BRAIN COMMUNICATIONS

Frequency-specific neural synchrony in autism during memory encoding, maintenance and recognition

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Working memory impairment is associated with symptom severity and poor functional outcome in autistic individuals, and yet the neurobiology underlying such deficits is poorly understood. Neural oscillations are an area of investigation that can shed light on this issue. Theta and alpha oscillations have been found consistently to support working memory in typically developing individuals and have also been shown to be functionally altered in people with autism. While there is evidence, largely from functional magnetic resonance imaging studies, that neural processing underlying working memory is altered in autism, there remains a dearth of information concerning how sub-processes supporting working memory (namely encoding, maintenance and recognition) are impacted. In this study, we used magnetoencephalography to investigate inter-regional theta and alpha brain synchronization elicited during the widely used one-back task across encoding, maintenance and recognition in 24 adults with autism and 30 controls. While both groups performed comparably on the working-memory task, we found process- and frequency-specific differences in networks recruited between groups. In the theta frequency band, both groups used similar networks during encoding and recognition, but different networks specifically during maintenance. In comparison, the two groups recruited distinct networks across encoding, maintenance and recognition in alpha that showed little overlap. These differences may reflect a breakdown of coherent theta and alpha synchronization that supports mnemonic functioning, or in the case of alpha, impaired inhibition of task-irrelevant neural processing. Thus, these data provide evidence for specific theta and widespread alpha synchrony alterations in autism, and underscore that a detailed examination of the sub-processes that comprise working memory is warranted for a complete understanding of cognitive impairment in this population.

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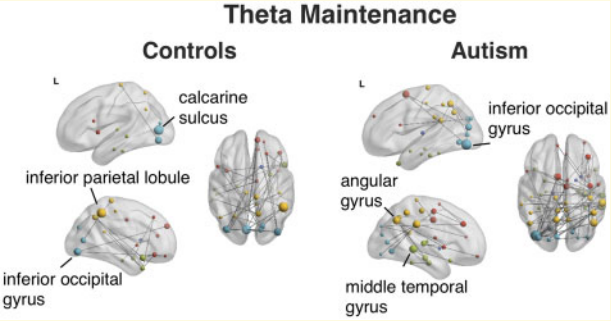
Abbreviations: DSC = Dice similarity coefficient; MEG = magnetoencephalography; NBS = network-based statistics; SOG = superior occipital gyri; SQUID = superconducting quantum interference device; wPLI = weighted phase lag index

Graphical Abstract



Introduction

Autism spectrum disorder (referred to hereafter as 'autism') is a neurodevelopmental disorder primarily characterized by deficient social and communication ability as well as restrictive and repetitive behaviours (American Psychiatric Association, 2013). It is also associated with certain cognitive deficits, including impairment of language, mental flexibility and working memory, the latter constituting the ability to maintain and/or manipulate information in mind over short periods of time (Baddeley, 2012; Kercood *et al.*, 2014). Recently, there has been a growing interest in understanding working memory capacity in autism, due to its critical role in social cognition and executive functioning, which are thought to contribute to the complex symptomatology observed in this population (Barendse *et al.*, 2013). Consistent with this, working memory deficits are associated with symptom severity and functional outcome in autism (Kercood *et al.*, 2014; Troyb *et al.*, 2014; Leung *et al.*, 2016).

In typical development, it is well-established that the attentional and central executive functions that underlie working memory are supported by frontal and parietal regions of the brain (Owen *et al.*, 2005; Chai *et al.*, 2018). There is also growing literature supporting the critical role of neural oscillatory mechanisms to successful working memory. Theta power sharply increases at the beginning of a working memory task and persists throughout, increasing with increasing working memory load (Raghavachari *et al.*, 2001; Jensen and Tesche, 2002). It is thought that theta is directly involved in working memory maintenance, and entraining neurons to this rhythm during retention has been shown to boost memory across short delays (Albouy *et al.*, 2017). Alpha oscillations are also consistently observed during working memory tasks. Some studies suggest that alpha plays a direct role in cognitive processes underlying memory maintenance (Herrmann *et al.*, 2004; Palva and Palva, 2011; Fukuda *et al.*, 2015), while others hypothesize that alpha is involved in filtering distractors (Bonnefond and Jensen, 2012) and inhibiting task-irrelevant brain regions (Klimesch *et al.*, 2007). While local alpha oscillatory activity may generally subserve inhibition, long-range synchronization is more precisely linked to task-relevant neural processing (Klimesch *et al.*, 2008; Palva and Palva, 2011).

Comparably little research has interrogated the neural substrates underlying working memory difficulties in autism, although the supporting neurobiology may be different. Studies utilizing functional magnetic resonance imaging indicate altered frontal and parietal lobe activity in autism compared to controls (Luna *et al.*, 2002; Koshino *et al.*, 2005, 2008), reduced load-dependent modulation of these regions (Vogan *et al.*, 2014, 2018, 2019) and reduced functional connectivity and efficiency within the frontoparietal control network during working memory tasks (Solomon *et al.*, 2009; Barendse *et al.*, 2018). Other studies have shown decreased engagement of frontal–temporal (Koshino *et al.*, 2008; Urbain *et al.*, 2016) and corticostriatal neural networks (Braden *et al.*, 2017), and increased engagement of regions that are not typically associated with working memory (Koshino *et al.*, 2008). Of the three studies that have directly examined neural oscillatory activity during working memory in autism, two studies with children indicated reduced inter-regional phase synchronization in the alpha frequency in frontotemporal networks (Urbain *et al.*, 2016), as well as altered activity in frontal, insular, medial temporal and parietal regions compared to controls during successful recognition of stimuli (Urbain *et al.*, 2015). Recently, Larrain-Valenzuela *et al.* (2017) found that adults with autism did not exhibit the same parametric modulation during working memory maintenance evident in controls—which consisted of alpha power in occipital regions, and theta power in prefrontal regions—in response to increasing memory load. Intriguingly,

neural differences during working memory tasks are often found despite comparable working memory performance between autism and control groups (Koshino *et al.*, 2005, 2008; Urbain *et al.*, 2015, 2016). It is thought that such network alterations in autism may reflect inadequate or possibly compensatory neural strategies that are able to support working memory function under low (Rane *et al.*, 2015; Johnson, 2017; Pillai *et al.*, 2018), but not high cognitive load (Rahko *et al.*, 2016; Barendse *et al.*, 2018; Vogan *et al.*, 2018).

While there is considerable evidence that working memory as a whole is affected in autism, it is important to appreciate that working memory is not a uniform process. It has long been understood that working memory can be subdivided into at least three components: encoding of initial information, maintaining that information over a short delay and retrieving or recognizing those items (Baddeley, 2012). While encoding and recognition are shared components with long-term memory processes (which have been found to have different neurobiological underpinnings in those with autism: Greimel *et al.*, 2012; Gaigg *et al.*, 2015; Cooper *et al.*, 2017*a*, *b*), maintenance is unique to working memory. The relative contribution of each of these to working memory deficits in autism is unknown, largely because the majority of studies used block-design functional magnetic resonance imaging tasks, precluding a detailed examination of the underlying working memory subcomponents. Neurophysiological technologies are far better adapted for these detailed analyses. Concordantly, an electroencephalography study examined the three sub-components of working memory and found an impairment of alpha and theta power modulation in adults with autism with working memory load, specifically during the maintenance interval of their modified Sternberg task, and not during encoding or recognition (Larrain-Valenzuela *et al.*, 2017).

While power and activation are aspects of neural signals that warrant exploration, autism is increasingly being considered a network disorder (Kana *et al.*, 2011; Watanabe and Rees, 2016; Yerys *et al.*, 2017), and no study to date has examined phase synchrony in autism compared to controls during encoding in the course of a working memory task, in isolation or alongside maintenance and recognition. Magnetoencephalography (MEG) has the ability to explore these questions with direct measures of neuronal activity with excellent temporal and good spatial resolution, utilizing the prevailing working memory task in the neuroimaging literature: the n-back task. Thus, we investigated inter-regional brain synchronization elicited during working memory processing across encoding, maintenance and recognition in adults with and without autism during a one-back task. We focused on theta (4–7 Hz) and alpha (8–14 Hz) frequencies due to their consistent involvement in working memory with typical development, and also because lower frequencies are involved in long-range neural communication shown to be impacted in autism (Schipul *et al.*, 2011; Just *et al.*, 2012). We hypothesized that given the low-load nature of the one-back task, adults with autism may perform comparably to typical adults at the behavioural level (Urbain *et al.*, 2015, 2016), but long-range connectivity involving slow oscillations would differ between groups. Given that studies of long-term memory indicate relatively intact encoding and impaired retrieval processes in autism (Cooper *et al.*, 2017*a*, *b*), we expected to see comparable encoding networks between those with and without autism, but altered maintenance (Larrain-Valenzuela *et al.*, 2017) and recognition processing (Urbain *et al.*, 2015, 2016), involving altered long-range fronto-posterior synchrony.

Materials and methods

Participants

Thirty-two adults with high-functioning autism, and 33 typically developing controls were recruited. To address confounds of motion and poor task performance on results, four participants with autism were excluded from the analysis for performing the task at chance level (<50% hits–false alarms), and four were excluded due to excessive head motion. In the case of excessive head motion, all trials with mean head position deviating more than 5 mm from the recording median were rejected (as detailed below), and subjects with <30 trials remaining were excluded. The present sample therefore consisted of 24 adults with high-functioning autism (15 males, 9 females, 18–39 years), and 30 controls (22 males, 8 females, 18–39 years). The groups were matched for age [autism: $M = 28.20$, $SD = 6.59$, controls: $M = 27.61$, $SD = 5.23$; $t(52) = 0.37$, $P = 0.71$], sex [$\chi^2(1) = 0.31$, $P = 0.58$] and intelligence quotient [autism: $M = 111.22$, $SD = 15.47$, controls: $M = 112.07$, $SD = 8.45$, $t(51) = -0.26$, $P = 0.8$]. Participants had no history of traumatic brain injury, prematurity (i.e. born ≤37 weeks gestational age), and had no magnetic resonance imaging or MEG contraindications. Controls additionally had no history of developmental, neurological or psychological disorders. All participants had normal/corrected vision, and no colour blindness. Within the autism group, 52% were taking a variety of psychoactive medications (a full list of medications can be found in the Supplementary material), as is typical for this population. Clinical diagnosis of autism was confirmed via a combination of expert clinical judgement, clinical records and scores on the autism diagnostic observation schedule (Lord *et al.*, 2012). Specifically, every participant either self-reported or provided documentation confirming diagnosis of autism by a clinician. Autism diagnostic observation schedule scores were used to confirm the diagnosis, administered by trained researchers or clinical staff. If a participant self-reported their diagnosis, a report from the clinician verifying clinical diagnosis of autism was requested and received. To

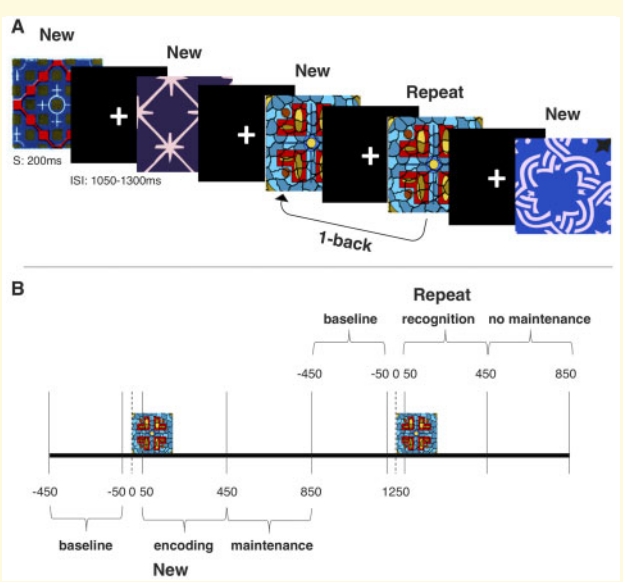


Figure 1 One-back memory task and epoch definition. (**A**) Subjects viewed abstract visual images one at a time and pressed a button when they identified the repetition of an image presented one trial earlier. (**B**) The time series for each trial was split into several epochs of equal length representing baseline, encoding, maintenance, recognition and no-maintenance memory conditions.

avoid selection bias, participants contacted the study co-ordinator via information received from recruitment flyers posted online and in the community, affiliated hospitals and other research studies in which they were participating. Experimental procedures were approved by the Research Ethics Board at the Hospital for Sick Children, and all participants gave informed written consent.

MEG task and procedure

A one-back task with complex multi-coloured abstract images was used to assess working memory processes. Participants were instructed to press a key when they identified the repetition of a picture presented one trial earlier (Fig. 1A). Stimuli appeared on a screen located 80 cm from the participant; the visual angle of the stimuli subtended ~4°. Each picture was presented for 200 ms, followed by a fixation cross with an inter-stimulus interval between 1050 and 1300 ms. We presented 285 trials, 190 of which were 'New' (the first presentation of a stimulus), and 95 of which were 'Repeat' target trials (second presentation of the stimulus). The one-back task is considered a low-load working memory task, often affording comparable behavioural performance between autism and control groups (Koshino *et al.*, 2005, 2008; Urbain *et al.*, 2015, 2016) and therefore allowing commensurate statistical power between groups with which to examine neural underpinnings supporting good performance. In addition, we were interested in memory maintenance afforded by the one-back task unimpeded by interfering trials and higher-order executive processes that occur in higher-load versions of the task. Accuracy scores were calculated for each participant as the per cent of correctly identified Repeated targets minus incorrect endorsement of New trials as old (%hits–false alarms), and mean reaction time was calculated for correct recognition of Repeat trials for each subject.

Data acquisition

MEG data were recorded using a MEG scanner with 151 axial gradiometers (Omega-151; CTF, Coquitlam, BC, Canada) in a magnetically shielded room at the Hospital for Sick Children (sampling rate: 600 Hz, filters: 0–150 Hz, third-order spatial gradient noise cancellation). Head position was continuously recorded by coils placed on three fiducial points on the subject's head (nasion, left and right pre-auricular points). After the MEG session, T_1-weighted MRI scans were acquired in all participants on a Siemens 3T system; fiducial points from the MEG session were recorded on MRI images to allow precise MEG/MRI co-registration.

Preprocessing

Preprocessing and connectivity analyses were performed using MATLAB (R2015a), Fieldtrip (version 8a6e5206), Statistical Parametric Mapping (SPM12) software and in-house scripts. MEG analyses were only conducted on trials (New/Repeat) associated with correctly recognized Repeat stimuli. MEG data were acquired at 600 Hz with continuous head localization and synthetic third order gradient for spatial attention of environmental noise. Data were imported into MATLAB with a 1–80 Hz fourth order two-pass butterworth bandpass filter and 60 Hz and harmonics line noise notch filter. We focused our analyses on theta (4–7 Hz) and alpha (8–14 Hz) due to strong hypotheses from the literature regarding the specific roles of these oscillations in mnemonic processing (Klimesch *et al.*, 2008; Sauseng *et al.*, 2009; Fell and Axmacher, 2011), and given that these lower frequencies support long-range neural communication which has proven to be impacted in autism (Schipul *et al.*, 2011; Just *et al.*, 2012). The time series for each trial (New; Repeat) was split into four epochs (Fig. 1B) of equal length representing baseline (New or Repeat: −450 to −50 ms), encoding (New: +50 to +450 ms), maintenance (New: +450 to +850 ms) and recognition (Repeat: +50 to +450 ms). A 'no-maintenance' epoch was also defined (Repeat: +450 to +850 ms) as a control of equal time and length for the maintenance epoch, where no maintenance processes were expected to occur. We extended our epochs beyond stimulus offset to capture early mnemonic processes that occur in the absence of direct visual processing. Since we did not want our results to be biased based on the number of samples included in each epoch,

we divided the trials into equal baseline, encoding, maintenance and recognition epochs of arbitrary but equal length (400 ms), where encoding/recognition epochs capture early processing and maintenance/no maintenance epochs capture late processing within a given trial. To remove artefacts, we identified and removed superconducting quantum interference device jumps from the data and performed manual-independent component analysis rejection of cardiac and ocular components. Epochs contaminated by motion (>5 mm) were excluded from the analyses. Forty-six participants had epochs removed (23 autism, 23 controls), leaving 75% of trials remaining in all cases (of those with trials removed, autism: M = 97% retained, SD = 3%, range = 87–99%; controls: M = 97% retained, SD = 5%, range = 75–99%).

MEG data were co-registered with each participant's MRI image and single shell head models were constructed (Nolte, 2003). MRIs were then normalized into standard Montreal Neurological Institute space. The coordinates of 90 seed locations (Supplementary Table 1) representing the cortical and subcortical areas from the automated anatomical labelling atlas (Tzourio-Mazoyer *et al.*, 2002) were then warped from standard Montreal Neurological Institute space into each individual headspace.

For each subject, a linearly constrained minimum variance beamformer (Van Veen et al., 1997) was used to estimate the broadband time-series for each trial and source location representing the activity of each of the 90 automated anatomical labelling sources. The beamformer technique is a spatial filtering approach to MEG inverse source modelling that relies on a minimization of total brain power, while being optimally sensitive to activity in a given brain location (each of the 90 seed locations). This results in the suppression of background noise (Brookes *et al.*, 2011), and ocular, cardiac and muscle artefact (Muthukumaraswamy, 2013). The linearly constrained minimum variance beamformer was run with 5% regularization and covariance matrices calculated on processed epochs.

Functional connectivity analysis

The time-series for each automated anatomical labelling seed region were filtered into canonical frequency bands: theta (4–7 Hz) and alpha (8–14 Hz). A Hilbert transform was applied to the filtered time-series to extract instantaneous phase at each frequency band and time point (from each of the four epochs). The weighted phase lag index (wPLI) was used to compute phase synchrony between all pairwise combinations of the automated anatomical labelling nodes, resulting in a 90 × 90 connectivity matrix for each subject, at each time point, for each frequency. The wPLI provides values ranging from 0 (no phase locking, random phase difference) to 1 (maximum phase locking, constant phase difference); and is based on the magnitude of the imaginary component of the cross-spectrum (Vinck *et al.*, 2011). To avoid spurious correlations or artefactual noise, wPLI assumes that true phase synchrony between two source-pairs should possess a consistent, non-zero phase difference (Vinck *et al.*, 2011). The wPLI values were *Z*-scored, subtracting the baseline mean from the entire time series then dividing by baseline variance. Within each frequency band of interest we averaged wPLI values over epochs (*Z*-scored encoding, maintenance, recognition) within each subject.

Network identification

We used network-based statistics (NBS; Zalesky *et al.*, 2010) to contrast connectivity for the active window>baseline for each memory condition (encoding/maintenance/recognition), within groups (autism/control) and frequency band (theta/alpha). NBS uses mass univariate methods to apply a test statistic to every connection in the network (a *t*-value in this study). Connections that survive a chosen test statistic threshold are used to identify topological clusters—non-random networks/components that might be rejected if considered on the basis of each individual connection alone. *P*-values for each component are derived with permutation tests (see Zalesky *et al.*, 2010 for methodological details). In this study, we used a breadth search of topological space. As an adaptive threshold as suggested by Zalesky *et al.* (2010), for each contrast, we iteratively identified the *t*-threshold for a network sparsity of 1% of the total 90 × 90 node connectivity matrices (~40 edges). This network-selection procedure allowed us to retain a single network for each memory condition and group. In total, six networks were selected, per frequency band, for further analysis (autism/control, Encoding/Maintenance/Recognition networks). To visualize the relative contribution of each node within the resulting networks, we calculated node strength—a graph theoretical metric calculated by taking the sum of all edges connected to a node, wherein nodes with greater strength have stronger and/or more numerous connections within the network. The resulting networks with corresponding node strengths were plotted using BrainNet Viewer (Xia *et al.*, 2013).

Between-group network analyses

Between-group statistics were computed using mean network connectivity scores. These scores were calculated for each subject (within frequency band) by masking each subject's connectivity during encoding, maintenance, recognition and no-maintenance epochs with corresponding group-level autism and control networks (as derived from the NBS analysis above) and taking the average. Specifically, network connectivity of each subject during encoding and recognition epochs were masked with the autism and control Encoding and Recognition networks, while connectivity during maintenance and no-maintenance were masked with the autism and

control Maintenance networks (see Supplementary Fig. 1). Our aim with this analysis was to compare network synchrony during the same time windows where the only difference was if the stimulus was New or Repeated. With this approach, we determined the degree to which a given group-level network was recruited for each subject within an epoch, with the expectation that stronger phase synchrony within a network would reflect stronger presence of that network. We determined the extent to which every participant leveraged the group-level autism or control networks during encoding, maintenance and recognition epochs for both New and Repeat stimuli, resulting in 12 mean network scores per subject.

Finally, we directly quantified the spatial similarity of autism versus control networks within encoding, maintenance and recognition for both frequencies with the Dice similarity coefficient (DSC; Dice, 1945; Sørensen, 1948), as defined with the following equation:

$$\text{Dice similarity coefficient} = \frac{2 \times \sum(N1 \times N2)}{\sum(N1 + N2)}.$$

In this study, $N1$ and $N2$ represent binarized matrices for each network to be compared. DSCs range from 0 (no spatial overlap) to 1 (complete spatial overlap). Thus, lower numbers reflect spatially unique networks and higher numbers reflecting greater spatial overlap between two networks. This metric measures spatial overlap between the edges of the two networks, and not the overlap of nodes. Two networks can have nodes in common, but if connectivity of those nodes differ, the Dice coefficient can still be zero. Thus, we interrogated the degree to which individuals with autism were using spatially similar networks to controls during each memory stage.

Statistical analyses

Statistical comparisons of the data were performed using RStudio (version 1.0.136, 2016) and MATLAB (R2015a). Demographic and behavioural differences between autism and control groups were analysed with two-tailed independent-samples *t*-tests and Chi-square tests. Group-level network identification with NBS was defined using permutation testing (active>baseline, $n = 2000$) and Family-Wise Error corrected *P*-values of <0.05. We adjusted the *P*-values for the 12 identified networks using the false discovery rate method (Benjamini and Hochberg, 1995) across group and frequency to minimize the possibility of false positives at this identification step. Significant group differences (autism versus controls) in network recruitment were tested using two-way permutation tests (group × stimulus type, $n = 10\ 000$) within each epoch. We used Still and White's (1981) approach to estimate *P*-values for the interaction effect between group and condition, and Anderson's (2001) approach to calculate the main effects. Alpha was always set to 0.05, and *P*-values for these permutation tests were additionally false discovery rate corrected across group and frequency band to account for multiple comparisons (Benjamini and Hochberg, 1995).

Data availability

Data are available upon request.

Results

Behavioural performance

There were no group differences in %hits–false alarms [autism: M = 90%, SD = 9%, control: M = 92%, SD = 10%, $t(52) = -0.53$, $P = 0.60$] or reaction time for hits [Supplementary Fig. 2, autism: M = 480 ms, SD = 80 ms, control: M = 440 ms, SD = 80 ms, $t(52) = 1.61$, $P = 0.11$]; both groups performed well on the task.

Theta network connectivity

Encoding

Both the theta Encoding network for controls (40 edges, $t = 3.4$, $P < 0.001$, Fig. 2A) and those with autism (40 edges, $t = 3.0$, $P < 0.001$, Fig. 2B) were strongly anchored in primary visual areas, with the cuneus and superior occipital gyri (SOG) demonstrating the greatest strength. In controls, these areas were connected to bilateral medial parietal, inferior temporal and midline motor structures (see Supplementary Table 2C, for a full list of nodes/strength in this network). In subjects with autism, this profile additionally included lateral parietal and right-lateralized frontal nodes (Supplementary Table 2D).

Permutation testing of mean connectivity of the control Encoding network as applied to each group (controls/autism) and condition (New/Repeat) during the encoding/recognition epoch (40–450 ms) revealed a main effect of condition [$F(1,104) = 8.84$, $P = 0.007$], with greater connectivity during the presentation of New (M = 2.06, SD = 1.35) than Repeat stimuli (M = 1.41, SD = 1.03). There was no main effect of group [$F(1,104) = 0.83$, $P = 0.404$], and no interaction between group and condition [$F(1,104) = 2.24$, $P = 0.168$]. For the Encoding network in autism, permutation tests indicated main effects of group [$F(1,104) = 5.43$, $P = 0.028$] and condition [$F(1,104) = 10.89$, $P = 0.004$], with greater connectivity within the autism group (M = 1.34, SD = 0.90) than the control group (M = 1.16, SD = 0.90), as well as during the presentation of New (M = 1.51, SD = 0.90) compared to Repeat trials (M = 0.97, SD = 0.82). There was no interaction between group and condition [$F(1,104)=0.05$, $P = 0.87$].

Differences in main effects found between these networks likely stems from differences in node recruitment (30 nodes recruited in the autism network and 23 in the control network) despite equivalent network size (40 edges). However, the lack of an interaction between group and condition within each network indicates that

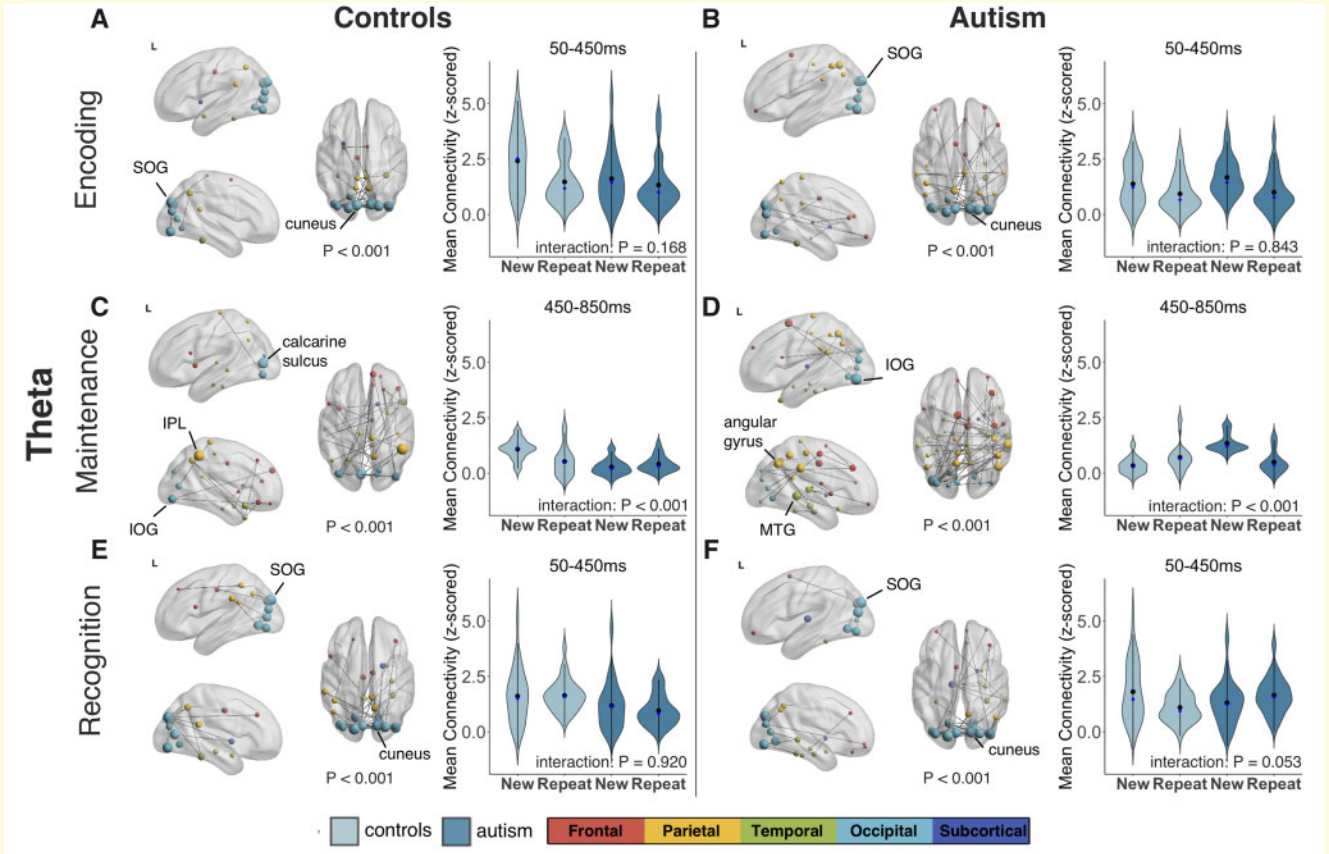


Figure 2 Network connectivity results within theta. (**A**) Encoding network in controls, (**B**) encoding network in autism, (**C**) maintenance network in controls, (**D**) maintenance network in autism, (**E**) recognition network in controls, (**F**) recognition network in autism. *P*-values under each brain represent statistical probability of the given group-level network during active windows compared to baseline, as calculated with NBS. The relative strength of each node within a network is plotted by size, wherein nodes with the greatest strength are relatively larger. Violin plots describe the distribution of mean connectivity within each network for individuals in each group (light blue: control subjects; dark blue: subjects with autism) and condition (during the presentation of New or Repeat stimuli), where the black dot represents the mean and the blue dot represents the median of each distribution. *P*-values on each violin plot represent statistical probability of a group by condition interaction of mean network connectivity as assessed by permutation testing (see Results section for main effects). IOG: inferior occipital gyrus; IPL: inferior parietal lobule; MTG: medial temporal gyrus; SOG: superior occipital gyrus.

these networks were not specific to group and condition. Consistent with this, the networks showed some spatial overlap (DSC = 0.36), indicating that the two groups were using partially overlapping networks to encode.

Maintenance

The Maintenance network in theta for controls (35 edges, $t = 2.8$, $P < 0.001$, Fig. 2C) was strongly anchored in the right inferior parietal lobule, and was mainly connected to medial parietal and primary occipital regions. The nodes with the second and third greatest strength were left calcarine sulcus and right inferior occipital regions respectively, both of which demonstrated local connections to other occipital nodes, as well as longer-range connections to parietal and frontal nodes. Also of note, the right temporal pole and right medial temporal lobe demonstrated connectivity with several dorsolateral and ventrolateral prefrontal cortex regions, mainly in the right hemisphere (Supplementary Table 3C). Permutation testing of mean connectivity of this network as applied to each group (controls/autism) and condition (New/Repeat) during the maintenance/no maintenance epoch (450–850 ms) showed main effects of group [$F(1,104) = 11.72$, $P = 0.004$] and condition [$F(1,104) = 9.13$, $P = 0.006$], due to greater connectivity within the control (M = 0.81, SD = 0.62) than the autism group (M = 0.35, SD = 0.36), as well as to New (M = 0.73, SD = 0.57) compared to Repeat stimuli (M = 0.48, SD = 0.54). There was a group by condition interaction [$F(1,104) = 15.11$, $P < 0.001$] driven by greater connectivity of this network within the control group following New stimuli (control New: M = 1.09, SD = 0.44; control Repeat: M = 0.53, SD = 0.64; autism New: M = 0.24, SD = 0.31; autism Repeat: M = 0.42, SD = 0.36).

The Maintenance network in the autism group (56 edges, $t = 2.7$, $P < 0.001$, Fig. 2D) had the greatest node strength in the left inferior occipital gyrus, followed by the right middle temporal and the right angular gyri. This network was strikingly characterized by interhemispheric connections, particularly dominant between parietal and temporal lobes, with generally greater strength in the right hemisphere (Supplementary Table 3D). Permutation testing of mean connectivity of this network as applied to each group (controls/autism) and condition (New/Repeat) during the maintenance/no maintenance epoch (450–850 ms) revealed a main effect of group [$F(1,104) = 17.74$, $P < 0.001$], with greater connectivity within the autism (M = 0.92, SD = 0.62) than control group (M = 0.53, SD = 0.54). There was no effect of condition [$F(1,104) = 1.50$ $P = 0.267$], but there was an interaction between group and condition [$F(1,104) = 13.81$, $P < 0.001$], driven by connectivity within the autism group following the presentation of New stimuli (autism New: M = 1.31, SD = 0.36; autism Repeat: M = 0.50, SD = 0.50; control New: M = 0.34, SD = 0.37; control Repeat: M = 0.71, SD = 0.62). There was no group spatial overlap between Maintenance networks in theta (DSC = 0), indicating that each group used a distinct network within theta during the successful maintenance of novel stimuli.

Recognition

The Recognition networks in theta for controls (41 edges, $t = 3.1$, $P < 0.001$, Fig. 2E) and autism (43 edges, $t = 2.8$, $P < 0.001$, Fig. 2F) were strongly anchored in primary visual areas (left SOG and right cuneus), with connections to parietal, right temporal and frontal areas (Supplementary Table 4C and D). Within the Recognition network in autism there were additionally connections between the left pallidum and right temporal areas. There were no main effects of group [$F(1,104) = 3.00$, $P = 0.103$] or condition [$F(1,104) = 0.18$, $P = 0.709$] within the control's Recognition network as applied to the encoding/recognition epoch (50–450 ms), and no interaction between group and condition [$F(1,104) = 0.01$, $P = 0.92$]. Similarly, there were no significant main effects of group [$F(1,104) = 1.17$, $P = 0.315$] or condition [$F(1,104) = 2.30$, $P = 0.161$] on mean connectivity in the Recognition network for the autism group, nor did these two interact reliably [$F(1,104) = 4.63$, $P = 0.053$]. Concurrently, there was some spatial overlap between the two networks (DSC = 0.27), demonstrating that the recognition networks were not specific to group or condition.

Alpha network connectivity

Encoding

The Encoding network in the alpha frequency for controls (38 edges, $t = 2.6$, $P < 0.001$, Fig. 3A) was anchored in primary visual areas (right calcarine sulcus, left cuneus) and was characterized by long-range connections to parietal, temporal, frontal and subcortical nodes (Supplementary Table 2A). Of interest, there was a group of well-connected nodes in the right dorsolateral prefrontal cortex, as well as several connected nodes in the left ventral and anterior temporal lobe. Permutation testing revealed main effects of group [$F(1,104) = 14.02$ $P < 0.001$] and condition [$F(1,104) = 23.22$, $P < 0.001$], with greater connectivity of this network within the control (M = 0.57, SD = 0.57) than the autism group (M = 0.18, SD = 0.39), and during the presentation of New stimuli (M = 0.59, SD = 0.61) compared to Repeated (M = 0.21, SD = 0.36) during the encoding/recognition epoch (50–450 ms). There was additionally an interaction between group and condition [$F(1,104) = 14.85$, $P < 0.001$], driven by strong connectivity in the control group during the presentation of New stimuli specifically (control New: M = 0.93, SD = 0.51; control Repeat: M = 0.21, SD = 0.37, autism New: M = 0.17, SD = 0.43, autism Repeat: M = 0.20, SD = 0.36).

In comparison, the Encoding network in alpha for the autism group (35 edges, $t = 2.5$, $P = 0.022$, Fig. 3B) was anchored in the left anterior cingulate, exhibiting connectivity with the left rectus, left amygdala, left inferior parietal lobe and right primary visual areas. Notably this network was also characterized by long-range connections from primary visual areas to right dorsolateral and ventrolateral prefrontal cortex and right posterior temporal cortex (Supplementary Table 2B). Permutation testing indicated main effects of group [$F(1,104) = 6.99$, $P = 0.015$] and condition [$F(1,104) = 8.77$, $P = 0.009$], with greater connectivity within the autism (M = 0.60, SD = 0.55) than the control group (M = 0.26, SD = 0.41), and during the presentation of New stimuli (M = 0.56, SD = 0.59) than Repeat (M = 0.26, SD = 0.36) during the encoding/recognition epoch (50–450 m). There was additionally an interaction between group and condition [$F(1,104) = 9.64$, $P = 0.004$], indicating that these main effects were largely driven by strong connectivity of this network in autism during the presentation of New stimuli (autism New: M = 0.96, SD = 0.48; autism Repeat: M = 0.23, SD = 0.32; control New: M = 0.22, SD = 0.43, control Repeat: M = 0.30, SD = 0.40). The Dice coefficient for these two networks indicated no spatial overlap (DSC = 0). Thus, within the alpha frequency band, controls and participants with autism utilized different networks to encode novel stimuli.

Maintenance

The Maintenance network for controls in alpha (36 edges, $t = 2.5$, $P = 0.02$, Fig. 3C) was characterized by relatively high node strength in the right ventrolateral prefrontal cortex, with connections to left anterior temporal, right occipital and bilateral frontal nodes. The node with the second greatest strength was the post-central gyrus, with connections to nearby parietal and frontal areas, as well as to the left hippocampus and left

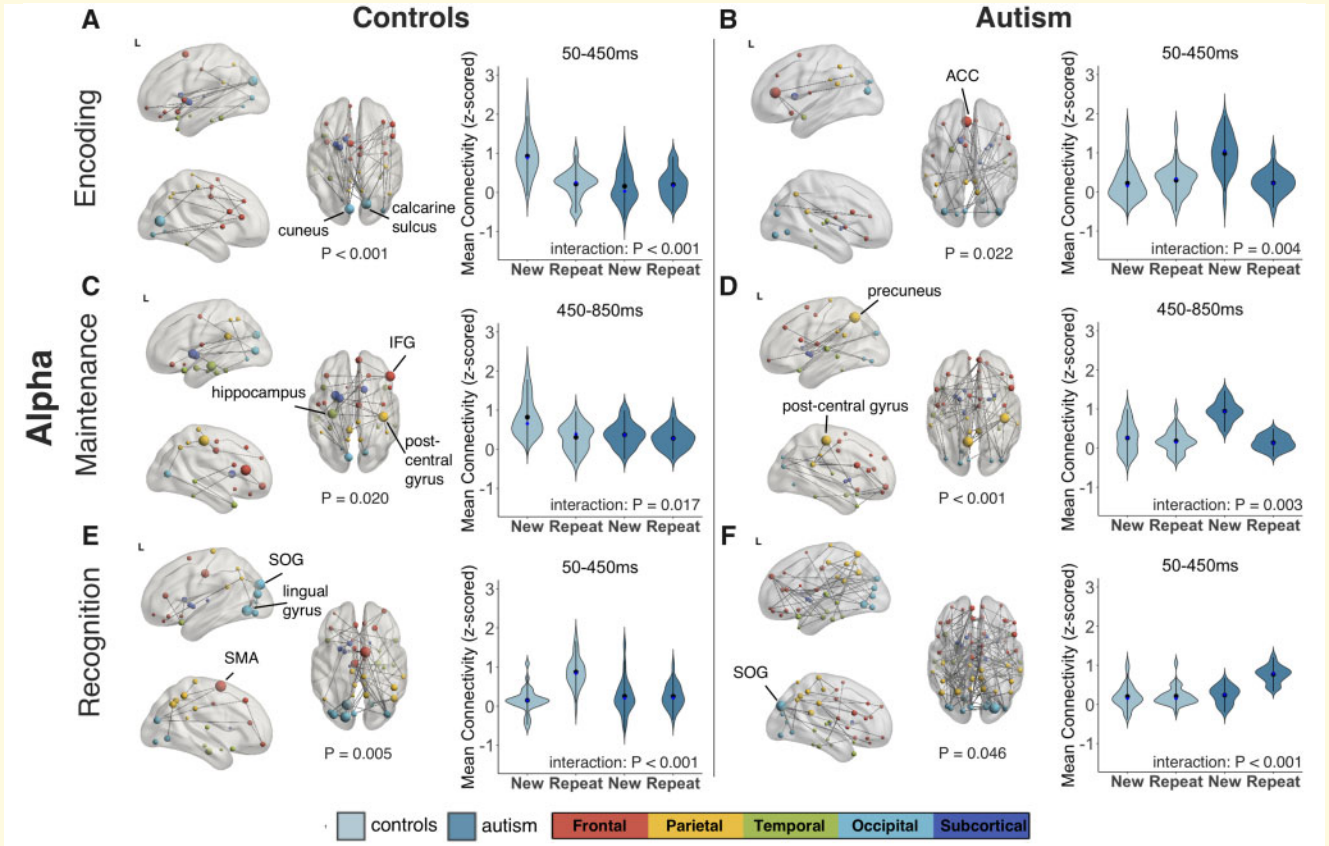


Figure 3 Network connectivity results within alpha. (**A**) Encoding network in controls, (**B**) encoding network in autism, (**C**) maintenance network in controls, (**D**) maintenance network in autism, (**E**) recognition network in controls, (**F**) recognition network in autism. *P*-values under each brain represent statistical probability of the given group-level network during active windows compared to baseline, as calculated with NBS. The relative strength of each node within a network is plotted by size, wherein nodes with the greatest strength are relatively larger. Violin plots describe the distribution of mean connectivity within each network for individuals in each group (light blue: control subjects; dark blue: subjects with autism) and condition (during the presentation of New or Repeat stimuli), where the black dot represents the mean and the blue dot represents the median of each distribution. *P*-values on each violin plot represent statistical probability of a group by condition interaction of mean network connectivity as assessed by permutation testing (see Results section for main effects). ACC: anterior cingulate cortex; IFG: inferior frontal gyrus; SMA: supplementary motor area; SOG: superior occipital gyrus.

subcortical nodes. The node with the third greatest strength was the left hippocampus, which was connected to temporal cortex nodes bilaterally, as well as midline frontal nodes on the right, the right post-central gyrus, left putamen and left pallidum (Supplementary Table 3A). Permutation testing revealed main effects of group [$F(1,104) = 7.82$, $P = 0.007$] and condition [$F(1,104) = 22.75$, $P < 0.001$], with greater connectivity of this network in controls ($M = 0.56$, $SD = 0.48$) than participants with autism ($M = 0.33$, $SD = 0.29$), and following presentation of New stimuli ($M = 0.62$, $SD = 0.47$) than Repeat stimuli ($M = 0.30$, $SD = 0.30$) during the maintenance/no maintenance epoch (450–850 ms). An interaction between group and condition [$F(1,104) = 6.38$, $P = 0.017$] indicated that these effects were driven by connectivity within the control group following New stimuli (control New: $M = 0.82$, $SD = 0.48$; control Repeat: $M = 0.31$, $SD = 0.33$; autism New: $M = 0.36$, $SD = 0.32$; autism Repeat: $M = 0.28$, $SD = 0.27$).

The Maintenance network in alpha for the autism group (54 edges, $t = 2.5$, $P < 0.001$, Fig. 3D) was more disperse by comparison. The node with the greatest strength was the left precuneus which was primarily connected to subcortical nodes, followed by the right post-central gyrus with widespread connectivity to parietal, frontal, temporal and occipital regions. This network was additionally characterized by many frontal nodes with widespread connections throughout the brain (Supplementary Table 3B). Permutation testing indicated main effects of group [$F(1,104) = 8.24$, $P = 0.007$] and condition [$F(1,104) = 31.02$, $P < 0.001$], with greater connectivity of this network within the autism group ($M = 0.54$, $SD = 0.46$) than the control group ($M = 0.22$, $SD = 0.33$), following presentation of New ($M = 0.56$, $SD = 0.47$) than Repeat stimuli ($M = 0.16$, $SD = 0.24$). In addition, there was a group by condition interaction [$F(1,104) = 10.86$, $P = 0.003$], which showed that these effects were driven by greater mean connectivity in the

autism group following the presentation of New stimuli (M = 0.94, SD = 0.27) compared to Repeat stimuli (M = 0.14, SD = 0.18), or either stimulus type in the control group (New: M = 0.26, SD = 0.37; Repeat: M = 0.18, SD = 0.29). There was very little spatial overlap between control and autism Maintenance networks (DSC = 0.05). Together these findings indicate that within the alpha frequency, the two groups used separate networks to retain novel images in memory.

Recognition

Within the Recognition network in alpha in controls (48 edges, $t = 2.5$, $P = 0.005$, Fig. 3E), the right supplementary motor area had the greatest node strength, with disperse connections to frontal, parietal, visual and subcortical areas. Visual areas such as the left lingual gyrus and SOG also demonstrated high node strength, with local connections to other occipital nodes as well as long-range connections to parietal, temporal and frontal nodes (Supplementary Table 4A). Permutation testing revealed main effects of group [$F(1,104) = 8.28$, $P = 0.006$] and condition [$F(1,104) = 31.37$, $P < 0.001$], with greater connectivity in the control (M = 0.51, SD = 0.51) than the autism group (M = 0.25, SD = 0.38), and for presentation of Repeat (M = 0.60, SD = 0.47) than New stimuli (M = 0.20, SD = 0.38) during the encoding/recognition epoch (50–450 ms). There was a group by condition interaction [$F(1,104) = 11.31$, $P < 0.001$], indicating greatest connectivity in the control group to Repeat stimuli specifically (control Repeat: M = 0.87, SD = 0.39; control New: M = 0.15, SD = 0.31; autism Repeat: M = 0.25, SD = 0.30; autism New: M = 0.22, SD = 0.42).

In contrast, the Recognition network in the autism group in alpha (133 edges, $t = 2.0$, $P = 0.046$, Fig. 3F) was quite disperse, being much larger than the other networks (there were no smaller networks across thresholds). The right SOG had the greatest strength, followed by the left lingual gyrus and the left superior parietal lobule, all of which had diffuse short- and long-range connections throughout the brain (Supplementary Table 4B). Permutation testing indicated main effects of group [$F(1,104) = 13.93$ $P < 0.001$] and condition [$F(1,104) = 16.15$, $P < 0.001$], with greater mean connectivity in the autism (M = 0.50, SD = 0.34) than the control group (M = 0.21, SD = 0.27), to Repeat (M = 0.46, SD = 0.36) compared to New stimuli (M = 0.22, SD = 0.26). A group by condition interaction [$F(1,104) = 21.51$, $P < 0.001$] demonstrated that it was connectivity within the autism group to Repeat stimuli that drove these effects (autism Repeat: M = 0.77, SD = 0.22; autism New: M = 0.24, SD = 0.22; control Repeat: M = 0.21, SD = 0.24; control New: M = 0.20, SD = 0.30). Again, there was little spatial overlap between control and autism Recognition networks (DSC = 0.03). All together these findings showed that each group used different networks during the successful recognition of Repeat stimuli.

Post hoc spectral power analysis

As group differences in network synchrony may be related to group differences in brain signal other than phase-locked activity, such as evoked or induced oscillatory power (Sato *et al.*, 2018), we examined differences in raw spectral power between our groups and conditions to determine if network differences between groups and conditions reflect true differences in phase synchrony, or rather if they reflect changes within the signal power spectrum. Spectral power estimates (averaged across trials, and relative to baseline) were computed for each node within a given network for each subject using a short-time Fourier transform (250 sample/416 ms Hamming sliding window, from −0.5 to 1.0 s in 5 ms increments, resulting in a frequency resolution of 2.4 Hz). We averaged spectral power across nodes within a given network to create average time-frequency decompositions of the raw signal for each of the 12 networks for each subject and condition (note that this means that the time-frequency decomposition included both evoked and induced activity in response to the stimulus). Time-frequency decompositions were averaged and plotted within each group (autism/control) and condition (new/repeat) for each network for visualization purposes. We focused on the theta and alpha bands to confirm the presence of oscillatory activity at these frequencies and to determine that changes in power spectra alone do not wholly account for our connectivity findings. Visual inspection of time-frequency representations (Supplementary Figs 3–6) revealed that peak spectral power appeared to be in alpha for most of the networks. To test for differences in spectral power between groups and conditions that may be impacting connectivity, we compared the mean spectral power for each group and condition within a given network in an analysis identical to that which we used to test for differences in network synchrony (taking the mean across the same time-windows and frequency bands as used in the connectivity analysis). While there was generally greater power for repeat stimuli than new stimuli, we found no group differences in power in any of the networks, for either frequency band (Supplementary Fig. 7), and no interactions between group and condition. These results indicate that while there are oscillations at the relevant frequencies, changes within the signal power spectrum were not driving differences in phase synchrony between groups.

Discussion

We examined neural phase synchrony in adults with autism and controls as they encoded, maintained and recognized patterns in a working memory task. We focused on theta and alpha frequencies due to their established involvement in working memory processes (Palva and Palva, 2007; Klimesch *et al.*, 2008), and because these frequencies support long-range neural communication

that is impacted in autism (Schipul *et al.*, 2011; Just *et al.*, 2012). Behaviourally, participants with autism performed comparably to age-matched controls on the task. Both groups used similar networks in theta to encode and recognize visual stimuli. However, those with autism were using different networks to maintain the stimuli across a short delay, consisting largely of interhemispheric connections rather than the long-range anterior–posterior pattern observed in controls. In contrast, the groups exploited distinct networks in the alpha frequency across encoding, maintenance and recognition. Of note, adults with autism showed less connectivity from the right lateral prefrontal cortex during encoding, weaker left medial temporal and right inferior frontal gyrus involvement during maintenance and were using quite disperse networks during the successful recognition of maintained stimuli. DSCs indicated very little spatial overlap of networks between groups, such that even when the same nodes were active in those with autism and controls, they were synchronized with different brain regions. Spectral power was comparable between the two groups within each network, indicating that brain activity other than phase synchrony was not driving group differences that we found in phase synchrony.

While we observed abnormal frontal and parietal lobe synchrony in this study (extending functional magnetic resonance imaging research highlighting altered activity in these regions: Koshino *et al.*, 2005, 2008), it is clear that altered network functioning was much more global, consistent with the view that autism is a network disorder characterized by abnormal differentiation of complex networks that underlie cognition (Belmonte *et al.*, 2004; Frith, 2004; Geschwind and Levitt, 2007; Minshew and Williams, 2007; Anagnostou and Taylor, 2011). The observation of fewer long-range anterior–posterior connections in autism during maintenance of stimuli in theta is consistent with a large body of functional magnetic resonance imaging work demonstrating anterior–posterior underconnectivity in this population (for reviews: Schipul *et al.*, 2011; Just *et al.*, 2012). Long-range synchronization and local amplitude modulations support working memory maintenance in typical adults (Sauseng *et al.*, 2005; Palva *et al.*, 2010, 2011), and are thought to establish transient neural communication in the service of information transfer across distributed working memory networks (Fell and Axmacher, 2011). High-level cognitive processes rely on optimal configuration of such networks to allow for the efficient transfer of information (Bassett *et al.*, 2009; Kitzbichler *et al.*, 2011; Just *et al.*, 2012), and it follows that altered networks in autism may be sub-optimal. In this study, we did not observe a working memory deficit despite differences in network configuration. It is likely that the one-back was too easy for this sample of high-functioning adults (indeed task performance was 90%+ in both groups), therefore not sensitive to behavioural deficit. However, comparable behavioural performance affords comparable number of trials and statistical power across groups in which to examine neural differences supporting performance. Other studies have also found that altered networks, while able to support working memory to a comparable degree as controls in some instances (Koshino *et al.*, 2005, 2008; Urbain *et al.*, 2015, 2016), are less well-equipped when taxed with higher task demands (Rahko *et al.*, 2016; Barendse *et al.*, 2018; Vogan *et al.*, 2018). It is also possible that altered autism networks reflect compensatory neural strategies that are able to support working memory functioning, at least under conditions of low cognitive load (Rane *et al.*, 2015; Johnson, 2017; Pillai *et al.*, 2018).

Our findings further indicate that network configuration in theta and alpha frequencies are differentially altered in autism depending on if they are encoding, maintaining or recognizing visual stimuli. We observed group differences in network connectivity within theta exclusively during memory maintenance, but globally throughout encoding, maintenance and recognition within alpha. It is understood that theta subserves working memory maintenance typically utilizing frontal, parietal and occipital sites (Jensen and Tesche, 2002; Scheeringa *et al.*, 2009; Michels *et al.*, 2010). It has been suggested that theta plays an integrative role during working memory, wherein phase coding supports integration of item-level information into working memory representations in a bottom-up manner, while inter-regional theta synchronization coordinates the brain regions necessary for item manipulation (Sauseng *et al.*, 2010). Our study suggests that encoding and recognition processes in autism may be relatively intact in theta, but are altered once theta is maintaining memory without direct visual input. This finding is in line with a deficit of inter-regional theta rhythmicity that fails to support item maintenance, rather than a deficit of bottom-up processing *per se*. This is not to say that bottom-up processing is unimpaired in people with autism. We only investigated the strongest connections available, and cannot rule out differences in sub-threshold connections, especially given that encoding and recognition in theta were strongly dominated by visual processing. Autism has recently been conceived of as a deficit of sensory processing, possibly due to impaired GABAergic signalling that may influence higher order social and cognitive deficits (Robertson and Baron-Cohen, 2017). Given the link between GABA function and gamma band neural synchrony (Muthukumaraswamy *et al.*, 2009; Gonzalez-Burgos *et al.*, 2011), a detailed examination of gamma activity would likely be better suited to answer this question.

Within alpha, globally observed network alterations may reflect a lack of inhibition of task-irrelevant processes, as others have suggested (Klimesch *et al.*, 2007). If alpha is failing to inhibit task-irrelevant neural processing in those with autism then we would not expect this dysfunction to be specific to a given sub-process of working memory—rather, the effect should be relatively inclusive. While alpha amplitude is related to inhibition during

working memory (Varela *et al.*, 2001), it is long-range inter-regional phase synchronization that subserves core working memory processing (Sauseng *et al.*, 2005; Klimesch *et al.*, 2007; Freunberger *et al.*, 2009). Studies of phase latency shifts in alpha have spurred the hypothesis that prefrontal alpha rhythmicity serves as a neural mechanism of top-down modulation of lower level posterior processes (Sauseng *et al.*, 2005; Palva and Palva, 2007). In this context, our results could reflect a breakdown of coherent long-range alpha synchronization that supports such mnemonic processing and control (Klimesch *et al.*, 2008; Palva and Palva, 2011). Alpha's influence, however, can also be quite local. A recent study of visual processing in autism showed gamma-mediated feed-forward connectivity in the visual cortex (from V1 to V4) to a comparable degree in subjects with autism and controls, while alpha-mediated feedback in connectivity (from V4 to V1) was reduced in autism (Seymour *et al.*, 2019). The authors reasoned that visual processing in autism is less modulated by alpha-mediated contextual feedback.

We showed for the first time that adults with autism utilize different networks in alpha during encoding of to-be-maintained stimuli in a working memory task. While typically overlooked in studies of working memory, encoding is commonly considered relatively intact in autism in long-term memory investigations, as providing cues or other supports for retrieval mitigates impaired memory (Bowler *et al.*, 2004; Crane *et al.*, 2013; Maras *et al.*, 2013). This suggests that the memories have been encoded and stored and that the issue is retrieving them. However, it has been argued that memory impairment observed in autism has more to do with cognitive control (Solomon *et al.*, 2016) and task support (Bowler *et al.*, 2004) than mnemonic encoding and retrieval processes *per se*. If this is the case then one might expect encoding to be impaired under situations of high cognitive control demands. There is evidence that people with autism have difficulty initiating strategic encoding processes (Meyer *et al.*, 2014) and organizing to-be-learned information (Bowler *et al.*, 2008; Gaigg *et al.*, 2008). Furthermore, cognitive control processes that are thought to subserve episodic memory are superintended by the lateral prefrontal cortices (Blumenfeld and Ranganath, 2006, 2007; Blumenfeld *et al.*, 2011). Activity in these regions is attenuated in autism during encoding and does not predict subsequent memory unlike in controls (Greimel *et al.*, 2012; Gaigg *et al.*, 2015; Cooper *et al.*, 2017*b*). The fact that working memory maintenance inherently requires some degree of cognitive control could be one reason why altered functioning is more consistently found during this component of working memory, and it is quite possible that the degree to which encoding and retrieval are impacted depends on task demands.

This study is not without limitations. As with much autism research, our sample was limited to high-functioning adults. More research is required to determine if our results are applicable to those who are more severely affected. Larger sample sizes are needed to assess the replicability and generalizability of these results. This study did not control for differences in medications for each group, and it is unclear how medication use in autism may affect these results. Given that we found no differences in working memory capacity between groups, further work is needed to understand the broader implications of these findings both cognitively and clinically. While the connectivity metric that we chose (wPLI) is advantageous at avoiding spurious correlations due to volume conduction or artefactual noise (Vinck *et al.*, 2011), it does have lower test re-test reliability compared to imaginary coherence and amplitude envelope correlation metrics (Colclough *et al.*, 2016). We also used three equal length windows to try to capture distinct stages of mnemonic processing, but future studies could use other options to determine more nuanced effects. In addition, mean connectivity of the networks in the alpha band was also relatively low (~1 *Z*-score from the mean), and it is unclear if this reflects low connectivity across the network or rather the average of strong positive and negative connections. While we have characterized the identified networks spatially and in terms of mean connectivity and strength, these measures do not inform more nuanced aspects of network dynamics such as characterization of positive and negative network weights or temporal dynamics within a given network. Finally, the networks described here are not isolated mnemonic networks, but include visual, attentional and executive processes—all of which are important for working memory. We argue that a holistic picture of broad network functioning subserving cognition is a valuable approach given observed deficits across multiple cognitive domains in autism, but more work is needed to parse the contribution of each of these areas to working memory functioning.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interests.

References

Albouy P, Weiss A, Baillet S, Zatorre RJ. Selective entrainment of theta oscillations in the dorsal stream causally enhances auditory working memory performance. Neuron 2017; 94: 193–206.

American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders, 5th edn. Washington, DC: American Psychiatric Press; 2013.

Anagnostou E, Taylor MJ. Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. Mol Autism 2011; 2: 4–9.

Anderson MJ. Permutation tests for univariate or multivariate analysis of variance and regression. Can J Fish Aquat Sci 2001; 58: 626–39.

Baddeley A. Working memory: theories, models, and controversies. Annu Rev Psychol 2012; 63: 1–29.

Barendse EM, Hendriks MPH, Jansen JFA, Backes WH, Hofman PAM, Thoonen G, et al. Working memory deficits in high-functioning adolescents with autism spectrum disorders: neuropsychological and neuroimaging correlates. J Neurodev Disord 2013; 5: 1–11.

Barendse EM, Schreuder LJ, Thoonen G, Hendriks MPH, Kessels RPC, Backes WH, et al. Working memory network alterations in high-functioning adolescents with an autism spectrum disorder. Psychiatry Clin Neurosci 2018; 72: 73–83.

Bassett DS, Bullmore ET, Meyer-Lindenberg A, Apud JA, Weinberger DR, Coppola R. Cognitive fitness of cost-efficient brain functional networks. PNAS 2009; 106: 11747–52.

Belmonte MK, Allen G, Beckel-Mitchener A, Boulanger LM, Carper RA, Webb SJ. Autism and abnormal development of brain connectivity. J Neurosci 2004; 24: 9228–31.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B (Methodol) 1995; 57: 289–300.

Blumenfeld RS, Parks CM, Yonelinas AP, Ranganath C. Putting the pieces together: the role of dorsolateral prefrontal cortex in relational memory encoding. J Cogn Neurosci 2011; 23: 257–65.

Blumenfeld RS, Ranganath C. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci 2006; 26: 916–25.

Blumenfeld RS, Ranganath C. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. Neuroscientist 2007; 13: 280–91.

Bonnefond M, Jensen O. Alpha oscillations serve to protect working memory maintenance against anticipated distracters. Curr Biol 2012; 22: 1969–74.

Bowler DM, Gaigg SB, Gardiner JM. Effects of related and unrelated context on recall and recognition by adults with high-functioning autism spectrum disorder. Neuropsychologia 2008; 46: 993–9.

Bowler DM, Gardiner JM, Berthollier N. Source memory in adolescents and adults with Asperger's syndrome. J Autism Dev Disord 2004; 34: 533–42.

Braden BB, Smith CJ, Thompson A, Glaspy TK, Wood E, Vatsa D, et al. Executive function and functional and structural brain differences in middle-age adults with autism spectrum disorder. Autism Res 2017; 10: 1945–59.

Brookes MJ, Wood JR, Stevenson CM, Zumer JM, White TP, Liddle PF, et al. Changes in brain network activity during working memory tasks: a magnetoencephalography study. NeuroImage 2011; 55: 1804–15.

Chai WJ, Hamid A, Abdullah JM. Working memory from the psychological and neurosciences perspectives: a review. Front Psychol 2018; 9: 1–16.

Colclough GL, Woolrich MW, Tewarie PK, Brookes MJ, Quinn AJ, Smith SM. How reliable are MEG resting-state connectivity metrics? NeuroImage 2016; 138: 284–93.

Cooper RA, Plaisted-Grant KC, Baron-Cohen S, Simons JS. Eye movements reveal a dissociation between memory encoding and retrieval in adults with autism. Cognition 2017a; 159: 127–38.

Cooper RA, Richter FR, Bays PM, Plaisted-Grant KC, Baron-Cohen S, Simons JS. Reduced hippocampal functional connectivity during episodic memory retrieval in autism. Cereb Cortex 2017b; 27: 888–902.

Crane L, Lind SE, Bowler DM. Remembering the past and imagining the future in autism spectrum disorder. Memory 2013; 21: 157–66.

Dice LR. Measures of the amount of ecologic association between species. Ecology 1945; 26: 297–302.

Fell J, Axmacher N. The role of phase synchronization in memory processes. Nat Rev Neurosci 2011; 12: 105–18.

Freunberger R, Fellinger R, Sauseng P, Gruber W, Klimesch W. Dissociation between phase-locked and nonphase-locked alpha oscillations in a working memory task. Hum Brain Mapp 2009; 30: 3417–25.

Frith C. Is autism a disconnection disorder? Lancet Neurol 2004; 3: 577.

Fukuda K, Mance I, Vogel EK. Alpha power modulation and event-related slow wave provide dissociable correlates of visual working memory. J Neurosci 2015; 35: 14009–16.

Gaigg SB, Bowler DM, Ecker C, Calvo-Merino B, Murphy DG. Episodic recollection difficulties in ASD result from atypical relational encoding: behavioral and neural evidence. Autism Res 2015; 8: 317–27.

Gaigg SB, Gardiner JM, Bowler DM. Free recall in autism spectrum disorder: the role of relational and item-specific encoding. Neuropsychologia 2008; 46: 983–92.

Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol 2007; 17: 103–11.

Gonzalez-Burgos G, Fish KN, Lewis DA. GABA neuron alterations, cortical circuit dysfunction and cognitive deficits in schizophrenia. Neural Plast 2011; 2011: 1–24.

Greimel E, Nehrkorn B, Fink GR, Kukolja J, Kohls G, Muller K, et al. Neural mechanisms of encoding social and non-social context information in autism spectrum disorder. Neuropsychologia 2012; 50: 3440–9.

Herrmann CS, Senkowski D, Röttger S. Phase-locking and amplitude modulations of EEG alpha: two measures reflect different cognitive processes in a working memory task. Exp Psychol 2004; 51: 311–8.

Jensen O, Tesche CD. Frontal theta activity in humans increases with memory load in a working memory task. Eur J Neurosci 2002; 15: 1395–9.

Johnson MH. Autism as an adaptive common variant pathway for human brain development. Dev Cogn Neurosci 2017; 25: 5–11.

Just MA, Keller TA, Malave VL, Kana RK, Sashank V. Autism as a neural systems disorder: a theory of frontal–posterior underconnectivity. Neurosci Biobehav Rev 2012; 36: 1292–313.

Kana RK, Libero LE, Moore MS. Disrupted cortical connectivity theory as an explanatory model for autism spectrum disorders. Phys Life Rev 2011; 8: 410–37.

Kercood S, Grskovic JA, Banda D, Begeske J. Working memory and autism: a review of literature. Res Autism Spectr Disord 2014; 8: 1316–32.

Kitzbichler MG, Henson RNA, Smith ML, Nathan PJ, Bullmore ET. Cognitive effort drives workspace configuration of human brain functional networks. J Neurosci 2011; 31: 8259–70.

Klimesch W, Freunberger R, Sauseng P, Gruber W. A short review of slow phase synchronization and memory: evidence for control processes in different memory systems? Brain Res 2008; 1235: 31–44.

Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition–timing hypothesis. Brain Res Rev 2007; 53: 63–88.

Koshino H, Carpenter PA, Minshew NJ, Cherkassky VL, Keller TA, Just MA. Functional connectivity in an fMRI working memory task in high-functioning autism. NeuroImage 2005; 24: 810–21.

Koshino H, Kana RK, Keller TA, Cherkassky L, Minshew NJ, Just MA. fMRI investigation of working memory for faces in autism: visual coding and underconnectivity with frontal areas. Cereb Cortex 2008; 18: 289–300.

Larrain-Valenzuela J, Zamorano F, Soto-Icaza P, Herrera C, Daiber F, Aboitiz F, et al. Theta and alpha oscillation impairments in autistic spectrum disorder reflect working memory deficit. Sci Rep 2017; 7: 1–11.

Leung RC, Vogan VM, Powell TL, Anagnostou E, Taylor MJ. The role of executive functions in social impairment in autism spectrum disorder. Child Neuropsychol 2016; 22: 336–9.

Lord C, Rutter M, DiLavore P, Risi S, Gotham K, Bishop S, Autism diagnostic observation schedule-2nd edition (ADOS-2). Los Angeles, CA: Western Psychological Corporation; 2012.

Luna B, Minshew NJ, Garver KE, Lazar NA, Thulborn KR, Eddy WF, et al. Neocortical system abnormalities in autism: an fMRI study of spatial working memory. Neurology 2002; 59: 834–40.

Maras KL, Memon A, Lambrechts A, Bowler DM. Recall of a live and personally experienced eyewitness event by adults with autism spectrum disorder. J Autism Dev Disord 2013; 43: 1798–810.

Meyer BJ, Gardiner JM, Bowler DM. Directed forgetting in high-functioning adults with autism spectrum disorders. J Autism Dev Disord 2014; 44: 2514–24.

Michels L, Bucher K, Luchinger R, Klaver P, Martin E, Jeanmonod D, et al. Simultaneous EEG–fMRI during a working memory task: modulations in low and high frequency bands. PLoS One 2010; 5: e10298.

Minshew NJ, Williams D. The new neurobiology of autism: cortex, connectivity, and neural organization. Arch Neurol 2007; 64: 945–50.

Muthukumaraswamy SD. High-frequency brain activity and muscle artifacts in MEG/EEG: a review and recommendations. Front Hum Neurosci 2013; 7: 1–11.

Muthukumaraswamy SD, Edden RA, Jones DK, Swettenham JB, Singh KD. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. Proc Natl Acad Sci 2009; 106: 8356–61.

Nolte G. The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. Phys Med Biol 2003; 48: 3637–52.

Owen AM, Mcmillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 2005; 25: 46–59.

Palva JM, Monto S, Kulashekhar S, Palva S. Neuronal synchrony reveals working memory networks and predicts individual memory capacity. Proc Natl Acad Sci 2010; 107: 7580–5.

Palva S, Kulashekhar S, Hamalainen M, Palva M. Localization of cortical phase and amplitude dynamics during visual working memory encoding and retention. J Neurosci 2011; 31: 5013–25.

Palva S, Palva JM. Functional roles of alpha-band phase synchronization in local and large-scale cortical networks. Front Psychol 2011; 2: 1–15.

Palva S, Palva JM. New vistas for α-frequency band oscillations. Trends Neurosci 2007; 30: 150–8.

Pillai AS, McAuliffe D, Lakshmanan BM, Mostofsky SH, Crone NE, Ewen JB. Altered task-related modulation of long-range connectivity in children with autism. Autism Res 2018; 11: 245–57.

Raghavachari S, Kahana MJ, Rizzuto DS, Caplan JB, Kirschen MP, Bourgeois B, et al. Gating of human theta oscillations by a working memory task. J Neurosci 2001; 21: 3175–83.

Rahko JS, Vuontela VA, Carlson S, Nikkinen J, Hurtig TM, Kuusikko-Gauffin S, et al. Attention and working memory in adolescents with autism spectrum disorder: a functional MRI study. Child Psychiatry Hum Dev 2016; 47: 503–17.

Rane P, Cochran D, Hodge SM, Haselgrove C, Kennedy D, Frazier JA. Connectivity in autism: a review of MRI connectivity studies. Harv Rev Psychiatry 2015; 23: 223–44.

Robertson CE, Baron-Cohen S. Sensory perception in autism. Nat Rev Neurosci 2017; 18: 671–84.

Sato J, Mossad SI, Wong SM, Hunt BAE, Dunkley BT, Smith ML, et al. Alpha keeps it together: alpha oscillatory synchrony underlies working memory maintenance in young children. Dev Cogn Neurosci 2018; 34: 114–23.

Sauseng P, Griesmayr B, Freunberger R, Klimesch W. Control mechanisms in working memory: a possible function of EEG theta oscillations. Neurosci Biobehav Rev 2010; 34: 1015–22.

Sauseng P, Klimesch W, Doppelmayr M, Pecherstorfer T, Freunberger R, Hanslmayr S. EEG alpha synchronization and functional coupling during top-down processing in a working memory task. Hum Brain Mapp 2005; 26: 148–55.

Sauseng P, Klimesch W, Heise KF, Gruber WR, Holz E, Karim AA, et al. Brain oscillatory substrates of visual short-term memory capacity. Curr Biol 2009; 19: 1846–52.

Scheeringa R, Petersson KM, Oostenveld R, Norris DG, Hagoort P, Bastiaansen M. Trial-by-trial coupling between EEG and BOLD identifies networks related to alpha and theta EEG power increases during working memory maintenance. NeuroImage 2009; 44: 1224–38.

Schipul SE, Keller TA, Just MA. Inter-regional brain communication and its disturbance in autism. Front Syst Neurosci 2011; 5: 1–11.

Seymour RA, Rippon G, Gooding-Williams G, Schoffelen JM, Kessler K. Dysregulated oscillatory connectivity in the visual system in autism spectrum disorder. Brain 2019; 142: 3294–305.

Solomon M, Mccauley JB, Iosif A, Carter CS, Ragland JD. Cognitive control and episodic memory in adolescents with autism spectrum disorders. Neuropsychologia 2016; 89: 31–41.

Solomon M, Ozonoff SJ, Ursu S, Ravizza S, Cummings N, Ly S, et al. The neural substrates of cognitive control deficits in autism spectrum disorders. Neuropsychologia 2009; 47: 2515–26.

Sørensen T. A method of establishing groups of equal amplitude in plant sociology based on similarity of species and its application to analyses of the vegetation on Danish commons. K Dan Vidensk Selsk 1948; 5: 1–34.

Still AW, White AP. The approximate randomization test as an alternative to the F test in analysis of variance. Br J Math Stat Psychol 1981; 34: 243–52.

Troyb E, Rosenthal M, Eigsti I-M, Kelley E, Tyson K, Orinstein A, et al. Executive functioning in individuals with a history of ASD who have achieved optimal outcomes. Child Neuropsychol 2014; 20: 378–97.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 2002; 15: 273–89.

Urbain CM, Pang EW, Taylor MJ. Atypical spatiotemporal signatures of working memory brain processes in autism. Transl Psychiatry 2015; 5: e617.

Urbain C, Vogan VM, Ye AX, Pang EW, Doesburg SM, Taylor MJ. Desynchronization of fronto-temporal networks during working memory processing in autism. Hum Brain Mapp 2016; 37: 153–64.

Van Veen BD, Van Drongelen W, Yuchtman M, Suzuki A. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Trans Biomed Eng 1997; 44: 867–80.

Varela F, Lachaux J, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2001; 2: 229–39.

Vinck M, Oostenveld R, Van Wingerden M, Battaglia F, Pennartz C. An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. NeuroImage 2011; 55: 1548–65.

Vogan VM, Francis KE, Morgan BR, Smith ML, Taylor MJ. Load matters: neural correlates of verbal working memory in children with autism spectrum disorder. J Neurodev Disord 2018; 10: 1–12.

Vogan VM, Morgan BR, Lee W, Powell TL, Smith ML, Taylor MJ. The neural correlates of visuo-spatial working memory in children with autism spectrum disorder: effects of cognitive load. J Neurodev Disord 2014; 6: 1–15.

Vogan VM, Morgan BR, Smith ML, Taylor MJ. Functional changes during visuo-spatial working memory in autism spectrum disorder: 2-year longitudinal functional magnetic resonance imaging study. Autism 2019; 23: 1–14.

Watanabe T, Rees G. Anatomical imbalance between cortical networks in autism. Sci Rep 2016; 6: 10.

Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One 2013; 8: e68910.

Yerys BE, Herrington JD, Satterthwaite TD, Guy L, Schultz RT, Bassett DS. Globally weaker and topologically different: resting-state connectivity in youth with autism. Mol Autism 2017; 8: 1–11.

Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. NeuroImage 2010; 53: 1197–207.