Atypical spatiotemporal signatures of working memory brain processes in autism

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INTRODUCTION

Autism spectrum disorder (ASD) is a severe neurodevelopmental disorder characterized by striking impairments in social interaction and the presence of circumscribed interests and stereotyped-repetitive behaviours.1 Deficits in working memory (WM) and inhibition processes are key aspects of developmental psycho-pathology theories,2 as there is substantial evidence suggesting strong relations between WM difficulties and social or cognitive deficits in patients with ASD, and also schizophrenia or attention deficit hyperactivity disorder.2–5 In that context, it has been suggested that WM difficulties might partly explain some symptoms of ASD, as a portion are related to poorer WM processes.6–9 WM is the ability to store and manipulate information transiently, in the service of complex cognition and behaviour.7 It is not only strongly associated with academic achievement9,9 but also has a central role in the online processing of complex cognitive information, such as social cognition and interpersonal interactions (for a recent review see Barendse et al.10).

Behavioural studies have shown that ASD patients are particularly impaired in the spatial domain of WM,5,11,12 (but see Schuh and Eigsti13) and that their difficulties increase when the tasks impose heavier WM demands.5,14–16 However, despite the importance of studying these processes in ASD, developmental research on WM functions in ASD is limited and overall findings are inconsistent as a number of studies have also found normal WM performance in this population.17–20

At a neuroimaging level, a handful of functional magnetic resonance imaging (fMRI) studies addressing this topic have indicated atypical WM-related brain processes in ASD, usually in the absence of clear behavioural differences between clinical and control populations.21–23 In most studies, atypical frontal connectivity patterns or decreased activity in the prefrontal cortex have been reported in adults and adolescents with ASD in visuospatial WM tasks.23 For instance, Silk et al.24 found WM processes involved in a mental rotation task were associated with reduced cortical activity of the anterior cingulate cortex (ACC), dorso-lateral prefrontal cortex (dPFC) as well as the caudate nucleus in ASD compared with age-matched typically developing (TD) adolescents. Vogan et al.25 found markedly reduced frontal activity in children with ASD compared with controls in a WM task, also using fMRI.25 However, atypical brain responses associated with WM processes in ASD were not restricted to the frontal lobe. Using a cognitive control WM task, Solomon et al.26 showed that adolescents with ASD presented less frontal (BA 10) but also less parietal (BA 7 and BA 40) and occipital (BA 18) activation than TD participants. Likewise, reduced recruitment of the right posterior temporal regions22 in addition to reduced prefrontal activity21,22 was identified in adults with ASD using two versions of the n-back task.

These atypicalities involved brain areas known to have a crucial role in WM processes. Whereas the prefrontal cortex acts as a control region, allowing the maintenance and manipulation of
information in WM, the inferior parietal lobe activity has been associated with an information buffer function and is associated with improved WM ability in healthy children.

Thus, these results suggest impairments in core WM processes yet compensatory strategies that allow, in the majority of cases, normative performance on specific WM memory tasks. However, compensatory brain processes do not rule out the possibility that individuals with ASD may be affected in more complex situations, according to the model that their WM deficits are related to specific disabilities in selecting appropriate processing strategies. Moreover, the poor temporal resolution of the fMRI studies reported above precludes an understanding of the timing of atypical WM components in ASD. Using magnetoencephalography (MEG), Hung et al. demonstrated significant WM-related brain processes involved in an n-back task occurring within the first few 100 ms after stimulus onset. Hence, MEG is a powerful technique that offers the ability to measure neuronal activity directly with millisecond time resolution, orders of magnitude higher than the time resolution of an fMRI (>1 s) and with excellent spatial resolution, allowing the detection and the localization of weak transient activations. We apply this approach to improve our understanding of specific WM difficulties in children with ASD.

In addition, despite the central role of WM in social cognition and in cognitive development, very few fMRI studies have investigated WM-related brain processes in ASD during development. The present study addresses this gap and explores, at the behavioural and the neurophysiological level, the complex spatiotemporal processes underlying WM in children with ASD. To do so, we used MEG recordings during an n-back task to compare WM-related brain activity across different complexity levels (1-back vs 2-back) between children with high-functioning ASD and age-matched controls.

MATERIALS AND METHODS

Participants

This study included 20 children with high-functioning ASD and 20 TD controls that were age-, sex-, handedness and intelligence quotient matched. See Table 1 for demographic characteristics.

Participants were selected from a larger series of 38 children with high-functioning ASD and 26 TD control children (age range: 7y1mo—13y11mo). Children with autism were not included if they had an associated genetic or metabolic disorder, the presence of other neurological disorders, any current significant Axis I psychiatric comorbidities, medical illnesses, uncorrected vision and a learning disability or developmental delay as the primary diagnoses. Clinical diagnoses of ASD were confirmed in all cases with a combination of expert clinical judgment and the Autism Diagnostic Observation Schedule-General. TD children were not included if they reported a learning disability, developmental delay, any neurological, psychiatric or academic problem, as well as uncorrectable visual impairment. We arrived at our final sample of 40 children (20 per group) after sex- and age-matching and excluding children with excessive movement in the MRI and MEG scanners and inadequate task performance.

A further six children with ASD and one TD child had been tested, but their data were excluded as they performed the task at a chance level, meaning that their percentage of correct recognition (HITS) was equal or higher than the percentage of false alarm (FA), whatever the task condition. Of the six children with ASD, five were not able to perform the 2-back condition, whereas one ASD child failed to perform the 1-back condition. The excluded TD child was not able to perform both the 1- and the 2-back condition.

Children with ASD were recruited through community support centres, parent support groups and hospital advertisements; TD children were recruited through flyers and brochures posted at the hospital and the surrounding community. MEG and MRI scanning, as well as clinical and cognitive testing, were performed at the Hospital for Sick Children in Toronto. Experimental procedures were approved by the Hospital’s Research Ethics Board. All children gave informed assent and the parents provided informed written consent.

Experimental MEG task and procedure

An n-back task requiring recognition of complex multi-coloured abstract images was used to investigate the WM ability of children with ASD. Children were instructed to press a key when they identified a repetition of a picture (target) presented 1 or 2 trials earlier (according to the 1-back or 2-back condition, see Figure 1).

Each n-back condition (1- and 2-back) was administered separately and counterbalanced across participants. All stimuli appeared on a projection screen located 80 cm from the children, where the visual angle of the stimuli subtended ~4° of their visual field. Each picture was followed by a fixation cross with an inter-stimulus interval varying between 1250 and 1500 ms. A photodiode was used to ensure accurate synchronization between the presentation of each visual stimulus and the trigger.

The 1-back condition had 230 trials, including 154 ‘NEW’ trials that is, first occurrence of a picture) and 76 ‘REPEAT’ (target) trials, whereas the 2-back condition (which is more difficult due to the higher memory load) had 330 trials including 221 ‘NEW’ and 109 ‘REPEAT’ stimuli. A total of 375 different complex, coloured patterns were used across tasks, and there was no overlap of stimuli between the 1- and the 2-back conditions. Prior to
entering the MEG, children were given a practice series to ensure that they understood the task and the two n-back conditions; this also gave them experience with the timing of the presentation for the stimuli. Stimuli used in the practice trials were not included in the experimental blocks.

MEG data acquisition
MEG was recorded in a magnetically shielded room using a CTF MEG scanner with 151 axial gradiometers (Omega-151; MISL, Coquitlam, BC, Canada). Data were acquired at a sample rate of 600 s with a bandpass of 0–150 Hz. Head position inside the MEG dewar was measured before each recording session of each condition and continuously monitored using three tracking coils placed at the nasion and pre-auricular points. Coils placements were carefully measured and photographed in order to allow the off-line coregistration of the MEG data to the anatomical MRI of each child for source analyses.

MRI data acquisition
Each child had a T1-weighted MRI (3D Sagittal MPRAGE: PAT, GRAPPA = 2, TR/TE/FA = 2300 ms/2.96 ms/90°, FOV = 28.8 × 19.2 cm, 256 × 256 matrix and 192 slices, slice thickness = 1.0 mm isotropic voxels) from a 3 T MR scanner (MAGNETOM Tim Trio, Siemens, Erlangen, Germany), with a 12-channel head coil.

Behavioural analyses
At the behavioural level, accuracy scores (percentage of correct recognition (Acc)), mean reaction times (RTs) and RT coefficient of variation (CV) (calculated for each subject as the s.d. of the mean RT divided by mean RT) associated with the target (repeat) stimuli were recorded in each n-back condition, and ‘repeat–correct’ trials (RC) were compared between groups with repeated measures analysis of variance to ensure adequate quality of behavioural results prior to source analysis.

Neuropsychological assessment
All children completed the Wechsler Abbreviated Scale of Intelligence as well as the Backwards Digit Recall, Listening Recall, Digit Recall, Mazes Memory and Block Recall subscales of the Working Memory Test Battery for Children (WMTB-C) to supplement behavioural data collected during the MEG task. Standardized scores on the subscales of the WMTB-C were compared across groups using repeated measures analysis of variance; age, sex and handedness were also compared across groups using t-tests for an independent sample.

MEG analyses
With MEG we investigated the neurophysiological WM processes involved in correct recognition in the 1- and 2-back conditions. ‘Correct recognition effects’, where RC trials elicited significantly stronger brain activity than New (N) trials have been described as a suitable comparison with identified WM-related brain activity. Such a contrast (RC vs N) allows the identification of brain regions that are associated specifically with the recognition of the repeated (target) trial, excluding common brain activity shared between the N and RC conditions (for example, visual processing, baseline activity, etc.).

Event-related fields associated with (1) correctly recognized target images (RC trials; please see Supplementary Figure S1) and with (2) ‘New’ trials were recorded and analyzed within memory condition (1- vs 2-back) and then compared between groups (ASD vs TD). Memory load effects (1-back vs 2-back) were then tested on between source effects (pseudo -tests for dependent samples (performed using Statistica version 7.0; Statsoft, Tulsa, OK, USA) were used to compare memory load effects (1- vs 2-back) on functional brain activations (pseudo z-values) associated with correct recognition effects (RC-New) at the between-group level. Statistical analyses performed on behavioural data were performed using Statistica version 7.0 (Statsoft).

RESULTS
WM behavioural performance
We found a significant main effect of condition (1- and 2-back) for all three behavioural measures, Acc, RTs and RT CV (Acc: F(1,38) = 136.08; RTs: F(1,38) = 138.58 and CV: F(1,38) = 17.16; all P < 0.0002) but no effect of the group (all P > 0.19) and no interaction between the factors (condition × group; all P > 0.24; see Table 2 for details of the behavioural data). Thus, there were no behavioural differences between ASD and TD children across dependent variables (Acc, RTs or CV). Subsequent least significant difference Fisher post hoc analyses demonstrated that both groups of children performed significantly better in the 1-back compared with the 2-back condition (all P > 0.003). Likewise, no effect of the group (P > 0.19) or interaction were found on the standardized subscales scores of the WMTB-C (subscales of the WMTB-C × group; P > 0.55). We found a main
effect of subscales of the WMTB-C ($F(4,148) = 8.73, P < 0.00001$) suggesting that regardless of the group of children, WM performance differed between subtests, with better performance for Digit Recall and Listening Recall than for Backward Digit Recall, Block Recall and Mazes Memory (all $P's < 0.016$), which otherwise did not differ from each other (all $P's > 0.23$) as demonstrated by least significant difference Fisher's post hoc analyses.

MEG results

Within-group working memory brain processes in TD and ASD Children. Significant within-group activations associated with the correct recognition effect, where event-related responses associated with RC trials were significantly greater than the encoding space volume for within-group comparisons (recognition effect in each group; RC vs New stimuli) and at 500 ms, TD children recruited the right middle cingulate cortex (MCC) followed by the ACC and the right orbito-frontal region, both marked by persistent long-lasting activity from 450 to 525 ms and 575 ms, respectively.

Within-group comparison (RC $>$ New; $P_{corr} < 0.05$) conducted on recognition effects in ASD children revealed activations first in the left dIPFC from 200 to 275 ms, followed by the right mPFC from 400 to 500 ms. Large, long-lasting activity occurred then from 425 to 500 ms bilaterally in the insulae while the right hippocampus was activated from 450 to 500 ms. Finally, children with ASD recruited the left orbito-frontal gyrus and the ACC from 500 to 550 ms, as well as the right MCC from 525 to 575 ms.

1-Back correct recognition effect in TD and ASD children: In TD children, correct recognition effects (RC $>$ New; $P_{corr} < 0.05$) were strongly associated with increased activity in the right medial temporal gyrus (375–425 ms) and large and sustained activity in the right hippocampus from 400 to 500 ms. The right precentral gyrus was also activated from 375 to 450 ms as well as the right medial prefrontal cortex (mPFC) from 400 to 450 ms. From 450 to 500 ms, TD children recruited the right middle cingulate cortex (MCC) followed by the ACC and the right orbito-frontal region, both marked by persistent long-lasting activity from 450 to 525 ms and 575 ms, respectively.

2-Back correct recognition effect in TD and ASD children: Within-group comparison (RC $>$ New; $P_{corr} < 0.05$) conducted on recognition effects in TD children in the 2-back condition revealed increased activity from 225 to 275 ms in the left insula and the left mPFC from 250 to 300 ms. From 325 to 375 ms, TD children recruited first the left intra-parietal sulcus (IPS) and the left dIPFC from 375 to 425 ms, followed by sustained activity in the right MCC from 425 to 500 ms.

Table 2. Mean behavioural performance on the n-back task

| Time windows | Brain area | Pseudo z-values | MNI coordinates |
|--------------|------------|----------------|-----------------|
| 1-Back       |            |                |                 |
| TD children  | 375–425    | R MTG          | 0.75            |
|              |            | R Precentral gyrus | 0.66 |
|              | 400–450    | R Hippocampus  | 0.87            |
|              |            | R Precentral gyrus | 0.57 |
|              | 425–475    | R Hippocampus  | 0.74            |
|              | 450–500    | R MCC          | 0.52            |
|              | 475–525    | L ACC          | 0.73            |
|              | 525–575    | R OGF          | 0.47            |
| 2-Back       |            |                |                 |
| TD children  | 200–250    | L dIPFC        | 0.52            |
|              | 225–275    | L dIPFC        | 0.64            |
|              | 400–450    | R mPFC         | 0.89            |
|              | 425–475    | R Insula       | 0.84            |
|              | 450–500    | R Insula       | 0.73            |
|              | 500–550    | L OGF          | 0.61            |
|              | 525–575    | R MCC          | 0.66            |

Abbreviations: Acc, accuracy; ASD, autism spectrum disorder; NS, not significant; RT, reaction time; TD, typically developing; V, coefficient of variability. Values are denoted as mean ± s.d.

Table 3. Areas of activation associated with correct recognition effect (RC $>$ New) in the 1-back memory load in TD and ASD children

| Time windows | Brain area | Pseudo z-values | MNI coordinates |
|--------------|------------|----------------|-----------------|
| 1-Back       |            |                |                 |
| TD children  | 375–425    | R MTG          | 0.75            |
|              |            | R Precentral gyrus | 0.66 |
|              | 400–450    | R Hippocampus  | 0.87            |
|              |            | R Precentral gyrus | 0.57 |
|              | 425–475    | R Hippocampus  | 0.74            |
|              | 450–500    | R MCC          | 0.52            |
|              | 475–525    | L ACC          | 0.73            |
|              | 525–575    | R OGF          | 0.47            |
| 2-Back       |            |                |                 |
| TD children  | 200–250    | L dIPFC        | 0.52            |
|              | 225–275    | L dIPFC        | 0.64            |
|              | 400–450    | R mPFC         | 0.89            |
|              | 425–475    | R Insula       | 0.84            |
|              | 450–500    | R Insula       | 0.73            |
|              | 500–550    | L OGF          | 0.61            |
|              | 525–575    | R MCC          | 0.66            |

Abbreviations: ACC, anterior cingulate cortex; ASD, autism spectrum disorder; dIPFC, dorso-lateral prefrontal cortex; L, left; MCC, middle cingulated cortex; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; MTG, medial temporal gyrus; OGF, orbito-frontal gyrus; PCG, precentral gyrus; R, right; RC, repeat-correct trial; TD, typically developing. Note: Statistical significance was set for the significant voxels of activation at $P < 0.05$, corrected for multiple comparisons in the whole source–space volume for within-group comparisons (recognition effect in each group; RC vs New stimuli) and at $P < 0.005$ uncorrected for between-group comparisons (recognition contrast (RC–New stimuli) by group, highlighted in bold.)
In children with ASD, correct recognition effects (RC > New; \( p_{corr} < 0.05 \)) were first associated with the left mPFC from 200 to 250 ms and large activity of the left angular gyrus from 250 to 325 ms. We then observed activity in the left dIPFC from 275 to 325 ms, followed by large activity in the left precuneus from 325 to 400 ms as well as sustained activity in the right MCC from 475 to 525 ms.

Between load (1-back vs 2-back) correct recognition effects in TD and ASD children: T-tests for dependent samples performed on recognition effects (RC—New) in TD children showed that the right hippocampus (from 400 to 475 ms) and the left ACC (from 450 to 500 ms) elicited stronger activation during the 1-back condition (all \( P < 0.01 \)). Whereas they recruited the left insula (from 225 to 275 ms) and the IPS (from 325 to 375 ms) more during the 2-back than the 1-back condition (all \( P < 0.03 \)).

Similar comparisons performed in children with ASD revealed more activation in the left dIPFC (\( P = 0.05 \)) and the bilateral insulae (all \( P < 0.01 \)) in the 1-back condition compared to the 2-back condition. The left mPFC and the left angular gyrus were active from 225 to 500 ms, whereas the high-memory load condition children with ASD showed more activity in the left precuneus (from 325 to 375 ms) compared with the low-memory load condition (\( P < 0.03 \); see Supplementary Table S1 in Supplementary Information for details).

**Comparison of WM brain processes between TD and ASD children.** Between-group comparisons performed on recognition-related brain activations observed in the within-group analyses revealed overlapping but also different WM networks in ASD and TD children both in the higher- (2-back) and lower- (1-back) memory load conditions (see Tables 3 and 4, in bold).

1-Back-related functional brain differences between TD and ASD children: Between-group comparison (see Figure 2a) performed on brain areas associated with correct recognition effects in the 1-back condition revealed important differences in five brain regions: the right hippocampus, the left dIPFC, the bilateral insulae, the ACC and the MCC. Children with ASD showed significantly stronger activity in the left dIPFC from 200 to 275 ms and in the bilateral insulae from 425 to 500 ms than TD children. Conversely, from 400 to 500 ms, TD children showed long-lasting activation in the right hippocampus where children with ASD only recruited this region at the same level as controls from 450 to 500 ms. Moreover, both the ACC and MCC were significantly more active from 450 to 500 ms in TD children than children with ASD.

2-Back-related functional brain differences between TD and ASD children: Between-group comparison (Figure 2b) of brain areas associated with correct recognition effects in the 2-back condition also revealed significant differences in WM brain processes in five regions. Children with ASD showed less activation in the left insula (from 225 to 275 ms), the left IPS (from 325 to 375 ms) and the right MCC (from 425 to 500 ms) than TD children. By contrast, children with ASD showed stronger WM-related activations of the left angular gyrus (from 250 to 325 ms) and of the left precuneus (from 325 to 400 ms).

**Correlation analyses**

Data inspection revealed a significant positive correlation coefficient between the right hippocampal activity and performance (that is, percentage of HITS—percentage of FA) in TD but not in ASD children (average \( r = 0.51; P = 0.02 \) in TD children vs \( r = -0.17; P = 0.45 \) in ASD children, see Figure 3a) during the 1-back condition. 2-Back-related activity in the left precuneus was a positively correlated performance (that is, percentage of HITS—percentage of FA) in ASD but not in TD children (average \( r = -0.2; P = 0.4 \) in TD children vs \( r = -0.47; P = 0.04 \) in ASD children, see Figure 3b). Finally, we observed a significant negative correlation between the ACC activity during the 1-back task and the severity of autistic symptoms assessed through the ADOS scores (average \( r = -0.5; P = 0.02 \) in ASD children, see Figure 3c). This last result indicates that the more severe the symptoms were in the children with ASD, the less they activated the ACC during the 1-back task.

**DISCUSSION**

Our study, particularly in relation to the sequence of activations revealed using the temporal resolution of MEG, highlights atypical WM-related brain processes in children with ASD. These

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**Table 4. Areas of activation associated with correct recognition effect (RC > New) in the 2-back memory load in TD and ASD children**

| Time windows | Brain area | Pseudo z-values | MNI coordinates |
|--------------|------------|----------------|-----------------|
| **TD children** |            |                |                 |
| 225–275      | L Insula   | 0.47           | -31 -22 12     | TD > ASD         |
| 250–300      | L mPFC     | 0.57           | -26 43 2       |                 |
| 325–375      | L IPS      | 0.46           | -41 -47 42     | TD > ASD         |
| 375–425      | L dIPFC    | 0.59           | -41 18 27      |                 |
| 425–475      | R MCC      | 0.46           | -12 47 42      | TD > ASD         |
| 450–500      | R MCC      | 0.43           | -2 42 42       | TD > ASD         |
| **ASD children** |          |                |                 |
| 200–250      | L mPFC     | 0.49           | -11 48 22      |                 |
| 250–300      | L Angular  | 0.46           | -41 -62 32     | ASD > TD         |
| 275–325      | L Angular  | 0.52           | -41 -52 32     | ASD > TD         |
| 325–375      | L Precuneus| 0.41           | -6 -67 37      | ASD > TD         |
| 350–400      | L Precuneus| 0.5            | -6 -67 42      | ASD > TD         |
| 475–525      | R MCC      | 0.42           | 4 13 47        |                 |
| 450–500      | R MCC      | 0.42           | -1 -2 57       |                 |

Abbreviations: ASD, autism spectrum disorder; dIPFC, dorso-lateral prefrontal cortex; IPS, intra-parietal sulcus; MCC, middle cingulated cortex; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; RC, repeat–correct trial; TD, typically developing. Note: statistical significance was set for the significant voxels of activation at \( P < 0.05 \), corrected for multiple comparisons in the whole source space volume for within-group comparisons (recognition effect in each group; RC vs New stimuli) and at \( P < 0.005 \) uncorrected for between-group comparisons (recognition contrast (RC—New stimuli) by group, highlighted in bold).
atypicalities showed significant, qualitative functional brain differences, where the groups recruited distinct brain regions to perform the WM task, as well as quantitative differences where both groups activated the same region but to a differing extent. Cerebral functional dissimilarities occurred despite any behavioural differences in performance between ASD and TD children, consistent with most results in the literature (for example, see Ozonoff and Strayer, 18 Russell et al.45 and Griffith et al.46). However, six children with ASD but only one TD child included in the original sample of participants tested, performed the task at the chance level. Among them, five ASD were unable to do the 2-back condition strengthening the hypothesis that behavioural WM impairments tend to appear in ASD in higher-memory load and/or complex conditions.2,12,47,48

Fronto-insular vs hippocampal WM-related brain differences
In the 1-back condition, children with ASD showed reduced WM-related activity of the right hippocampus from 400 to 450 ms and of the ACC and the MCC from 450 to 500 ms. In contrast, WM processes during the 1-back condition were associated with stronger activity of left dIPFC from 200 to 275 ms and of the insulae bilaterally from 425 to 500 ms in children with ASD compared with controls. Interestingly, in TD children, both the right hippocampus and the MCC were more active during the low-than the high-memory load condition. These results demonstrate qualitative group differences in the WM brain processes underlying the lower WM cognitive load condition, as recognition effects did not rely on either the insula or the dIPFC recruited in TD children during the 1-back condition.

The central role of the right hippocampus in the 1-back WM task in TD children was further strengthened by the presence of a positive correlation between increased activity in this region and improved behavioural performance (percentage of HITS – percentage of FAs), whereas a similar correlation was not present in children with ASD. Moreover, although with different timing, the

Figure 2. WM-related brain differences between TD and ASD children in (a) the 1-back and (b) the 2-back conditions. Brain images: significant brain activations associated with correct recognition effects (RC > New, \( P < 0.05 \)) that were stronger in TD children than children with ASD (left panel in blue) or stronger in children with ASD than in TD children (right panel in green, all \( P < 0.005 \)). Each brain image is associated with two overlaid time-course plots (y axes: pseudo z-values; x axes: time in seconds) representing statistical comparisons (\( P < 0.5 \), red dots) between virtual sensors associated with RC (dark blue in TD and dark green in ASD children) and New (light blue in TD and light green in ASD children) trials. ASD, autism spectrum disorder; RC, repeat–correct’ trial; TD, typically developing children.

Figure 3. Significant correlation coefficients (all \( P < 0.05 \)) between event-related MEG activity in (a) the right hippocampus (1-back; from 450 to 500 ms) and (b) the left precuneus (2-back; from 325 to 375 ms), and behavioural performance in TD (blue) and ASD (green) children. (c) Significant correlation coefficient (\( P < 0.05 \)) between event-related MEG activity in ACC (1-back; from 450 to 500 ms) and ASD symptom severity in ASD. ACC, anterior cingulate cortex; ASD, autism spectrum disorder; FA, false alarm; MEG, magnetoencephalography; TD, typically developing children.
In both groups of children, correct recognition effects partly relied on inferior parietal regions during the 2-back condition. However, the specific recruitment of the left angular gyrus (from 250 to 325 ms) and the left precuneus (from 325 to 400 ms) in children with ASD instead of the left insula (from 225 to 275 ms) and the left IPS (from 325 to 375 ms) in controls showed that WM-related brain processes qualitatively differed between groups, as seen in the low-memory load condition.

Reduced activity of WM-related left IPL and, in particular, lower-connectivity processes between the left IPS and the cingulate cortex have been reported in ASD using a WM fMRI study using a single-letter n-back paradigm. Structural abnormalities in the left inferior parietal cortex have been related to attention deficits in children with ASD and attention deficit hyperactivity disorder. IPL activity is associated with the ability to complete WM tasks in healthy children and is recognized as a key region for n-back WM tasks in a range of fMRI studies. IPL has an important role in attention and spatial processing and hence, has been related to more sophisticated levels of WM performance. Interestingly, the literature indicates a clear and reliable dissociation between the dorsal parietal cortex (including the IPS) being described as the dorsal ‘top-down/executive’ (non-automatic, goal directed and having high-executive demands) and the ventral parietal cortex (including the angular and supramarginal gyri), associated with ventral ‘bottom-up/automatic’ processes across multiple domains beyond attention and episodic memory (see Humphreys and Lambon Ralph for a recent meta-analysis). According to this view, the involvement of the dorsal parietal cortex (that is, IPS) in controls and the ventral angular gyrus in children with ASD reflects the recruitment of different brain processes and functional strategies to reach a similar level of performance.

We suggest that the recruitment of the left precuneus in children with ASD also contributes to WM performance. The precuneus has been related to children’s limited access to inferior parietal regions and is often activated in cognitively demanding tasks requiring enhanced voluntary attention and increased memory load conditions. This interpretation is reinforced by the observation of a negative correlation between performance (that is, percentage of HITS – percentage of FA) and increased activity in the left precuneus in children with ASD, but not in TD children. Moreover, complementary analyses showed that children with ASD tended to recruit this region more in the high-compared with the low-memory load condition. The precuneus is also a hub region that allows the monitoring of cognitive function (for example, the differences in the precuneus of cognitive and is involved in a variety of processing, including visuo-spatial imagery, visual attention and episodic memory retrieval. Future research is needed to understand the functional impact of using these different regions (insulae-IPL vs angular gyrus-precuneus) and their possible specific relations with WM processes in children with ASD.

Frontal-related WM brain differences

Between-group differences observed in the frontal areas were mainly quantitative. In both groups, late-sustained event-related components were activated in the cingulate cortices but to a lesser extent in children with ASD. Delayed activations were observed both in the ACC and MCC in children with ASD (500–550 and 525–575 ms, respectively) compared with TD children (450–525 and 450–500 ms, respectively) in the 1-back condition. Moreover, activity in the MCC was also delayed in children with ASD (475–525 ms) compared with TD children (425–500 ms) during the 2-back condition. Reduced activity in the MCC has been related to functional deficits of the attentional networks in autism and correlating with increased impairments in communication and language abilities in children with ASD.
Although contradictory with some data, atypical WM-related activity in the ACC in ASD is reminiscent of a previous fMRI study conducted in adolescents with ASD. Moreover, alterations in activity in the cingulate, demonstrated by reduced glucose metabolism or disrupted white matter, have been shown throughout the anterior, mid- and posterior cingulate cortex in patients with autism. The crucial impact of atypical ACC activity in the symptomatology of ASD is strengthened by our results. We found a significant correlation between reduced activity in the ACC and an increase in autistic symptoms severity in our population of children with ASD. Therefore, given the critical role of the anterior and midcingulate cortex in attentional circuits that help the regulation of both cognitive and emotional processing (for a review see Bush et al.), we suggest that future research investigates the specific associations of cingulate-related WM functions and their relations with social and communication deficits in ASD.

Potential impact on social deficits of autism

Our results suggest that, although different brain networks were able to support similar WM behavioural performance in TD and ASD children, in the context of the n-back task, the neurocognitive strategies observed in children with ASD might also affect the processing of complex social situations. Executive functions including WM have been implicated in the processing of social information requiring, for instance, theory of mind skills that are reported impaired or delayed in ASD. Accordingly, our results identified abnormal brain activity in the ACC, the MCC, the insula, the medial temporal lobe and the inferior parietal lobes that have been involved in high-level executive and social cognition processes. Moreover, the atypical functioning of the ACC and the insula in the context of cognitively challenging situations has been considered as a key aspect of psychopathology in several neurological and psychiatric disorders, including fronto-temporal dementia, autism and anxiety disorders. Thus, our results suggest that the abnormal spatiotemporal brain processes identified in children with ASD, both in the low- and high-cognitive load WM conditions, may contribute to the social deficits of autism.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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