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Reduced beta band connectivity during number estimation in autism



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ABSTRACT

Recent evidence suggests that disruption of integrative processes in sensation and perception may play a critical role in cognitive and behavioural atypicalities characteristic of ASD. In line with this, ASD is associated with altered structural and functional brain connectivity and atypical patterns of inter-regional communication which have been proposed to contribute to cognitive difficulties prevalent in this group. The present MEG study used atlas-guided source space analysis of inter-regional phase synchronization in ASD participants, as well as matched typically developing controls, during a dot number estimation task. This task included stimuli with globally integrated forms (animal shapes) as well as randomly-shaped stimuli which lacked a coherent global pattern. Early task-dependent increases in inter-regional phase synchrony in theta, alpha and beta frequency bands were observed. Reduced long-range beta-band phase synchronization was found in participants with ASD at 70–145 ms during presentation of globally coherent dot patterns. This early reduction in task-dependent inter-regional connectivity encompassed numerous areas including occipital, parietal, temporal, and frontal lobe regions. These results provide the first evidence for inter-regional phase synchronization during numerosity estimation, as well as its alteration in ASD, and suggest that problems with communication among brain areas may contribute to difficulties with integrative processes relevant to extraction of meaningful 'Gestalt' features in this population.

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1.0. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a broad continuum of severity. Increasing prevalence of this disorder is accompanied by growing evidence that individuals with ASD can benefit from research-based interventions. For instance simple adaptations of sensory stimulation can overcome difficulties in sensory perception in ASD and on larger scales foster independence and participation in society (Gepner and Féron, 2009; Lainé et al., 2011). Therefore, to properly identify target systems for intervention strategies, research into the neurocognitive mechanisms underlying ASD is becoming increasingly urgent.

ASD is diagnosed on the basis of impairments in social interaction and communication (including social–emotional reciprocity), and restrictive/repetitive behaviours (including atypical sensory processing; APA, 2013) and is marked by abnormalities in various cognitive domains. Individuals with ASD typically show symptoms related to impaired sensory and perceptual processing (Dawson, 2002; Minshew et al., 1997, 2002), including impaired integration of stimuli during the perception of faces and emotions (Nackaerts et al., 2012). In everyday situations, however, perceiving and interpreting parts of stimuli in terms of their context is often required to “see the big picture”. Individuals with ASD tend to take narrow perspectives, utilizing local processing styles over global integrative information processing styles (Happé, 1999) and focusing on details at the expense of integrating separate features into one coherent object or concept (Frith, 1989). Several studies provide evidence for a reduced ability in individuals with ASD to unify visual components into single coherent representations (for a review see Happé and Frith, 2006).

Human stimulus processing capacities are limited and attention helps to select and integrate stimulus features in noisy environments.

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Functional disabilities in ASD may in part be attributable to impaired selective attention. ASD is linked to problems with rapid coordination of attention between sensory modalities, impaired orienting of attention to living stimuli (i.e. people of interest), and impaired early selection of relevant objects or object features (Belmonte and Yurgelon-Todd, 2003; Courchesne et al., 1994; Leekam and Moore, 2001; Rinehart et al., 2001). These findings suggest problems with higher-order attentional control networks in ASD.

Neuroscience has traditionally focused mainly on characterizing the function of individual brain regions and neurons. Recent findings, however, suggest that various cognitive symptoms of ASD may originate from abnormalities in coordinated functioning involving widely distributed brain regions (Belmonte and Bourgeron, 2006; Uhlhaas and Singer, 2006). The coordination of neural oscillations across the brain has been described as a basis for communication in brain networks (Fries, 2005; Uhlhaas et al., 2009a; see Donner and Siegel, 2011 for a review). The underlying mechanism for communication through coherence is understood to be the synchronization of presynaptic potentials in a neuronal population which enhances their impact on postsynaptic neurons in the target area (Azouz and Gray, 2000; Bruno and Sakmann, 2006; Siegel and Donner, 2012). Encoding of sensory stimuli primarily involves local cortical interactions. Sensory and perceptual integration, however, requires coordination among distant brain regions. Several studies have shown that long-range cortical interactions often involve correlated neuronal interactions in the beta band (Donner and Siegel, 2011; Engel et al., 2001; Varela et al., 2001). Synchronization of beta band oscillations have been related to feature integration, as well as the development of these processes throughout childhood and adolescence (Uhlhaas et al., 2006; Uhlhaas et al., 2009b). Moreover, disruption of long-range beta band synchronization has been associated with impaired integration of facial features in psychiatric populations (Uhlhaas et al., 2006). Reduced salience of social cues in ASD patients has been explained by alterations in high-level attentional processes that modulate the synchronization of neural activity between early visual and fusiform areas (while watching faces vs. houses; Bird, 2006). This impaired top-down modulation of fast sensory processing in ASD may be explained by reduced neural connectivity (Frith, 2003). Findings of weaker neural connectivity in ASD have supported the notion of impaired attentional control relying on neuronal feedback connections from fronto-parietal areas (Belmonte and Bourgeron, 2006; see Uhlhaas and Singer, 2006 for a review).

In line with such findings, the underconnectivity theory in autism attributes the symptoms of ASD to functional underconnectivity between frontal and posterior brain areas (Just et al., 2007, 2012). This has been found consistently with electrophysiological (Khan et al., 2013) and haemodynamic measures during execution of various tasks (Anagnostou and Taylor, 2011; Darmala et al., 2010; Koshino et al., 2005; see Baribeau and Anagnostou, 2013 for a review) as well as during resting state measurements (Barttfeld, 2011; see Müller et al., 2011 and Schipul et al., 2011 for reviews) and with computational modelling (Lewis and Elman, 2008). Those deficits in functional connectivity typically increase over age and are associated with alterations in structural connectivity in adults diagnosed with ASD which have been observed using diffusion tensor imaging (DTI) methods (Lee et al., 2007; Mak-Fan et al., 2013; see Travers et al., 2012 for review). Individuals with ASD typically show abnormal brain maturation and overgrowth of white matter in childhood (Casanova et al., 2006; Piven et al., 1996; Mak-Fan et al., 2013), but have reduced white matter and smaller corpus callosum size in adulthood (Vidal et al., 2006; Duerden et al., 2012). Recent studies consistently find general reductions in functional neuronal connectivity across various brain regions in ASD (Barttfeld, 2011; Domínguez et al., 2013; Khan et al., 2013; Wass, 2011). In summary, atypical sensory processes due to impaired top-down attention regulation and altered integrative mechanisms in ASD may be the result of atypical synaptic interactions between cortical regions (Courchesne and Pierce, 2005; Just et al., 2007,

2012) and reduced neural synchronization (Baribeau and Anagnostou, 2013; Belmonte et al., 2004, 2006; Brock et al., 2002; Hill and Frith, 2003; White, 2009).

The synchronization of neuronal activity has been related to the integration of visual information (Uhlhaas et al., 2006, 2009a,b). Reduced functional connectivity between early visual and frontal regions has been linked, for instance, to impaired visual task performance (Villalobos et al., 2005). In autism, impaired integration of visual information has been attributed to diminished neuronal synchrony of high frequency oscillations (Dakin and Frith, 2005; Sun et al., 2012) whereas typically developing individuals process visual information for overall Gestalt at the expense of processing the details (Frith, 1989). Visual information integration becomes relevant if multiple grouped items are present, for example, when a quick estimate of the number of items is needed. Numerosity estimation involves distinct neurocognitive mechanisms and requires processing of local features, rather than focusing on the Gestalt. Thus, differences in stimulus processing between ASD and typically developed individuals might occur when global processing is required (i.e. if stimulus patterns provide globally meaningful characteristics). In a previous study from our group, performance during a numerosity estimation task was worse in controls if dots were arranged in animal shapes conveying a global meaning, compared to dot patterns organized in random shapes, whereas in adults with ASD, the accuracy of estimates was insensitive to the global meaningfulness of dot arrays (Meaux et al., 2014). Widespread differential activation of brain regions was found at several stages of neural processing during number estimation, suggesting atypical strategies in ASD. In accordance with the weak central coherence theory, instead of searching for meaningful patterns, individuals with ASD may orient towards local features when processing visual input for numerosity estimations.

The current study investigated neural network connectivity (phase synchrony), underlying visual stimulus perception in a numerosity estimation task in adults with ASD and age and sex matched controls. First, we investigated magnetoencephalographic (MEG) connectivity dynamics underlying normative numerosity estimation during perception of animal patterns with global meaningfulness and randomly shaped dot patterns. Second, we determined whether long-range connectivity dynamics were altered in ASD. We hypothesized that participants with ASD would show a reduced network synchronization relevant for integrative processes during number estimation of globally meaningful animal stimuli, compared to typically developed controls.

2.0. Methods

2.1. Participants

Data were recorded from fourteen adults with ASD (10 males; mean = 24.77 years \pm 3.96) and fourteen controls (10 males; mean = 24.92 years \pm 3.78). ASD participants had been diagnosed by a registered medical professional experienced with autistic spectrum disorders according to DSM-IV (APA, 1994) criteria, using the Autism Diagnostic Observation Schedule (ADOS, module 4; Rutter et al., 2002). IQ was assessed using the WASI (Wechsler, 1999; ASD: 108 \pm 14.2; controls: 120 \pm 8.5). Controls were age- and sex-matched to the ASD participants. Two Mann–Whitney tests showed that age and IQ did not significantly differ between the groups. Medication use was screened prior to inclusion, and none of the participants had a history of behavioural, psychiatric or neurological disorders (other than autism in the ASD group), or any metallic implants or ferromagnetic dental work which would interfere with MEG recordings. This set of exclusion criteria, together with age and sex matching, was designed to maximize sample size while retaining a degree of homogeneity well suited for a clinical neuroimaging study. All participants had normal or corrected-to-normal vision and gave informed written consent. The study was approved by the Research Ethics Board at the Hospital for Sick Children in Toronto.

2.2. Task and stimuli

Stimuli consisted of 224 pictures and were composed of between 80 and 150 dark grey dots (each 0.17°) on a light grey background. The dot position was randomized, with dots either located within a meaningful animal shape (animal condition) or within a non-meaningful shape (non-animal condition; 112 pictures in each condition). Pattern size and shape were independent of the number of dots. Eight different animal shapes (butterfly, camel, chicken, dog, donkey, mouse, panther and seal) and 8 different non-animal shapes were used. The stimulus display and time course are depicted in Fig. 1.

The stimuli were projected centrally onto a screen positioned 60 cm in front of the participant using Presentation software (Neurobehavioural Systems, Albany CA). Stimuli subtended a visual angle of 8.38° horizontally and 6.52° vertically. The order of stimuli was randomized. Stimuli were shown for 600 ms, followed by a brief single tone starting 100 ms after stimulus offset. In order to avoid anticipation effects stimuli were presented at an irregular interval with a jitter. A fixation cross was thus presented in between stimuli for a randomized duration of 4500–5500 ms. Participants were instructed to give a verbal estimation of the number of dots. To prevent MEG contamination by mouth movement, participants were instructed to wait for the tone before answering. To ensure that participants understood the task, the experiment started with a training session outside the magnetically shielded room, during which ten pictures were shown on a computer screen. During training, feedback about the number of dots contained in the picture was presented after the participants' responses. Head movements were monitored continuously throughout recording.

2.3. Behavioural data analysis

The absolute estimation error was defined as the difference between the estimated number of dots and the actual number of dots. A repeated measures ANOVAs (Dot shape (2: Animal/Non-animal) * Group (2: ASD/TD)) was performed on the data.

2.4. Data acquisition

MEG data were recorded at a 600 Hz sampling rate using a 151-channel whole-head MEG system with axial gradiometers (CTF/MISL, Coquitlam, B.C.) at the Hospital for Sick Children in Toronto. Data were recorded continuously with an on-line bandpass of 0–100 Hz, and filtered off-line to 0.1–30 Hz. Fiducial coils were placed at the nasion and pre-auricular points to localize the subject's head relative to the MEG sensors at the start and finish of the experiment. Participants lay

supine in the MEG dewar while completing the task inside a dimly lit magnetically shielded room. Head localizations (with an accuracy of 1 mm) were completed before and after the experimental procedure. Head movements were continuously monitored throughout the recording procedure using a video camera. The MEG study required 15–20 min. Following the MEG recordings, for structure-function co-registration purposes, fiducial coils were replaced with MRI contrast markers in the same locations and an anatomic MRI was acquired on a 3 T MAGNETOM Tim Trio MRI scanner (Siemens AG, Erlangen, Germany). A high-resolution T1-weighted volumetric MRI image was acquired for each participant using a 3D MPRAGE sequence.

2.5. Data analyses

2.5.1. Preprocessing and source reconstruction

In accordance with movement thresholds for MEG studies in clinical populations (Herdman and Cheyne, 2009; Hung et al., 2012), subjects were excluded if they moved more than 10 mm between the beginning and the end of the recording session. Data epochs were extracted from 100 ms prior to 800 ms after stimulus onset. MEG data were co-registered with each participant's individual MRI image. Multisphere head models were constructed based on initial fiducial positions using each individual's MRI scan (Lalancette et al., 2011). MRIs were normalized into standard MNI space. Non-linear normalization was performed using SPM2 (see Ashburner and Friston, 1999; Ashburner et al., 1997; Friston et al., 1995). The coordinates of 90 seed locations representing all cortical and subcortical areas from the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) were then unwarped from standard MNI space into each individual's headspace. Scalar beamformer analysis (Cheyne et al., 2006) was used to estimate broadband time series for each source location and trial for each subject representing the activity of each of the 90 sources. This method implements a spatial filter to estimate the contribution of a single target location to the measured field while attenuating activity from other sources and thereby minimizes ocular and non-ocular artefacts (Robinson and Vrba, 1998; Sekihara et al., 2001; Cheyne et al., 2006, 2007). Using beamformer to estimate activity from various locations in source space, and calculating connectivity among reconstructed source time series is congruent with the emerging view that source space connectivity findings are preferable to sensor-space analysis due to the ability to infer the putative role of specific brain regions (see Schoffelen and Gross, 2009 for review). Moreover, the specific combination of beamformer reconstruction with MEG of oscillatory coherence/synchrony has emerged as a standard practice in the field (i.e. Doesburg et al., 2013; Gross et al., 2001; Herdman, 2011).

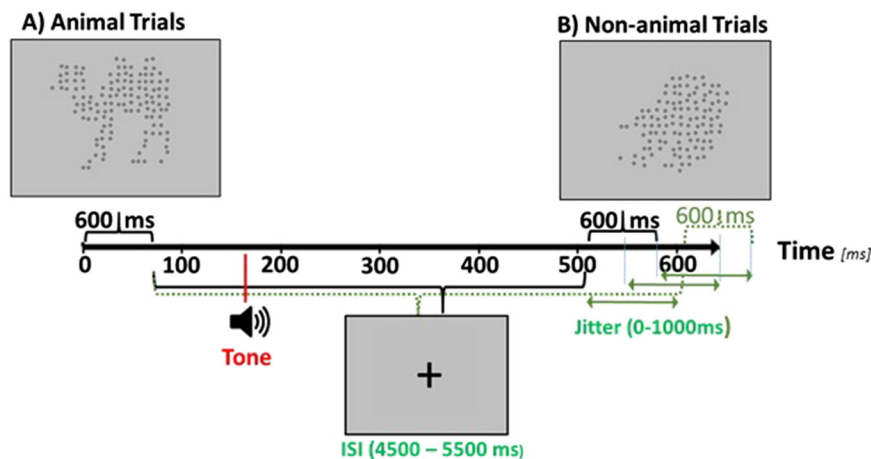


Fig. 1. The stimulus display and its time course, including a representative example of A) animal stimuli, followed by B) a non-animal stimulus. Participants verbally reported an estimate of the number of dots after a brief tone. Order of trial type was randomized and the inter-stimulus interval (ISI) was varied to induce a jitter.

2.5.2. Inter-regional phase-locking analysis

Data were filtered into theta (4–7 Hz), alpha (8–14 Hz) and beta (15–30 Hz) frequency ranges for inter-regional phase-locking analysis. Digital filtering was performed using FFT filters as implemented in the EEGLAB toolbox (see [Delorme and Makeig, 2004](#)). These frequency ranges were selected as prior research has indicated they are critical for organizing communication among distributed brain areas ([von Stein and Sarnthein, 2000b](#); [Palva and Palva, 2007](#); [Donner and Siegel, 2011](#)). Although prior research has suggested that synchronous gamma oscillations are relevant for integrative processes, we chose to exclude this frequency range from analysis as many synchronization responses initially reported in the gamma-band (i.e. [Rodriguez et al., 1999](#)) have been indicated by more recent studies to be centred in the beta-band (i.e. [Uhlhaas et al., 2006, 2009b](#)). This is consistent with the emerging view that gamma oscillations are more relevant for local processes, whereas coherence in lower frequency ranges is more pertinent for large-scale network integration (see [Donner and Siegel, 2011](#)). Moreover, accumulating evidence suggests that task-dependent changes in gamma can more easily arise from artefactual sources than is the case for lower frequency ranges (i.e. [Yuval-Greenberg et al., 2008](#)). Accordingly, we did not include the gamma frequency range in this analysis.

The Hilbert transform was used to obtain time series of instantaneous phase measures for each source, epoch and frequency. The phase lag index (PLI) was calculated across trials for each time point, and used as an indicator of functional connectivity. PLI is a measure of asymmetry of the distribution of phase differences between two sources. In this case, PLI represents the stability of phase angles between a pair of sources for a given time point across analysed trials, with the addition of a constraint which is intended to attenuate spurious synchronization from common sources (see [Stam et al., 2007](#)). Specifically, PLI quantifies the reliability of interregional phase locking by removing/attenuating synchronization that occurs at/near zero phase difference and thus reducing the influence of spurious synchronization originating from shared sources ([Stam et al., 2007](#)). As a result, source-by-source (90×90) adjacency matrices were obtained for each time point within each analysed frequency band, for each subject. To study task-dependent connectivity dynamics, PLI was averaged across source pairs for each time point and subsequently averaged across individuals, producing time series representing global network connectivity dynamics for each group and trial condition. Identification of relevant time windows for further statistical analyses was based on these adjacency matrices together with average network connectivity time series, obtained by averaging PLI across sources for each time point.

Time windows exhibiting peaks in network connectivity were selected, and for each frequency, adjacency matrices representing this task-dependent increase in network connectivity were obtained for each subject by averaging the adjacency matrices across time points in the (active) peak window for each condition. Corresponding baseline adjacency matrices were constructed by averaging across an equivalent number of time points in the pre-stimulus interval. Baseline and active window adjacency matrices were contrasted to investigate task-dependent changes in connectivity. To investigate group differences, task-dependent changes in connectivity were indexed by subtracting the baseline adjacency matrix from the active window adjacency matrix, for each subject for each condition.

The non-parametric Network-Based Statistic (NBS) approach was used for statistical comparison of connectivity differences between active and baseline task intervals and differences across groups ([Zalesky et al., 2010, 2012](#)). NBS initially performs multiple univariate tests on all analysed edges (in this case each element in the adjacency matrix; see also [Maris and Oostenveld, 2007](#) and [Nichols and Holmes, 2002](#) for similar approaches). The size of contiguously connected components is recorded, group membership is shuffled and the largest contiguously connected component is derived using the same univariate threshold to index the largest component that could occur by chance, assuming the

null hypothesis. This process is then repeated 5000 times to create a surrogate distribution, and the rank ordering of the extent of connectivity components in the real data, relative to the extent of connectivity components in the surrogate distribution, is then used to test for statistical significance. Since the maximum extent of a differentially connected component is obtained considering all elements in the adjacency matrix, this method effectively controls for false positives due to multiple comparisons ([Zalesky et al., 2010](#)). Statistical correction for multiple comparisons was performed within each frequency range, but the various bands were treated independently, consistent with emerging statistical approaches in the field of oscillatory network connectivity ([Doesburg et al., 2013](#); [Mazaheri et al., 2009](#)). Using the NBS method, statistical significance is assigned at the level of the connectivity component as a whole, rather than at the level of the individual connections. As different stringencies for initial univariate threshold can yield differential sensitivities under various scenarios of differential connectivity (for example, small focal changes compared with weak diffuse changes) this threshold must be adapted to the data distribution under investigation (see [Zalesky et al., 2010, 2012](#)). Accordingly thresholds were set to $t = 4.0$ (which corresponds to $p = 0.0005$, two-tailed) for analysis of task-dependent connectivity (active window vs. baseline) and $t = 3.0$ (which corresponds to $p = 0.006$, two-tailed) for comparison of ASD participants with controls. Time series of node strengths were calculated from the adjacency matrices using the Brain Connectivity Toolbox ([Rubinov and Sporns, 2010](#)) to index the network involvement of particular regions. Results obtained using NBS and graph theoretical analysis for individual regions were plotted using the BrainNet Viewer toolbox ([Xia et al., 2013](#)). Specifically, nodes and edges belonging to statistically significant components were plotted, and the size of each node represented differences in connectivity strength for nodes in the significant connectivity component.

3.0. Results

3.1. Behavioural results

Comparing task performance between participants with ASD ($M = 25.9$; $SD = 8.3$) and controls ($M = 21.1$; $SD = 3.9$), the mean absolute error of estimation (number of dots) showed a non-significant trend towards being larger in individuals with ASD. The arrangement of dots (animal vs. non-animal) significantly influenced performance accuracy ($F(1,26) = 13.3$; $p = .001$, $\eta^2 = 0.33$) in favour of non-animal shapes and significantly interacted with group (ASD vs. control) on task performance ($F(1,26) = 11.3$; $p = 0.002$; $\eta^2 = 0.33$). ASD subjects presented the same mean error for non-animal ($M = 24.8$; $SD = 6.8$) and animal ($M = 25.2$; $SD = 9.9$) dot pattern whereas controls had more difficulty accurately estimating the number of dots arranged in animal shapes ($M = 24.9$; $SD = 4.5$) than estimating non-meaningful (non-animal) patterns ($M = 17.2$; $SD = 3.4$). The behavioural data from this study have previously been published in [Meaux et al. \(2014\)](#).

3.2. MEG results

3.2.1. Task-dependent increase in oscillatory synchrony

For both groups and both stimulus conditions animated connectivity matrices over time and mean connectivity plots over time indicated that peaks of increased theta, alpha and beta-band connectivity occurred around 200, 150, and 100 ms after stimulus onset, respectively (see [Fig. 2A](#) for the time course of task-dependent beta band network connectivity). The time courses of task-dependent connectivity appeared roughly similar between ASD participants and controls and across task conditions. Therefore, we investigated brain connectivity dynamics by selecting mean PLI active intervals of 75 ms length in the corresponding time ranges: 165–240 ms for theta, 125–200 ms for alpha, and 70–145 ms beta for frequency ranges. Those active windows were statistically compared to $-75-0$ ms baseline windows for all three

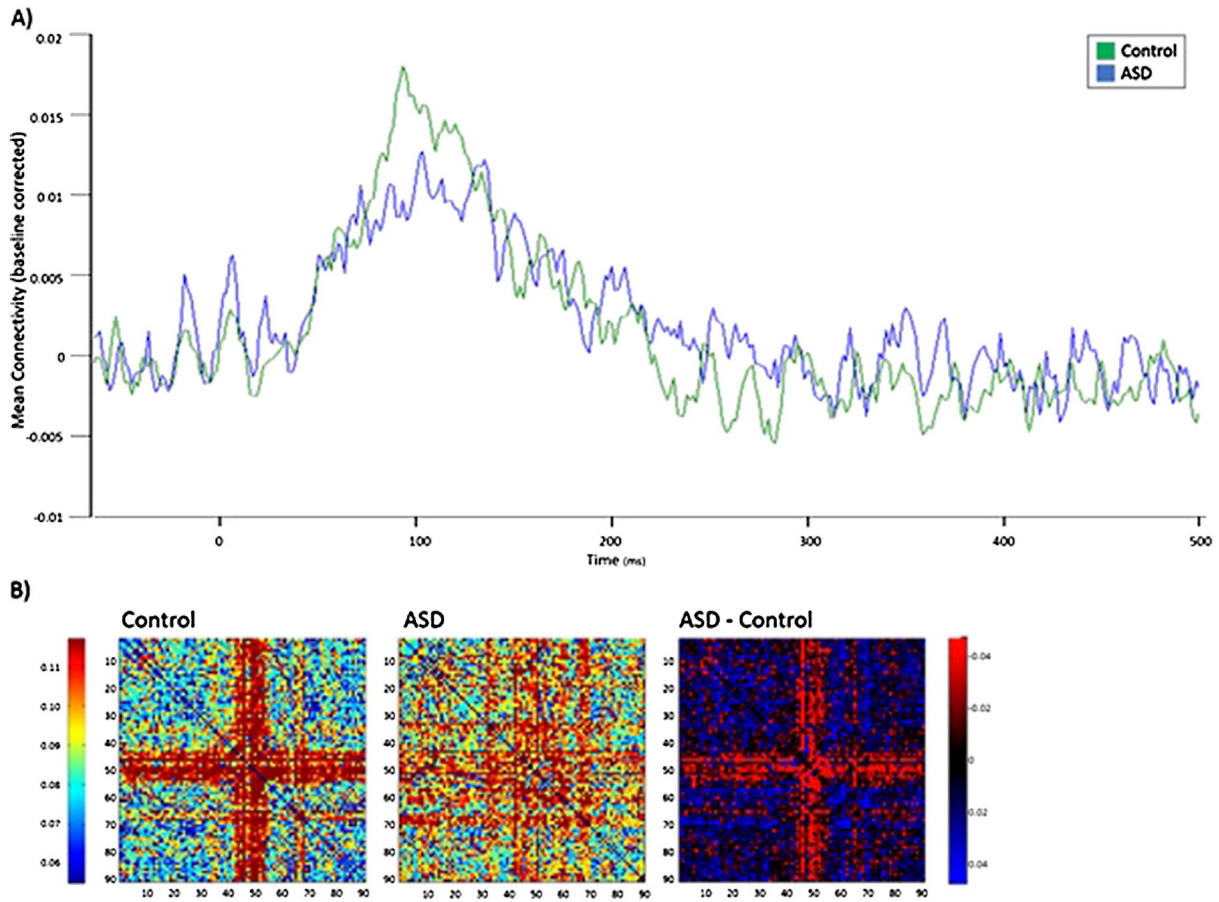


Fig. 2. A) Time course of task-dependent beta band network connectivity for ASD and control participants, obtained by averaging over all analysed region pairs and correcting for baseline connectivity. B) Adjacency matrices depicting beta connectivity for each region pair during the peak (100 ms) of task-dependent synchronization. Note the clear pattern of increased connectivity in the control participants, which corresponds to increased connectivity between visual cortical regions and other brain areas (left). Conversely, visual inspection suggests a more disorganized pattern of task-dependent connectivity for the ASD participants (middle), and this contrast is also evidence in the visualization of group differences (right). See Fig. 3 for more detailed spatial information about regions that constitute the network of task-related connectivity differences and Fig. 4 for differences between groups.

frequency bands for both conditions and for both groups separately. For the controls, NBS results yielded significant task-related connectivity increases in theta ($p < 0.001$ for animal and non-animal), alpha (animal:

$p < 0.002$; non-animal: $p < 0.001$) and beta frequency ($p < 0.001$ for animal and non-animal) bands peaking around 100 ms following both, animal and non-animal stimulus arrangements (see Table 1).

Table 1
NBS output indicating statistical significance of task-related connectivity increases (upper panel) and group differences in task-based connectivity (lower panel) for analysed frequency ranges.

f range	Active window	Baseline window	Animal		Non-animal	
			Controls	ASD	Controls	ASD
θ	165–240 ms	-75–0 ms	** 	** 	** 	**
α	125–200 ms	-75–0 ms	* 	* 	** 	*
β	70–145	-75–0	** (Fig. 3A)	n.s.	** (Fig. 3A)	n.s.
			Controls vs. ASD		Controls vs. ASD	
θ	165–240	-75–0	n.s.		n.s.	
α	125–200	-75–0	n.s.		n.s.	
β	70–145	-75–0	* (Fig. 3B)		n.s.	

Note: ** Statistical significance at $p=0.001$, * Statistical significance at $p=0.05$

Control participants showed strong task-dependent increases in functional connectivity in the theta band encompassing all four lobes of the cortex (with strong involvement of right temporal areas for animal processing). During animal stimulus processing higher alpha band connectivity appeared in a network including right hemispheric occipitotemporal connections, connections from right occipital to bilateral parietal lobes and connections to frontal lobes. In comparison, networks that showed task-related alpha connectivity included fewer regions (nodes) during non-animal stimulus processing (see Table 1). Fig. 3A shows increased beta band connectivity in controls during perception of animal stimuli. The network of increased connectivity mainly included right occipital regions (including lingual gyrus and right cuneus). Although the thresholding in Fig. 2B appears to indicate that task-dependent beta connectivity increases in the control group between early occipital brain regions and numerous other areas, statistical thresholding as presented in Fig. 3 indicates that this pattern is selective. Specifically, occipital regions showed task-dependent phase synchronization with a network encompassing frontal regions as well as temporal (including amygdala, parahippocampus, fusiform and insula of the right hemisphere) and parietal regions. During processing of non-animal stimuli, overall increase in functional connectivity in beta band appeared less pronounced. This network of increased functional beta connectivity mainly included connections from occipital regions to left frontal, parietal and temporal (parahippocampus, hippocampus and fusiform area) areas. Interestingly,

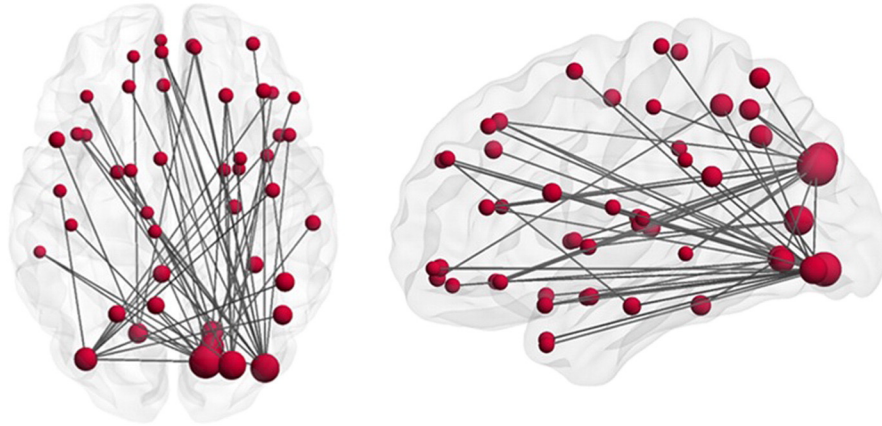
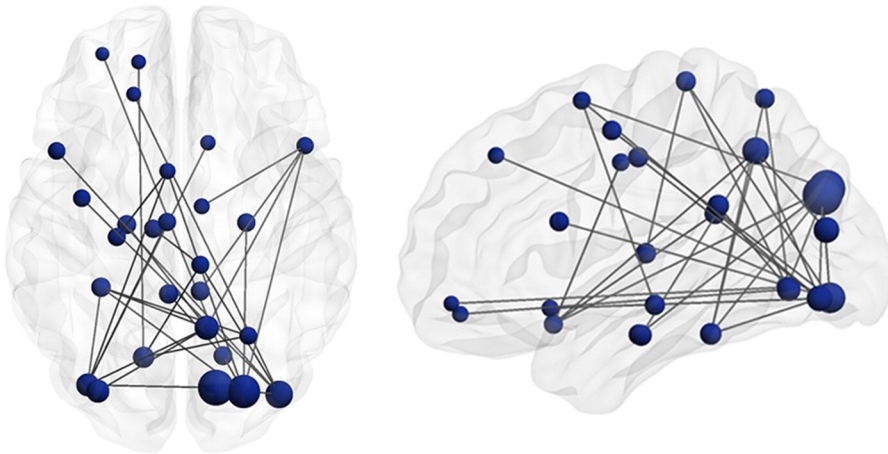
A) Controls: Active > Baseline (Animal Shapes)**B) Controls: Active > Baseline (Nonanimal Shapes)**

Fig. 3. A) Increased beta band connectivity in control participants during processing of the animal shapes. Lines represent the connections among regions that comprise the network of statistically significant increases in synchrony above baseline, and the size of each sphere denotes task-dependent increases in connectivity strength, calculated across all 90 analysed regions. B) Increased beta connectivity in controls during processing of the non-animal shapes. Note that in both stimulus pattern the dominant pattern of connectivity suggests communication between visual cortical regions and other, widespread brain areas.

in both conditions right, but not left, occipital lobe showed high connectivity to frontal regions. For controls only while viewing meaningful animal stimuli, the network of significantly increased connectivity encompassed connections from inferior occipital regions to both amygdalae (implicated in processing of social cues).

For the ASD group, task-dependent connectivity increases were found only for theta ($p < 0.001$ for animal and non-animal) and alpha (animal: $p < 0.004$; non-animal: $p < 0.002$) frequency bands, peaking around 100 ms poststimulus (during presentation of both stimulus types). For this group no significant task-dependent connectivity changes were found for the beta band (Table 1). ASD participants showed increased theta connectivity with disorganized patterns during presentation of meaningful animal stimuli. Task-dependent connectivity increases were widely spread and involved a large number of connections to occipital regions. Similar connectivity dynamics were observed during non-animal stimulus processing. Right occipital areas appeared more functionally connected than left occipital areas and increased connectivity from right parietal to temporal and frontal regions was observed. In the alpha band, only few connections from left visual to bilateral parietal showed increased synchronization during processing of animal stimuli. Similar patterns were found for the non-animal condition with additional slight increases in connectivity strength for left temporal and frontal regions. In summary, we found modulations in

beta band connectivity across experimental conditions in controls but not in ASD group.

3.2.2. Reduced beta band synchronization in ASD

To compare connectivity dynamics between ASD and typically developed participants during stimulus processing, mean PLI in 65–140 ms active intervals, contrasted with $-75-0$ ms baseline windows were compared between groups. Patterns of task-dependent synchrony appeared clearly organized in controls, while connectivity in ASD participants appeared more diffuse and disorganized (see Fig. 2B). Compared to controls, participants with ASD showed significantly reduced inter-regional phase-locking in the beta frequency band during meaningful animal stimuli presentation ($p = 0.045$; Fig. 4, Table 2). This network of reduced connectivity included occipital areas, showing reduced task-dependent beta connectivity to frontal (including orbitofrontal cortex), parietal and temporal areas (including right hippocampus and rolandic operculum). Interestingly, group differences in functional connectivity involving frontal areas incorporated connections with right but not left occipital nodes. Left occipital areas showed decreased beta connectivity exclusively to right occipital and right parietal areas. No latency differences were observed between groups. No significant group differences were found for the non-animal (i.e. non-meaningful shapes) trials. No significant group

Control > ASD (animal shapes)

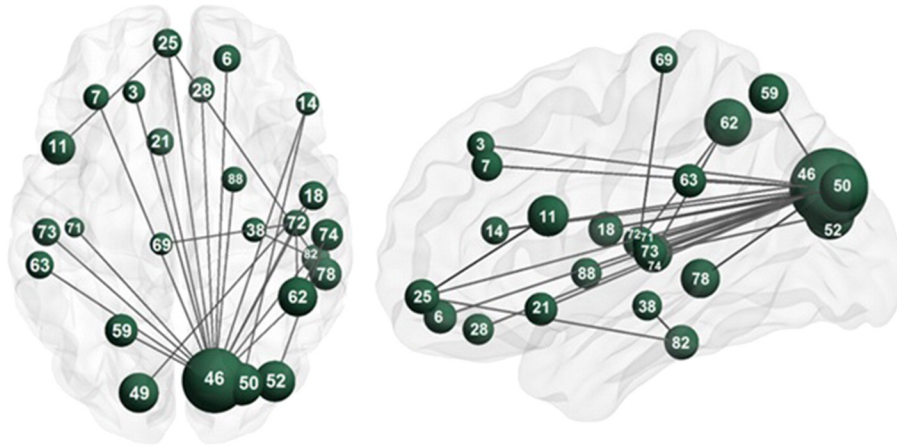


Fig. 4. Reduced beta band connectivity during number estimation in participants with ASD. Each line indicates significant reductions in task-dependent network synchronization, relative to controls. The size of each region expressing one or more significant reductions in connectivity reflects the strength of between-group connectivity differences, within the significantly differentially connected component. Numbering of nodes corresponds to region names according to the AAL atlas (see Supplementary material). Note the scaling of node size differs from that in Fig. 4 due to differences in the magnitude of overall task effects, in contrast to group differences (see Fig. 2). See Supplementary material for region names corresponding to numbers.

differences were observed for either trial type or for any other analysed frequency range.

4.0. Discussion

We present the first findings of task-dependent neuromagnetic increases in inter-regional connectivity in theta, alpha and beta band connectivity during the performance of a numerosity estimation task. Task-dependent modulation of beta band connectivity was found in the control, but not in the ASD group and the pattern of beta connectivity during performance of the task appeared more disorganized in participants with ASD, relative to controls. Importantly, this rapid

synchronization was reduced in the ASD group only during the processing of coherent, meaningful dot patterns, suggesting the relevance of this synchronization to the disrupted integrative processes in sensation and perception in ASD.

Task-dependent increases in inter-regional theta synchrony were observed for both groups 165–240 ms after stimulus presentation. Theta rhythms are thought to be critical for regulating oscillations across the cortex (Belluscio et al., 2012; Canolty and Knight, 2010; Doesburg et al., 2012a,b) and for representation and organization of multiple task-relevant items during sensory and memory processing (Lisman and Jensen, 2013). Our results are consistent with earlier findings of wide-spread task-induced increases in theta band connectivity appearing 150 ms after stimulus onset in ASD and normally developed populations (Doesburg et al., 2013).

Our findings also revealed task-dependent increases in long-range alpha frequency coupling during early number estimation. Several cognitive processes that are possibly relevant for numerosity estimation induce alpha oscillatory activity, e.g. mental imagery (Cooper et al., 2003; Hari et al., 1997; von Stein et al., 2000a), mental calculations, short-term memory retention and retrieval and maintenance of object representations in, and retention and retrieval from visual working memory (Klimesch, 1996; Palva et al., 2005; Palva and Palva, 2007; von Stein et al., 2000a). Local alpha synchrony (power) is understood to be relevant for sensory stimulus inhibition during tasks that require attention to internal cognitive processing (Jensen et al., 2002; Jensen and Mazaheri, 2010; Klimesch et al., 2000). Long-range synchronization in the alpha band, conversely, may be relevant for functional integration (see Palva and Palva, 2007; von Stein and Sarnthein, 2000b). For our control subjects, synchrony in alpha band frequencies appeared more widespread for animal stimuli (compared to non-animal) and were strongly connected in the orbitofrontal cortex, which is responsible for sensory integration and processing of affective stimulus properties (Kringelbach et al., 2005). Task-based cognitive processing (e.g. mental imagery and retrieval of information from memory), possibly associated with the meaningfulness of the animal stimuli, might explain these findings. This is congruent with our behavioural findings of decreased performance during normative number estimation for meaningful stimuli (animal shapes).

Task-dependent increases in long-range beta band synchrony were found very early, at 70–145 ms after stimulus onset in the adult controls but not in individuals with ASD. Synchrony in the beta frequency band has consistently been found in long-range cortical interactions among

Table 2

List of connections from region A to region B, comprising the neural network showing statistically significantly reduced beta-band inter-regional phase-locking in ASD during presentation of animal stimuli.

Region A (AAL)	Region B (AAL)
46 Cuneus R	74 Sup temporal gyrus R 72 Heschl's gyrus R 78 Mid temporal gyrus R 73 Sup temporal gyrus L 71 Heschl's gyrus L 59 Sup parietal gyrus L 63 Supramarginal gyrus L 88 Pallidum R
11 Inf frontal operculum L 14 Inf frontal triangularis R	25 Med orbitofrontal gyrus L 49 Sup occipital R 46 Cuneus R
7 Mid frontal gyrus L 25 Mid orbitofrontal gyrus L	46 Cuneus R 82 Sup temporal R 46 Cuneus R
3 Sup frontal gyrus L 6 Sup orbitofrontal gyrus R 21 Olfactory L 38 Hippocampus R 52 Mid occipital gyrus R 69 Paracentral lobule L 62 Inf parietal lobule R	46 Cuneus R 46 Cuneus R 46 Cuneus R 82 Sup temporal gyrus R 82 Sup Temporal gyrus R 72 Heschl's gyrus R 72 Heschl's gyrus R 82 Sup temporal R
28 Rectus R 18 Rolandic operculum R	46 Cuneus R 46 Cuneus R 50 Sup occipital gyrus L

Note: R denotes right and L denotes left hemisphere. Inf–inferior, Sup–superior, Mid–middle. See Supplementary material for full region names.

distant brain regions (Donner and Siegel, 2011; Engel et al., 2001; Varela et al., 2001). Beta band synchrony is thought to be related to various cognitive functions potentially involved at early processing stages of number estimation: focused attention underlying stimulus selection (Buschman and Miller, 2007; Donner et al., 2007; Gross et al., 2004), perceptual grouping and feature binding (Uhlhaas et al., 2009b; Fries et al., 2001), top-down attention serving feature integration (Donner and Siegel, 2011), maintenance of visual cues in short term memory (Tallon-Baudry, 2004), and accumulation of sensory evidence for decision making (Donner et al., 2007; Siegel et al., 2011; Wang, 2008). Moreover, electrophysiological studies have provided evidence for rapid processing of visual stimuli indexed by event-related potentials (ERPs) over occipital regions (Batty and Taylor, 2002; Taylor and Khan, 2000; Van Voorhis and Hillyard, 1977). Normative numerosity estimation based on visual cues requires numerical mental representations (Fink et al., 2001; Meaux et al., 2014; Santens et al., 2010) which can occur at early processing stages (Kadosh et al., 2007; Koten et al., 2011) and MEG and EEG studies have shown that the perception of Gestalt (integration of local elements into a global shape) can occur very early, within the N1 time range. The first visual processing stage affected by global/local perception occurs just before 100 ms (Han et al., 1997, 2000; Heinze et al., 1998; Tanskanen et al., 2008; Yamaguchi et al., 2000). Estimation of quantity may occur as early as 200 ms in parietal, temporal and frontal regions (Hyde and Spelke, 2009; Libertus et al., 2007; Meaux et al., 2014; Nan et al., 2006; Pagano and Mazza, 2012).

Our results regarding normative number estimation reveal early task-related neural network connectivity which shows strong involvement of right temporal regions which may be relevant for rapid processing of dot patterns and their integration into meaningful animal shapes. Processing of randomly shaped stimuli not conveying a global meaning, however, elicited an asymmetric network of beta connectivity (with fewer right temporal regions showing connectivity above the threshold). These results are in agreement with findings of higher right (tempo-parietal) activation for a global interpretation style (Gestalt perception) and with leftward lateralization for local processing styles of visual information (Fink et al., 1997, 2001; Flevaris et al., 2010; Huberle and Karnath, 2012; Robertson and Lamb, 1991, 1988; Volberg et al., 2009; Weissman and Woldorff, 2005; Yovel et al., 2001). Moreover, right unilateral temporal lobe damage is associated with impaired feature integration relevant for recognition of familiar faces (prospagnosia; Evans et al., 1995; Mayer et al., 2007). Earlier MEG findings show involvement of right temporal regions in early (120–220 ms) processing of meaningfully shaped dot patterns, but not randomly shaped stimuli, during number estimation. Thus, if dot patterns convey a global meaning, early integration of several distinct objects at the global level may occur (Meaux et al., 2014). As it is the case for all statistical thresholds, in interpreting the results one should keep in mind that effects that are just below the threshold may not differ greatly from some effects that pass thresholds.

Modulations of task-induced beta connectivity in fronto-occipital connections were observed very early, from 70 to 145 ms. These involved a more spatially extended network when meaningful (animal) stimuli were processed, encompassing the lingual gyrus, cuneus, amygdala, parahippocampus, fusiform and insula of the right hemisphere and with parietal regions. Early integration of stimulus features to meaningful animal shapes would recruit different cognitive resources and therefore explain reduced behavioural performance when coherent, globally meaningful stimuli were presented to typically developed controls. This is consistent with our findings of reduced beta connectivity in ASD in a widespread cortical network including orbitofrontal cortex and hippocampus. Quick recognition of stimulus patterns (e.g. face perception) have been crucial for human survival and our findings highlight the flexibility of rapid processing of single stimulus elements in meaningful contexts. Findings of early task-dependent interregional neuronal communication suggests rapid feature integration (Tallon-Baudry et al., 2008) and are consistent with the view that cognitive deficits in ASD

may originate from problems with integrative processes beginning at the sensory level (APA, 2013).

Compared to controls, the ASD group showed decreased connectivity in a network encompassing early visual processing areas (right cuneus) being connected to areas typically involved in spatial attention (superior parietal gyrus) (see Table 1). Additionally, for the controls processing of animal stimuli elicited a neuronal network that included stronger connectivity between the superior parietal gyrus (spatial attention) and the inferior occipital lobule (associated with visual object and face perception; Gainotti and Marra, 2011; Martin et al., 1996). Moreover, the precuneus, as part of the superior parietal lobule, is involved in directing attention in space (Cavanna and Trimble, 2006; Simon et al., 2002) and showed task-based activity linked with occipital regions for both, animal perception and non-animal perception.

Considered together, these findings suggest that typical visual stimulus evaluation involves early processing components (possibly related to attention to social stimuli and top down modulation of attention by visual working memory) that are impaired in autism and might result in different processing strategies (local over global processing). Task-dependent modulations in beta band connectivity were not found in the ASD group and their task-related connectivity pattern appeared much more disorganized. Meaux et al. (2014) found atypical activity in visual areas in the early phase (80–120 ms) and in temporal regions (120–290 ms) of numerosity processing in ASD patients for stimuli that allowed meaningful global pattern integration, suggesting atypical global stimulus processing in ASD. Our behavioural results show that while ASD participant's abilities to estimate numerosity were not affected by the global meaningfulness of dot patterns control subjects performed less accurately for animal shapes than non-animal shape patterns. Overall task accuracy however did not differ between groups. This suggests that observed differences in connectivity patterns were not caused by differences in performance, but rather were due to differences in cognitive strategies across participants. Reduced long-range task-dependent connectivity has been found in ASD in combination with no group differences in behaviour (Doesburg et al., 2013). These findings suggest that despite impaired connectivity in ASD, normative behavioural performance can be achieved by compensatory use of different brain networks (resulting in different connectivity patterns). Also, while controls showed early modulations of MEG signals by the animal shapes in temporal areas, this effect was not found in ASD participants, suggesting an involvement of temporal cortices in local/global perception during numerosity processing and possible impairment in autism.

In this study reduced beta band synchrony was primarily observed in occipitofrontal, occipitotemporal and occipitoparietal connections with a rightward lateralization of decreased connectivity for the ASD group. Structural, as well as functional abnormalities during a wide variety of tasks have been reported in primary visual brain areas in ASD (Amaral et al., 2008; Batty et al., 2011; Hyde et al., 2010; Jemel et al., 2010; Vandenbroucke et al., 2008). In line with this hemispheric asymmetry in neural connectivity (Fiebelkorn et al., 2013; Gabard-Durnam et al., 2013; Sutton et al., 2005), underconnectivity between the cerebral hemispheres (Casanova et al., 2011; Just et al., 2007; Piven et al., 1997), and early (120–180 ms) decreases in right temporal activity during processing of stimuli with a global meaning compared in a numerosity task have been found for ASD participants (Meaux et al., 2014). Taken together, current findings suggest reduced communication among brain regions in ASD, combined with atypical hemispheric specialization, as a reason for a processing bias of local over global stimulus properties (Fiebelkorn et al., 2013).

Some of the sources implicated in network synchronization effects involve deep structures. Discussion surrounding signal detectability from deep sources using MEG continues in the literature. Increasing evidence, however, supports the view that MEG is able to detect even weak signals from various deep brain structures (Cornwell et al., 2008a,b) including the hippocampus (Hamada et al., 2004; Kirsh et al.,

2003), the amygdala (Hung et al., 2010; Luo et al., 2007) and the thalamus (Bardouille and Ross, 2008; Bish et al., 2004). Recent studies using realistic simulations (Attal and Schwartz, 2013; Balderston et al., 2013) – including those focusing on CTF MEG systems such as the one used in our study (Mills et al., 2012; Quraan et al., 2011) – have indicated that MEG is indeed able to detect activity originating from deep gray matter structures. For this reason, together with the relevance of deep sources for cognition and altered brain function in ASD, we feel that the potential knowledge gained by imaging connectivity involving deep sources outweighs the disadvantages associated with continued uncertainty surrounding MEG and deep sources.

In summary, our results provide additional evidence for the functional relevance of neuronal synchronization across distant regions. This study is the first to show significantly reduced long-range beta band synchrony in ASD during the performance of a number estimation task. Our findings support the hypothesis that individuals with ASD have atypical long-range coordination of neural activity. These results are relevant for current theories regarding ASD, which emphasize that core aspects of the disorder may result from functional underconnectivity among distant brain regions and fewer long-range interactions (Belmonte and Bourgeron, 2006; Müller et al., 2011; Uhlhaas and Singer, 2006). The present study provides the first evidence for reduced large-scale beta band neuronal synchronization during a number estimation task in adults with ASD. This altered connectivity included several occipito-frontal, occipito-temporal and occipito-parietal connections, suggesting that coordination among task-relevant brain regions in ASD is less effective. Reduced ability to recruit beta band synchronization in large-scale networks may contribute to cognitive difficulties prevalent in ASD. Our results add to the growing body of literature indicating atypical oscillatory coherence in brain networks is associated with cognitive difficulties in neurodevelopmental disorders.

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Appendix A. Supplementary data

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