2). Such hemispheric specialization indicates a possible role of the left pPFC in providing early and efficient top-down facilitation of lexical access (Marinkovic et al., 2003). In contrast, the L-ASD group showed a less clear N250m in both hemispheres. The H-ASD group showed right-dominant N250m activity in the pPFC, suggesting atypically lateralized top-down facilitation of lexical access in ASD.

During the subsequent processing stage, the N400m was left-lateralized in the LTC in TD participants only, suggesting highly specified and efficient recruitment of the canonical language circuit underlying semantic access and contextual integration. Such left-dominant engagement was again absent in ASD participants, although this was mediated by their levels of language proficiency. The H-ASD group was characterized by relatively intact N400m in the left LTC which was additionally accompanied by enhanced N400m in the right LTC. This atypical pattern of lateralization is consistent with a common rightward shift of functional networks in high-functioning ASD (Cardinale et al., 2013), as the additional recruitment of the right hemisphere may serve a compensatory function during demanding cognitive tasks. In line with this notion, compensatory activation of bilateral language-related regions has been reported in individuals who were initially diagnosed with ASD, but who subsequently lost all symptoms of ASD and achieved normative cognitive and social functions (Eigsti et al., 2016). Furthermore, among young children with ASD, language ability correlates positively with the degree of rightward asymmetry shift, which is suggestive of compensatory neural recruitment (Joseph et al., 2014; Redcay and Courchesne, 2008). The L-ASD group, however, showed dampened N400m in the left LTC overall, broadly consistent with reports of hypoactivity in language-related left temporal cortices among ASD individuals (Boddaert et al., 2003; Gaffrey et al., 2007; Lombardo et al., 2015; Müller et al., 1999), and reduced left temporal gray matter volume among ASD adults with delayed language onset (Floris et al., 2016).

4.3. Intact temporal and reduced prefrontal activity to PW and AN in ASD

Despite findings of differential left temporal response to word conditions at ~ 250 ms in neurotypical adults (Grainger and Holcomb,

2009; Marinkovic et al., 2014b; Martin-Loeches et al., 2001), we did not observe reliable word-specific N250m activity in the left LTC in any of our groups, possibly reflecting distinct spatiotemporal profiles for adults and adolescents.

However, the subsequent N400m in the left LTC and the scalp-measured N400 were enhanced to PW relative to SW in all of our participants, consistent with a "pseudoword effect" observed in neurotypical adults (Bentin et al., 1999; Deacon et al., 2004; Federmeier and Laszlo, 2009; Halgren, 1990; Holcomb et al., 2002; Smith and Halgren, 1987; Wydell et al., 2003). This finding supports the temporal semantic hub as a necessary substrate of access to meaning (Patterson et al., 2007; Ralph et al., 2017), as it is well-preserved in our high-functioning ASD participants who are able to perform the lexical decision task of this study. The H-ASD participants additionally recruited the right LTC during PW (vs. AN) processing, which may reflect a compensatory function in view of performance levels on par with TD participants.

The pPFC was the principal area where word-specific N400m activity differed as a function of ASD diagnosis and the level of language proficiency. Our data showed greater N400m to PW than SW only in the TD group in the left pPFC, but not in either of the ASD groups. This could suggest deficient recruitment of the prefrontal cortex during attempts to access semantic stores in ASD. Alternatively, as responses needed to be withheld for meaningless letter strings (PW trials) during the lexical decision task, the PW vs. SW contrast in this task may reveal areas critically involved in response inhibition. Given the crucial role the inferior prefrontal cortex plays in inhibitory control (Gläscher et al., 2012; Hung et al., 2018; Munakata et al., 2011), the observed lack of PW-elicited activity in the left pPFC may suggest impaired inhibitory processes in adolescents with ASD. In fact, the inferior prefrontal cortex is not only involved in inhibitory control, but also cognitive control in general, including task switching and updating of current task representations (Brass et al., 2005). Therefore, our results may indicate broader deficits of cognitive control and maintenance of task demands in ASD groups. Even though the lexico-semantic processing and response inhibition are engaged during consecutive processing stages by the double-duty lexical decision task, there is also a significant amount of overlap, precluding their delimitation. To better tease apart these cognitive processes, future work may employ separate tasks that independently probe semantic access/integration and response inhibition.

Animal word trials (AN trials) required category-specific semantic retrieval and response switching compared to the standard SW trials, resulting in greater engagement of cognitive control. Semantic tasks with additional control demands and increased task difficulty are known to elicit bilateral prefrontal activity in neurotypical individuals (Badre and Wagner, 2007; Binder et al., 2009; Curtis and D'Esposito, 2003; Rosen et al., 2016; Wagner et al., 2014). In the present study, AN vs. SW contrast revealed bilateral pPFC activations in the TD group, whereas the H-ASD group recruited only the left pPFC and the L-ASD group showed no differential activation in pPFC at all. Combined with lower performance accuracy to AN in the L-ASD group, insufficient pPFC recruitment in this subgroup may have contributed to impaired targeted semantic retrieval and cognitive control (Boucher, 2012; Hill, 2004; Poljac and Bekkering, 2012).

Group-specific patterns of word condition effects were found in the LTC and pPFC. All participants demonstrated intact attempts to access semantic stores in the left LTC (as reflected in the PW vs. SW effect), whereas activity in the pPFC was attenuated in ASD participants, especially those with lower language proficiency. Undifferentiated pPFC recruitment to PW and AN trials in ASD is consistent with deficient prefrontal semantic access, and with impaired executive function in this population, further confirming the critical role pPFC plays in targeted semantic retrieval and cognitive control, i.e. maintaining the latest task representation and retrieving relevant semantic information that matches the task set (Brass et al., 2005; Munakata et al., 2011).

4.4. Prefrontal N400m latency is delayed in the L-ASD group

In neurotypical adults, the N400m onset latency is reported to be quite stable and insensitive to experimental manipulations, task difficulty, and contextual factors (Federmeier and Laszlo, 2009). We investigated group differences in the N400m onset latency in the left LTC and pPFC, respectively, and identified a similar pattern of group differences as with the N400m amplitude. The groups did not differ in the N400m latency in the left LTC, which is indicative of preserved timing of semantic access in ASD. In the left pPFC, however, the N400m latency was delayed in the L-ASD relative to the TD and H-ASD groups. The delayed N400m latency in the participants with lower language abilities is broadly consistent with previous reports of delayed N400 in children with ASD (DiStefano et al., 2019) and with developmental language impairment (Cummings and Čeponienė, 2010). Since the N400 reflects binding of distributed information into a coherent unit of meaning in time (Federmeier and Laszlo, 2009), delayed latency may indicate a slower rate of semantic access and contextual integration, which is often observed in younger children with limited language development (Holcomb et al., 1992), bilinguals processing the non-dominant (vs. dominant) language (Leonard et al., 2010; Moreno and Kutas, 2005), and adults with neurological or psychiatric disorders (Grillon et al., 1991; Olichney et al., 2002).

4.5. Spatiotemporal dynamics associated with language heterogeneity in ASD

We contrasted the overall spatiotemporal dynamics of lexico-semantic processing in the H-ASD vs. L-ASD group to investigate the neural signature of the phenotypic heterogeneity in language proficiency in this ASD sample. First, participants with higher language proficiency were characterized by increased right prefrontal and bilateral lateral temporal activity during the N250m and N400m time windows, respectively. Second, those with higher language proficiency showed intact N400m enhancement to AN (vs. SW) and typical N400m onset latency in the left prefrontal cortex. Third, they demonstrated enhanced N250m and N400m in the bilateral aPFC and IPC (see Supplemental Information), which is suggestive of compensatory recruitment to maintain normative performance.

It is possible that individuals with various levels of language proficiency may follow different neurodevelopmental trajectories, resulting in distinct neuroendophenotypes. The exact time course and the neurobiological mechanisms of these differential atypical developmental trajectories, however, remain unclear. Both genetic and environmental factors during perinatal or postnatal development stages may impact the acquisition and development of language skills among individuals with ASD (Chow et al., 2012; Smith, 2007; Toma et al., 2011). Those with better language functions may have received more effective interventions early in life and achieved near-normative language functions through preserved neurotypical activation, and more importantly, recruitment of alternative, compensatory neural networks. This may be partially reflected in over-recruitment among H-ASD participants of the brain regions that typically subserve attentional, lexico-semantic and executive functions (Corbetta et al., 2008; Jefferies, 2013; Lau et al., 2008; Marinkovic et al., 2003; Marinkovic et al., 2014b; Thompson-Schill, 2003). Specifically, compensatory activation of the non-dominant hemisphere is a common neural mechanism to "boost" cognitive performance. It is not only observed in ASD but also in clinical populations with language impairments (Johnson et al., 2013; Pecini et al., 2005; Wehner et al., 2007), and in neurotypical individuals processing unconventional stimuli, such as non-pronounceable nonwords (Marinkovic et al., 2014b), unfamiliar letter strings and objects (Seghier and Price, 2011), and inverted faces (Marinkovic et al., 2014a).

5. Conclusions

Simultaneous acquisition of aMEG and limited EEG data during a lexical decision task that combined semantic access with demands on cognitive control allowed us to identify distinct spatiotemporal patterns in adolescents with ASD and TD participants. Unlike their TD peers who predominantly recruited the canonical left-lateralized frontotemporal cortices during lexico-semantic processing, the ASD participants showed bilateral engagement during both lexical access (N250m) and semantic integration (N400m). The ASD participants were stratified into high- (H-ASD) vs. low-performance (L-ASD) groups based on their task performance. Even though their accuracy was on par with TD peers, the H-ASD group relied on compensatory recruitment of a distinct network of regions comprising bilateral anterior prefrontal, parietal, and right temporal cortices. The absence of differential PW vs. SW prefrontal activity in both ASD groups is indicative of deficient recruitment of the canonical prefrontal networks subserving semantic and contextual access and inhibitory control. Additionally, a lack of left prefrontal engagement to AN and delayed N400m onset latency in L-ASD compared to H-ASD participants is consistent with impaired lexico-semantic processing and deficient cognitive control. Combined, these findings not only highlight specific spatiotemporal activity profiles underlying atypical language and executive processes in adolescents with ASD, but also reveal significant neural heterogeneity as a function of language proficiency within the ASD group, which may be due to differential neurodevelopmental trajectories and adoption of compensatory strategies.

CRediT authorship contribution statement

Yuqi You: Conceptualization, Data curation, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Angeles Correas:** Methodology, Formal analysis, Investigation. **David R. White:** Formal analysis. **Laura C. Wagner:** Investigation. **R. Joanne Jao Keehn:** Investigation, Writing – review & editing. **Burke Q. Rosen:** Methodology, Software. **Kalekirstos Alemu:** Investigation. **Ralph-Axel Müller:** Conceptualization, Funding acquisition, Writing – review & editing. **Ksenija Marinkovic:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix: Supplemental Information

Results

Group-specific engagement of the aPFC and IPC

There were additional areas that showed group differences during the N250m and N400m time windows (Fig. 2A, B). During the N250m time window, group differences were observed in the aPFC [$F(2,57) = 4.66$, $p = .013$] and IPC [$F(2,57) = 4.59$, $p = .014$], respectively. In the aPFC, the H-ASD group demonstrated stronger activity than the L-ASD [$t(27.8) = 2.52$, $p = .018$] and TD groups [$t(39) = 2.31$, $p = .026$]. In the IPC, both TD and H-ASD groups showed stronger activity than the L-ASD group [TD vs L-ASD: $t(38) = 3.03$, $p = .004$; H-ASD vs L-ASD: $t(27.5) = 2.72$, $p = .011$]. The same group effects in the aPFC [$F(2,57) = 3.39$, $p = .004$] and IPC [$F(2,57) = 5.14$, $p = .009$] persisted during the subsequent N400m window, with the H-ASD group showing the highest activity in the aPFC [H-ASD vs. L-ASD: $t(29.4) = 2.24$, $p = .033$; H-ASD vs. TD: $t(39) = 1.95$, $p = .058$], and both TD and H-ASD groups demonstrating greater activity than the L-ASD group in the IPC [TD vs L-ASD: $t(38) = 3.14$, $p = .003$; H-ASD vs L-ASD: $t(30.4) = 2.90$, $p = .007$].

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