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Emotional face processing in autism spectrum disorder: Effects in gamma connectivity

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ABSTRACT

Impairments in social functioning are characteristic of autism spectrum disorder (ASD). Differences in functional networks during face processing in ASD compared to controls have been reported; however, the spatial-temporal dynamics of networks underlying affective processing are still not well understood. The current magnetoencephalography study examined whole-brain functional connectivity to implicit happy and angry faces in 104 adults with and without ASD. A network of reduced gamma band (30–55 Hz) phase synchrony occurring 80–308 ms following angry face presentation was found in adults with ASD compared to controls. The network involved widespread connections primarily anchored in frontal regions, including bilateral orbitofrontal areas, bilateral inferior frontal gyri, and left middle frontal gyrus extending to occipital, temporal, parietal, and subcortical regions. This finding suggests disrupted long-range neuronal communication to angry faces. Additionally, reduced gamma band-specific connectivity may reflect altered E/I balance in brain regions critical for emotional face processing in ASD.

1. Introduction

Pronounced socio-emotional impairments, such as atypical emotional face processing, are inherent to autism spectrum disorder (ASD; American Psychiatric Association, 2013). Emotional face processing involves widespread brain areas, such as right occipital temporal and parietal cortices and bilateral amygdalae, insular cortices, and frontal areas (i.e., orbitofrontal, medial prefrontal and anterior cingulate cortices; ACC; Adolphs, 2002; Haxby, Hoffman, & Gobbini, 2002); many of these brain areas are activated atypically in ASD (Harms, Martin, & Wallace, 2010).

Task-based functional connectivity studies using functional magnetic resonance imaging (fMRI) have highlighted differences in functional networks during face and emotional face processing in ASD relative to controls (Kana, Patriquin, Black, Channell, & Wicker, 2015; Kleinhans et al., 2008; Monk, 2010; Rudie et al., 2011; Sato, Toichi, Uono, & Kochiyama, 2012; Welchew et al., 2005; Wicker et al., 2008). For instance, Kana et al. (2015) observed a network of reduced functional connectivity in ASD among the medial prefrontal cortex and other key emotion processing regions, including the amygdalae, temporal and parietal lobes, and fusiform gyri (FG) during implicit emotion processing. The authors suggested that given implicit emotion processing is automatic and rapid, this ability may be particularly impaired in those with ASD.

The more recent use of magnetoencephalography (MEG) to study task-based functional connectivity in ASD has extended our understanding of the spatial-temporal dynamics of functional networks in this population, greatly complementing haemodynamic approaches. A small number of MEG studies have reported atypical interregional differences in phase synchrony of neural oscillations (an index of functional connectivity and fundamental to coordinating information among neural networks supporting socio-cognitive processes; Fries, 2005; Stam, Nolte, & Daffertshofer, 2007), to emotional faces in ASD. Using MEG, Safar, Wong, Leung, Dunkley, and Taylor (2018)) examined whole-brain phase synchrony of eight *a priori* regions of interest (i.e., bilateral amygdalae, FG, insulae and ACC) during an implicit emotional faces

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task in 20 children with ASD and 22 typically developing controls between the ages of 7 and 10 years. They found increased alpha band phase synchrony 0–400 ms following happy face perception in children with ASD compared to controls in a network involving key emotion processing areas, such as the bilateral orbitofrontal cortices, right inferior frontal gyrus, left FG, right superior temporal gyrus and right insula. Additionally, alpha band connectivity strength of the left FG and right insula was greater in children with ASD than controls, suggesting that these two regions were more strongly connected in whole-brain analyses in ASD than controls during happy face processing. Similarly using MEG and the same task, Leung, Ye, Wong, Taylor, and Doesburg (2014) examined whole-brain phase synchrony during implicit happy and angry face perception in 22 adolescents with and 17 without ASD. Adolescents with ASD demonstrated a network of reduced interregional beta band phase synchrony during the first 400 ms of angry face processing compared to adolescent controls, which importantly involved the bilateral insulae, right supramarginal gyrus and right FG, as well as frontal brain regions, including the left middle frontal gyrus, right superior frontal gyri and left inferior frontal gyrus. Furthermore, the right insula was the hub of reduced beta-band connectivity strength, eigenvector centrality, and clustering. These results were interpreted to reflect disrupted communication and atypical recruitment of brain regions typically part of socio-emotional circuitry in ASD. Using the same task in adults with ASD and controls (n = 22 in each group), Mennella, Leung, Taylor, & Dunkley (2017) found that similar to adolescents with ASD, adults with ASD also showed reduced whole-brain beta band phase synchrony around 300 ms following the presentation of angry faces compared to controls. This hyposynchronous network involved predominantly connections among frontal, limbic and occipital areas. Interestingly, the left amygdala, left insula and striatum, which play a key role in affective processing, were underconnected in this network (Mennella et al., 2017).

Overall, MEG studies have highlighted networks of atypical functional neural circuitry during implicit happy and angry face processing in ASD at different developmental periods, which suggests altered maturation of neural networks underpinning socio-emotional processing in this population; however, a limitation of the above work is the relatively small sample sizes of ASD and control groups. Given the heterogeneity in ASD (O'Reilly, Lewis, & Elsabbagh, 2017), it is essential to investigate neural networks involved in emotion processing in larger groups. The current study used MEG to investigate whole-brain functional connectivity in a sample of adults with ASD and age- and sex-matched controls (n = 104) during the implicit perception of happy and angry faces. Based on few studies reporting reduced functional connectivity during angry face processing in adolescents and adults using MEG (Khan et al., 2013; Leung et al., 2014; Mennella et al., 2017), we hypothesized that adults with ASD would show reduced functional connectivity during the implicit processing of angry faces compared to controls. We did not expect group differences in functional connectivity to happy faces.

2. Methods and materials

2.1. Participants

One hundred and four subjects were included in the analysis: 44 adults with ASD (M age = 26.5 years, SD = 5.99, range = 18.5–39.5 years, 32 males, 80% right-handed) and 60 age- and sex-matched controls (M age = 26.6 years, SD = 5.21, range = 18.5–38.8 years, 40 males, 88% right-handed). A subset of adults with ASD (n = 18) and controls (n = 19) were included in Mennella et al. (2017). Data from 25 additional participants (n = 15 ASD) were excluded from the analysis due to excessive artefacts and head motion resulting in fewer than 40 good MEG trials in each stimulus condition (n = 10), experiment error (n = 2), task incompletion (n = 4), and no equivalent age/sex participant to be matched (n = 9). We assessed full-scale IQ using the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999, 2011); both groups scored comparably within the normal range (ASD: M = 110.44, SD = 15.91; controls: M = 114.52, SD = 8.67; t(60.9) = -1.52, p = 0.135)[1] . In adults with ASD, diagnosis was confirmed by expert clinical judgement using the DSM-V, medical diagnostic reports, and the Autism Diagnostic Observation Schedule (i.e., ADOS-G and ADOS-2 modules 3 and 4; Hus & Lord, 2014; Lord et al., 2012, 2000). The mean calibrated severity score for adults with ASD was 6.86 (SD = 2.15), the mean Social Affect (SA) score was 9.2 (SD = 2.76), the mean Restricted Repetitive Behaviours (RRB) score was 3.61 (SD = 2.02), and the mean total score was 12.85 (SD = 4.1). The protocol was approved by the Hospital for Sick Children Research Ethics Board. All participants provided written informed consent in accordance with the Declaration of Helsinki.

2.2. Emotional faces task

During MEG data acquisition, adults performed an implicit emotional faces task, in which each trial consisted of a happy or angry face and a scrambled version of the face (target stimulus) simultaneously presented on either side of a central fixation cross. Participants were instructed to attend to the fixation cross and indicate as rapidly as possible on which side, left or right, the target, scrambled pattern appeared, using a MEG-compatible button-pad. Happy and angry face stimuli (25 faces in each condition, 12 males and 13 females) with a minimum validity rating of 0.8 proportion correct were chosen from the NimStim Set of Facial Expressions (Tottenham et al., 2009). Adobe® Photoshop software was used to generate the scrambled pattern stimuli equivalent in low-level visual properties (luminescence and colour) by applying a mosaic filter to each of the face stimuli and parcellating each image into 64 square tiles that were then shuffled and Gaussian blurred (10.0 pixels). Participants saw 50 trials per face type, presented twice in each hemifield yielding a total of 200 randomized happy and angry face trials. In each trial, stimuli were presented using Presentation® software (Neurobehavioral Systems) for 80 ms (to reduce saccades), followed by an inter-stimulus interval that jittered from 1300 to 1500 ms. Stimuli were presented from a viewing distance of 79 cm and subtended 6.9° of visual angle (Fig. 1). Behavioural measures of reaction time and accuracy were recorded.

2.3. Neuroimaging data acquisition

MEG data were recorded while participants lay supine in a magnetically shielded room, with a 151 channel CTF system (CTF MEG International Service Ltd., Coquitlam, BC, Canada). Data were continuously sampled at a rate of 600 Hz with an online 150 Hz antialiasing filter. To cancel external noise, a third-order spatial gradient was used. Fiducial coils placed at the left and right pre-auricular points and the nasion registered head movement continuously throughout the recording. Fiducial coils were later replaced with radio-opaque markers for the MRI scan to allow MEG co-registration with each participant's MRI. A T1-weighted MRI image (3D SAG MPRAGE, GRAPPA = 2, TR/TE/FA = 2300 ms/2.96 ms/90°, FOV = 28.8 cm x 19.2 cm, 240 × 256 matrix, 192 slices, slice thickness = 1.0 mm isotropic voxels) was collected for all subjects on a Siemens 3 T MR scanner (Siemens Healthcare GmbH, Erlang, Germany).

2.4. MEG pre-processing and source reconstruction

In MATLAB R2017b software, the FieldTrip toolbox (git commit 4c12371; Oostenveld, Fries, Maris, & Schoffelen, 2011) was used for MEG pre-processing and source reconstruction. Trial epochs were

[1] Full scale IQ scores were missing from one ASD and four control participants.

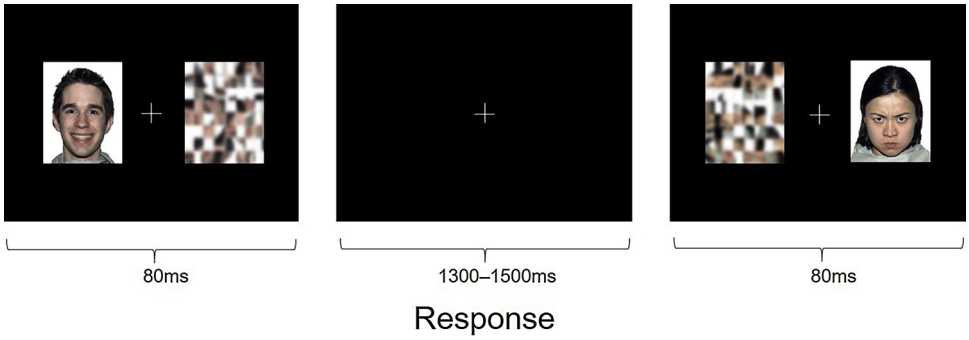

Fig. 1. Emotional faces task. On each trial, adults saw a happy or angry face paired with a scrambled pattern (target) on either side of a central fixation cross. Adults were instructed to indicate the left or right position of the target as rapidly as possible following stimulus onset using a MEG-compatible button-pad.

identified in the continuous MEG data by condition (happy or angry), -200 to 800 ms relative to stimulus onset. Trials with incorrect responses were rejected from the analysis. Independent component analysis (ICA) and artefact detection was applied to the trial epochs and surrounding data (−300 ms pre-epoch and 500 ms post-epoch) to ensure trial epochs were not contaminated by peri-epoch artefact. ICA was applied to remove artefacts (i.e., ocular and cardiac) in the MEG signal; components were manually rejected based on visual inspection. Following application of ICA, trials were rejected from analysis if any given trial exceeded 5 mm from the initial median head position and/or if the MEG signal from sensors was greater than 2000 fT. A Mann-Whitney U test calculated due to non-normality of the distribution revealed no significant difference in maximum head motion between ASD and control groups (ASD: $M = 0.68$, $SD = 0.56$, $Mdn = 0.5$; controls: $M = 0.49$, $SD = 0.24$, $Mdn = 0.45$; $U = 1077$, $z = -1.6$, $p = 0.11$). Additionally, all epoched trials were visually examined and excluded if contaminated with other sources of artefact (e.g., muscle). A Mann-Whitney U test calculated due to non-normality of the distribution revealed no significant between group difference in the number of happy (ASD: $M = 86.61$, $SD = 9.6$, $Mdn = 90$; controls: $M = 89.1$, $SD = 8.01$, $Mdn = 91$) trials ($U = 1501$ $z = 1.19$, $p = 0.232$), or angry (ASD: $M = 87.05$, $SD = 8.94$, $Mdn = 89.5$; controls: $M = 88.57$, $SD = 8.62$, $Mdn = 90.5$) trials ($U = 1445$, $z = 0.824$, $p = 0.41$) included in the analysis. Furthermore, a related-samples Wilcoxon Signed Rank test revealed no significant condition difference across group in the number of happy ($M = 88.05$, $SD = 8.76$, $Mdn = 91$) compared to angry trials ($M = 87.92$, $SD = 8.75$, $Mdn = 90$) included, $T = 1883$, $p = 0.506$).

Continuous MEG data were filtered with a 4th order Butterworth band-pass filter at 1–150 Hz and a discrete Fourier transform notch filter at 60 and 120 Hz to eliminate line noise. The data were then co-registered with each participant's MRI. A single shell head model for each subject was generated based on his/her own MRI. The centroids of the first 90 sources of the Automated Anatomical Labelling (AAL) atlas comprising all subcortical and cortical brain regions (Tzourio-Mazoyer et al., 2002) were computed in standard template space (ICBM 152; Fonov, Evans, McKinstry, Almli, & Collins, 2009) and non-linearly warped to equivalent locations in each individual's subject space. The broadband time series data for each of the 90 seed locations of the AAL were reconstructed using a linearly constrained minimum variance (LCMV) beamformer (Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997) with 5% Tikhonov regularization. To remove the centre-of-head bias, the neural activity index (NAI) was computed by normalizing the reconstructed timeseries amplitude with the estimated amplitude of projected noise.

2.5. Functional connectivity: phase synchrony

The timeseries data for each source location was filtered into canonical frequency bands: theta (4–7 Hz), alpha (8–14 Hz), beta (15–29 Hz) and gamma (30–55 Hz) using a two-pass FIR filter (MATLAB's fir1 and filtfilt functions). To obtain the instantaneous timeseries of phase values for each source location and frequency band, we used the Hilbert transform. Phase data were epoched based on previously identified trial segments. To measure whole-brain functional connectivity of neural oscillations between source locations, we computed the cross-trial phase-lag index (PLI) based on Stam et al. (2007), which estimates instantaneous phase synchrony at each sample across the time series between two source locations. The PLI characterizes the phase difference (i.e., leads and lags in phase), while accounting for spuriously correlated sources with zero or near zero phase lag, therefore reducing the possibility of artificial phase synchrony (i.e., volume conduction). PLI was calculated pairwise for each of the 90 AAL source locations, yielding a 90×90 adjacency matrix for each time point within each frequency band, for each condition and subject. The PLI values at each time point were normalized by a baseline interval of -200 to 0 ms by z-scoring.

2.6. Statistical analysis: the network-based statistic

We selected time windows of phase synchrony for statistical analysis for each frequency band by calculating the full width at half maximum (FWHM). We defined maximum as the peak in phase synchrony, averaged across conditions, in ASD and control groups. The FWHM for each frequency band was determined by calculating the mean phase synchrony (PLI) across all pairs of the 90 regions, then identifying the FWHM window within the time series. This technique revealed the following active time windows: 74–537 ms (theta band), 72–342 ms (alpha band), 28–340 ms (beta band) and 80–308 ms (gamma band). The normalized PLI values were averaged across these active time windows to produce an adjacency matrix for each participant, for each frequency band, for both happy and angry faces.

To determine statistically significant within- and between-group differences in phase synchrony, we used the Network-Based Statistic (NBS), an established non-parametric technique for the statistical analysis of large networks, where the family-wise error rate (FWER) is controlled (https://www.nitrc.org/projects/nbs/; Zalesky, Cocchi, Fornito, Murray, & Bullmore, 2012; Zalesky, Fornito, & Bullmore, 2010). The primary component forming threshold was set to $t = 3.1$ ($p = 0.0002$) for within-group and between-group analyses to $t = 2.5$ ($p = 0.007$); 5000 permutations were run.

3. Results

3.1. Behavioural results

For measures of reaction time (ms) and accuracy (percent correct), we calculated Mann-Whitney U tests due to non-normality of the distributions for both happy and angry faces. Adults with and without ASD performed comparably in their reaction times to happy $U = 1260$, $z = -0.395$, $p = 0.693$ and angry faces $U = 1278$, $z = -0.276$, $p = 0.782$.

Similarly, for accuracy, no significant group differences were found for happy $U = 1543.5$, $z = 1.5$, $p = 0.135$, or angry faces $U = 1472.5$, $z = 1.021$, $p = 0.307$ (see Supplemental Material Table 1 for descriptive information). Comparable between-group behavioural performance was expected given that the task was implicit and undemanding, and it assures that between-group differences in functional networks are not due to unequal performance between groups.

3.2. Between-group results: reduced gamma band phase synchrony in ASD

Between-group contrasts for each emotional face type (i.e., happy and angry) and frequency band (i.e., theta, alpha, beta and gamma) were calculated. We found a network of reduced phase synchrony 80–308 ms following angry face presentation in the gamma frequency band in adults with ASD compared to controls (52 edges and 51 nodes; $p_{corr} = 0.001$). This network of reduced phase synchrony involved long-range connections anchored in frontal regions, including bilateral superior frontal gyri (medial and orbital), bilateral orbital frontal gyri (medial), bilateral inferior frontal gyri, and left middle frontal gyrus. These frontal areas were connected to primary visual and face processing areas, such as the left calcarine, right middle occipital lobe, and right FG. Additionally, the network involved connections between frontal and temporal regions, such as between the right orbital frontal gyrus (medial) and right inferior temporal gyrus, and right inferior frontal gyrus and right temporal pole. The network also included connections between frontal and parietal areas, such as between the right orbital frontal gyrus (medial) and the left inferior parietal gyrus, as well as the left superior parietal gyrus, and between the right orbitofrontal cortex and left superior parietal gyrus. Importantly, the network consisted of connections between frontal regions and the bilateral amygdalae; specifically, between the left inferior frontal gyrus (triangular) and the left amygdala, and the right inferior frontal gyrus (opercular) and the right amygdala (Figs. 2 and 3). See Table 1 for a complete list of brain regions involved in the network and number of connections. No significant between-group differences were found to happy faces in the gamma band, or to happy or angry faces in the theta, alpha or beta frequency bands after Bonferroni correction for multiple comparisons across emotion and frequency bands (Bonferroni adjusted p-values are reported).

A 2 (group: ASD, controls) x 2 (condition: happy, angry) ANOVA (with group as a between-subjects factor and condition as a within-subjects factor) using NBS was also calculated. No significant main effects of group or emotion were found in the theta, alpha, beta or gamma frequency bands, after Bonferroni correction for multiple comparisons. An interaction was found only in the gamma frequency band, but it did not pass Bonferroni correction for multiple comparisons (see Supplemental Material).

3.3. Within-group results: gamma band

Phase synchrony following happy and angry face onset within ASD and control groups was examined in the active window (80–308 ms) relative to the baseline window (-200–0 ms) for happy and angry faces separately. We focused on the gamma frequency band given the between-group finding. Results showed significantly increased gamma band phase synchrony following happy and angry stimuli in controls. The network of increased phase synchrony to happy faces in controls encompassed 48 edges and 45 nodes ($p_{corr} < 0.002$) and involved interregional connections primarily anchored in frontal regions connecting to occipital and temporal regions, as well as the FG – critical for face processing. Specifically, the network involved connections between the left superior frontal gyrus (orbital) and the right FG, the right superior frontal gyrus (orbital) and the left FG, the right middle frontal gyrus (orbital) and the left FG, and the left orbital frontal gyrus (medial) and the right FG. Additionally, several connections were anchored in bilateral temporal regions extending to frontal and occipital regions, such as between the left middle temporal gyrus and bilateral calcarine, and the right inferior temporal gyrus and right inferior frontal gyrus (triangular; Fig. 4a). To angry faces, the network involved 45 edges and 42 nodes ($p_{corr} < 0.002$), encompassing long-range connections mostly from frontal to occipital and parietal areas, as well as to the FG, and mid and posterior cingulate gyrus. For instance, the network involved connections between the bilateral inferior frontal gyrus (triangular) and the right middle occipital lobe, right calcarine, left angular gyrus and right FG. The network also involved connections from the left inferior frontal gyrus (orbital) to the mid cingulate gyrus, and the bilateral orbital frontal gyri (medial), to the left mid cingulate gyrus, left angular gyrus, left posterior cingulate gyrus and right middle occipital lobe. Additionally, connections existed between the bilateral amygdalae and left angular gyrus and left posterior cingulate gyrus (Fig. 4b).

In ASD, we found a network of increased gamma band phase synchrony compared to baseline to happy faces, 13 edges and 13 nodes ($p_{corr} < 0.002$). The network involved long range connections anchored in the left ACC, the right parahippocampal gyrus, and the left temporal pole (Fig. 4c). There was no differentiation between the emotional faces and baseline in the ASD group following angry face stimuli. Bonferroni adjusted p-values are reported for all contrasts.

4. Discussion

The current study investigated whether functional connectivity is disrupted during the implicit perception of emotional faces in a large sample of adults with and without ASD. We found a network of reduced gamma band phase synchrony 80–308 ms following angry face onset in adults with ASD compared to controls. This hyposynchronous network in MEG primarily involved connections among frontal regions and occipital and occipitotemporal regions, including the left calcarine, right middle occipital lobe, and right FG. The network also involved frontal connections to right temporal areas known to be involved in face and emotional face processing (Haxby, Hoffman, & Gobbini, 2000; Olson, Plotzker, & Ezzyat, 2007), including the right inferior temporal gyrus and right temporal pole. In addition, the network involved connections from frontal to parietal regions, including the right angular gyrus, left superior parietal gyrus and left inferior parietal gyrus. Connections were also found between frontal regions and the bilateral amygdalae – known to be essential for angry face processing (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002). Interestingly in ASD, no significant increase in gamma phase synchrony was found following the presentation of angry faces relative to baseline. Given that frontal brain regions play a critical role in the recognition of emotion via bridging perceptual information with conceptual knowledge, as well as in evaluating the salience and reward value of emotional stimuli and appropriately moderating behavioural responses, such as response inhibition and reversal learning (Adolphs, 2002; Blair, Morris, Frith, Perrett, & Dolan, 1999; Bush, Luu, & Posner, 2000; Rolls, 2000), our findings suggest that these regions are atypically recruited in ASD and thus may underlie impaired implicit processing of angry faces in ASD.

Reduced functional connectivity to angry faces mainly implicating frontal areas in ASD is corroborated by previous MEG studies (Khan et al., 2013; Leung et al., 2014; Mennella et al., 2017). Mennella et al. (2017) found decreased phase synchrony to angry faces in the beta frequency band that involved mostly long-range connections between occipital and frontal areas, along with additional regions key for emotional face processing (e.g., temporal and limbic brain areas). Another MEG study examined local functional connectivity of the right FG as indexed by phase-amplitude coupling (PAC) and long-range connectivity between the right FG and the rest of the brain to emotional faces and houses in ASD and control adolescents and young adults, aged 14–20 years (Khan et al., 2013). They found face-specific reduced PAC between alpha band phase and low and high gamma band amplitude in the right FG in ASD. Moreover, they reported reduced alpha band long-

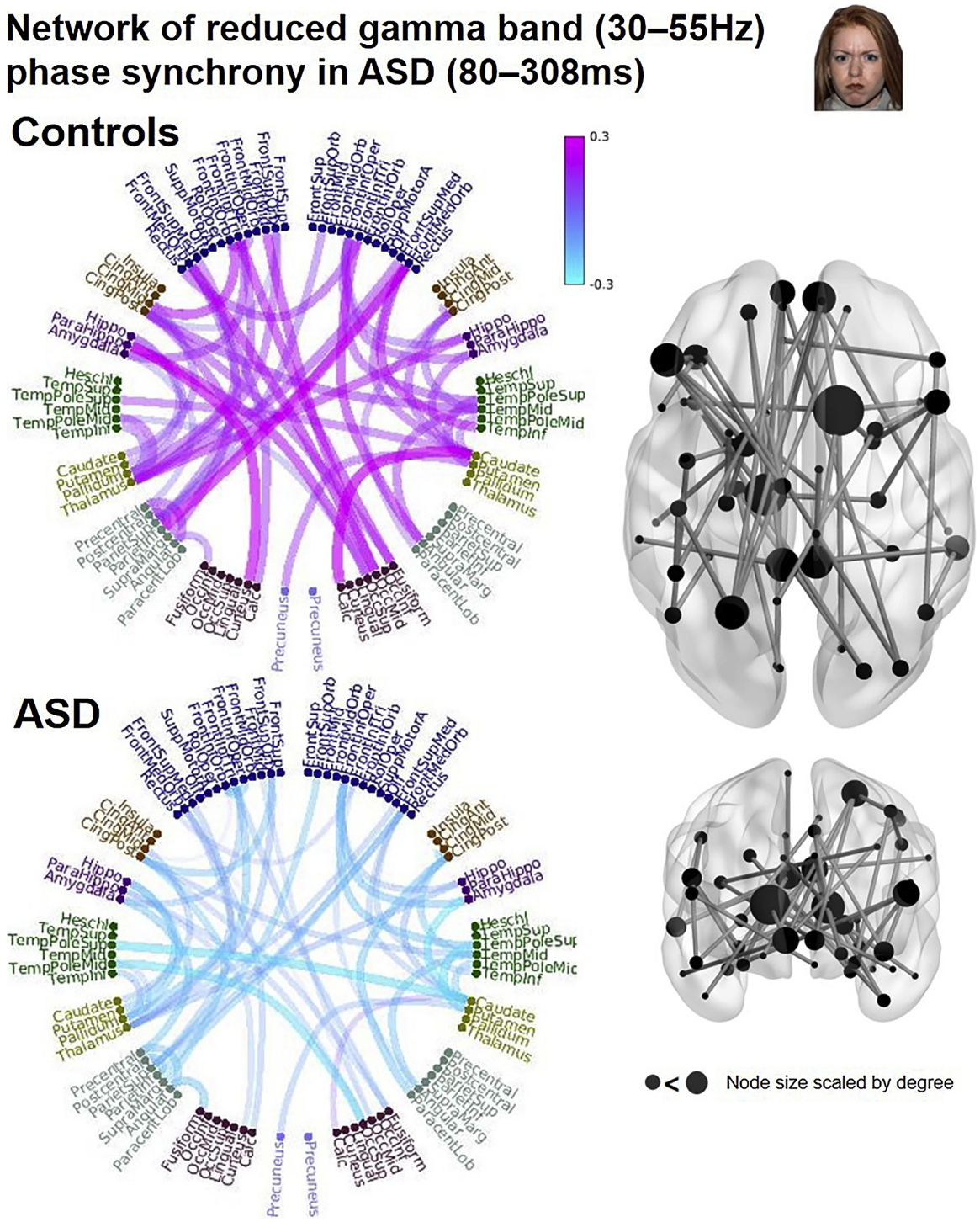

Fig. 2. Network of reduced gamma band phase synchrony 80–308 ms following angry face perception in ASD compared to controls. This network involved 52 edges and 51 nodes (p_{corr} = 0.001). All significant connections are illustrated in the circle plots, where the width, opacity and colour (see colour axis) of the edges are scaled by connection strength, showing the widespread reduced connectivity in the ASD group. The network is also represented in the brains on the right, where node size is scaled by degree.

range connectivity to emotional faces between the right FG and the left precuneus, left inferior frontal gyrus and left ACC in ASD compared to controls. Given that the phase synchrony of neural oscillations underlies the orchestration of large-scale brain networks driving socio-cognitive processes via neuronal communication (Fries, 2005; Uhlhaas & Singer, 2006), we propose that reduced phase synchrony in ASD reflects a network of disrupted interregional communication primarily among frontal areas, but also connections between frontal and occipital, temporal, parietal and subcortical areas important for emotional face processing.

While we observed decreased functional connections during presentation of angry faces in ASD, connectivity in response to happy faces did not show any significant group differences - a finding consistent with previous work also reporting hypoconnectivity to angry faces, but not happy faces, in adolescents and adults with ASD (Khan et al., 2013; Leung et al., 2014; Mamashli et al., 2018; Mennella et al., 2017). Angry

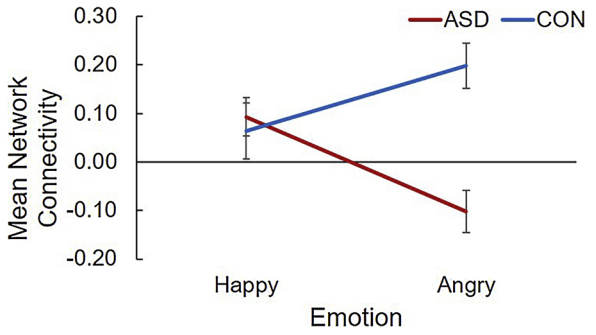

Fig. 3. Gamma band mean network connectivity in controls compared to ASD. The line graph represents the mean network connectivity strength for the significant between-group gamma band network in adults with ASD and controls, following angry face onset. The mean connectivity for the significant network is plotted for both the angry and happy conditions, showing that this network is specific to angry faces.

faces are social signals that are often expressed in response to recurrent socially inappropriate behaviours or those that violate social rules (Averill, 1982) and communicate that a change or suppression of behaviour is required, such as response inhibition or reversal learning (Blair et al., 1999). A conceptual understanding and recognition of angry faces may be challenging for individuals with ASD since understanding of appropriate social norms and behaviour is often impaired in those with the disorder (Berkowitz, 2005; Leung et al., 2015; Zeman & Garber, 1996). Since the orbitofrontal cortex is implicated in the restraint of inappropriate responses and reversal learning, which may be evoked by angry faces (Blair et al., 1999; Elliott, 2000), we suggest that the reduced connectivity in the network implicating the orbitofrontal cortex in the current study reflects atypical engagement of this brain area in ASD, which would negatively affect response inhibition or reversal learning.

Other studies have highlighted abnormal gamma band oscillations in ASD during the perception of emotional expressions (Rojas & Wilson, 2014). It has been proposed that an excitatory-inhibitory imbalance (E/I imbalance) in synaptic transmission may underpin ASD pathology, including socio-emotional impairments (Le Magueresse & Monyer, 2013; Rojas & Wilson, 2014; Rubenstein & Merzenich, 2003; Uzunova, Pallanti, & Hollander, 2015). This imbalance is thought to be related to either increased glutamatergic or a reduction in GABAergic synaptic transmission. Inhibitory mechanisms and E/I balance play a fundamental role in establishing local synchrony of gamma band oscillations (Buzsáki & Wang, 2012; Fries, Nikolić, & Singer, 2007; Le Magueresse & Monyer, 2013; Uzunova et al., 2015), which provide the foundation for dynamics of coordinated neural activity among widespread neural circuits (Khan et al., 2013; Zikopoulos & Barbas, 2013). Therefore, our findings of gamma band specific disrupted neural circuitry may reflect altered E/I balance in brain regions critical for emotional face processing in ASD, given that local neuronal dynamic disruptions may likely be propagated to long-range functional connectivity.

Although our findings were specific to the gamma frequency band, reduced connectivity to angry facial expressions has been previously documented using MEG in the beta and alpha frequency bands in adults (Mennella et al., 2017) and adolescents and young adults (Khan et al., 2013), respectively. It is possible that discrepancies in frequency band may be due to methodological differences across studies, for instance using a region of interest vs. whole brain approach, sample size, participant age range, and connectivity metric, to name a few. This is the largest sample size for these studies to date, but with increases in the future in sample size, these effects can be confirmed and other complementary analysis approaches explored.

Along with previous reports of atypical functional neural networks in children and adolescents with ASD (Leung et al., 2014; Safar et al., 2018), the current findings suggest altered maturation of affect processing in ASD. Unlike children with ASD (Safar et al., 2018) adults with the disorder showed decreased functional connectivity to angry faces. These differences in patterns of functional connectivity at different developmental stages are consistent with a recent hypothesis that age-related changes may explain differences in the direction of connectivity patterns (Mamashli et al., 2018; Uddin, Supekar, & Menon, 2013). Since the current study was restricted to an adult cohort, an important future direction will be to examine an extended age span to determine whether alterations in the neurodevelopmental trajectory of emotional face processing progress with age in ASD.

In conclusion, we observed reduced functional connectivity to angry faces only in the gamma frequency band in adults with ASD compared to controls. Our findings highlight disrupted interregional neuronal communication among higher-level brain areas and between regions underlying affective processing in ASD. We further suggest that reduced connectivity of the orbitofrontal cortex to angry faces particularly may

Table 1
Brain regions and associated number of connections (degree) involved in the network of reduced gamma band phase synchrony in adults with ASD compared to controls to angry faces.

Brain Regions (nodes)	Number of Connections (degree)
R Caudate	6
L Thalamus	5
L Inferior frontal gyrus, triangular	4
R Superior frontal gyrus, medial orbital	4
Cingulate gyrus, posterior part	4
R Superior parietal gyrus	4
L Superior parietal gyrus	4
R Inferior frontal gyrus, opercular	3
L Inferior frontal gyrus, orbital	3
L Superior frontal gyrus, medial orbital	3
L Pallidum	3
R Middle temporal gyrus	3
L Precentral gyrus	2
L Superior frontal gyrus, orbital	2
R Inferior frontal gyrus, triangular	2
L Cingulate gyrus, mid part	2
L Hippocampus	2
R Hippocampus	2
L Parahippocampus	2
L Amygdala	2
R Amygdala	2
R Superior occipital lobe	2
R Middle occipital lobe	2
R Fusiform gyrus	2
L Postcentral gyrus	2
L Inferior parietal gyrus	2
L Angular gyrus	2
R Angular gyrus	2
R Putamen	2
R Temporal pole, superior temporal gyrus	2
L Temporal pole, middle temporal gyrus	2
R Superior frontal gyrus, orbital	1
L Middle frontal gyrus	1
L Inferior frontal gyrus, opercular	1
L Superior frontal gyrus, medial	1
R Superior frontal gyrus, medial	1
L Rectus	1
R Cingulate gyrus, mid part	1
L Calcarine	1
R Calcarine	1
L Cuneus	1
L Fusiform gyrus	1
L Supramarginal gyrus	1
L Precuneus	1
R Paracentral lobule	1
L Caudate	1
L Putamen	1
L Temporal pole, superior temporal gyrus	1
R Temporal pole, middle temporal gyrus	1
L Inferior temporal gyrus	1
R Inferior temporal gyrus	1

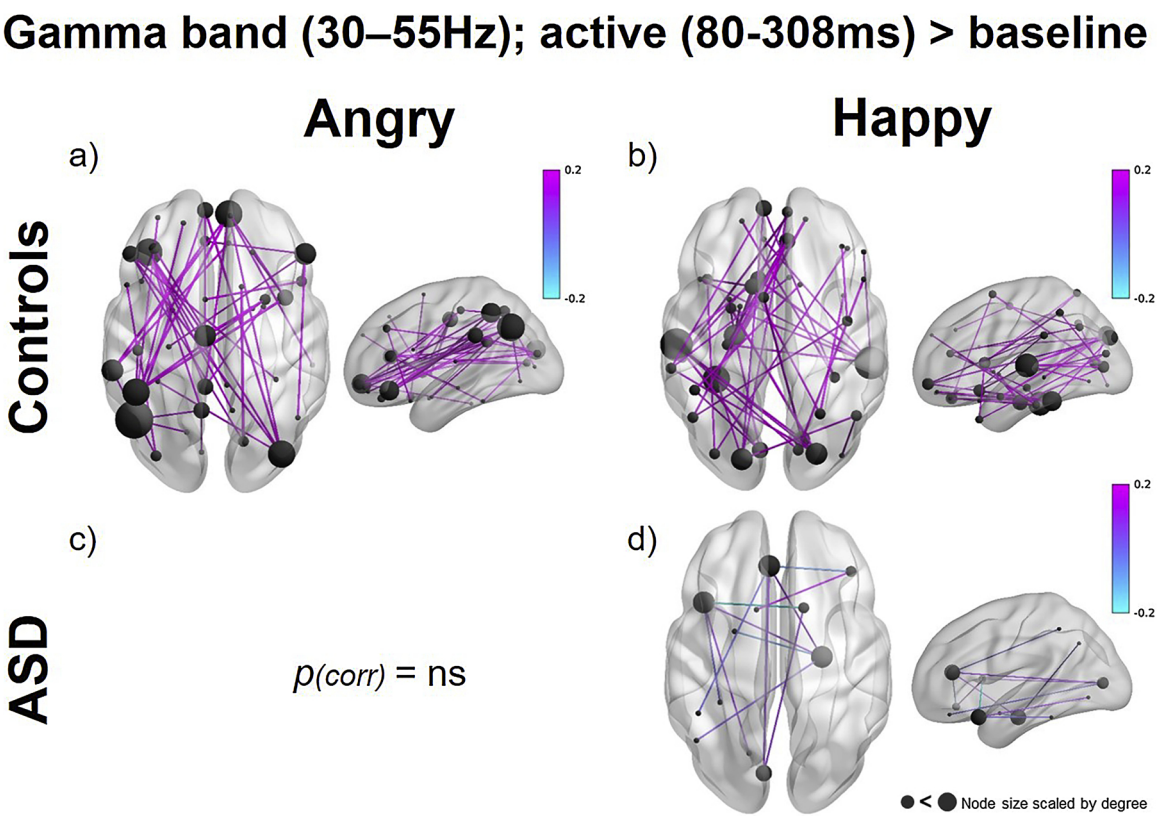

Fig. 4. Significantly increased networks of gamma band phase synchrony 80–308 ms following angry and happy face onset relative to baseline. In controls, a) to happy faces, the network involved 48 edges and 45 nodes ($p_{corr} < 0.002$), b) to angry faces, the network involved 45 edges and 42 nodes ($p_{corr} < 0.002$). In ASD, c) to happy faces, the sparse network involved 13 edges and 13 nodes ($p_{corr} < 0.002$). Edges are scaled by connection strength and nodes are scaled by degree. No significant increase in gamma band phase synchrony was found in adults with ASD to angry faces relative to baseline.

underlie deficits in inhibition of emotional responses and reversal learning in this group. Given that ASD is widely heterogeneous (O'Reilly et al., 2017) it will be important for future work to study functional networks underlying emotional face processing in even larger samples to elucidate deficits in social functioning in this population.

Declaration of Competing Interest

All authors have no declarations of interest to report.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopsycho.2019.107774.

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