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Decreased brain coordinated activity in autism spectrum disorders during executive tasks: Reduced long-range synchronization in the fronto-parietal networks

J.L. Perez Velazquez [a,b,*], F. Barcelo [c], Y. Hung [a], Y. Leshchenko [a], V. Nenadovic [a], J. Belkas [a], V. Raghavan [a], J. Brian [d], L. Garcia Dominguez [a]

[a] Brain and Behaviour Centre, Neurosciences & Mental Health Programme, Division of Neurology, Hospital for Sick Children, Toronto, Canada M5G1X8
[b] Department of Paediatrics and Institute of Medical Science, University of Toronto, Toronto, Canada M5G1X8
[c] Department of Psychology, Universidad de las Islas Baleares, 07122 Palma de Mallorca, Spain
[d] Autism Research Unit, Hospital for Sick Children and Bloorview Research Institute, Toronto, Canada

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ABSTRACT

Current theories of brain function propose that the coordinated integration of transient activity patterns in distinct brain regions is the essence of brain information processing. The behavioural manifestations of individuals with autism spectrum disorders (ASD) suggest that their brains have a different style of information processing. Specifically, a current trend is to invoke functional disconnection in the brains of individuals with ASD as a possible explanation for some atypicalities in the behaviour of these individuals. Our observations indicate that the coordinated activity in brains of children with autism is lower than that found in control participants. Disruption of long-range phase synchronization among frontal, parietal and occipital areas was found, derived from magnetoencephalographic (MEG) recordings, in high-functioning children with ASD during the performance of executive function tasks and was associated with impaired execution, while enhanced long-range brain synchronization was observed in control children. Specifically, a more significant prefrontal synchronization was found in control participants during task performance. In addition, a robust enhancement in synchrony was observed in the parietal cortex of children with ASD relative to controls, which may be related to parietal lobe abnormalities detected in these individuals. These results, using synchronization analysis of brain electrical signals, provide support for the contention that brains of individuals with autism may not be as functionally connected as that of the controls, and may suggest some therapeutic interventions to improve information processing in specific brain areas, particularly prefrontal cortices.

1. Introduction

Autism and related disorders (autism spectrum disorders; ASD) are accompanied by different brain information processing, often reflected in the behavioural features of individuals with ASD. Current brain theories propose that the coordinated integration of transient activity patterns in distinct brain regions is essential for information processing (von der Malsburg, 1981; Varela et al., 2001). Brock et al. (2002) suggested that there could be a temporal binding deficit in autism. Considering that widespread activation of brain areas is thought to give rise to conscious processing, a modification of the old idea advanced by the Russian psychologist Luria that the dynamic interplay between brain areas is crucial for brain function, it is conceivable to hypothesise that the synchronization patterns in individuals with autism during performance of specific tasks will differ from those in control participants.

The Austrian psychiatrist Kanner (1943) originally described information processing in autism as "the inability to experience wholes without full attention to the constituent parts". Studies have suggested that some behavioural characteristics in autism may be reflected in a bias towards local, rather than global, processing (Frith, 1989). This has been termed the "weak central coherence" (WCC) theory, where individuals with autism show detail-focused processing, rather than perceiving global configurations (Frith, 1989; Frith and Happe, 1994; Happe and Frith, 2006). We consider this a different style of information processing rather than a deficit *per se* (Hill, 2004). The WCC hypothesis could then be reflected in decreased global versus enhanced local synchrony patterns in electrophysiological brain recordings. Proposals of disruption of coordinated timing in neuronal activity in autism have been recently advanced (Herbert, 2005), along with the possibility of reduced brain synchronization (Welsh et al., 2005; Wickelgren, 2005; Uhlhaas and Singer, 2007). Recent neuroimaging evidence supports the concept of reduced

* Corresponding author. Neurosciences & Mental Health Programme, 555 University Avenue, Toronto, Ontario, Canada M5G1X8.
E-mail address: jose-luis.perez-velazquez@sickkids.ca (J.L. Perez Velazquez).

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functional connectivity in autism (Ring et al., 1999; Just et al., 2004; Villalobos et al., 2005; Cherkassky et al., 2006; Kana et al., 2007). These observations, together with functional magnetic resonance and similar methods, provide indications of correlated activation amongst brain areas. However, a more direct approach to assessing functional connectivity is facilitated by electrophysiological recordings that have greater time resolution thus allowing for the study of transient brain synchronization patterns. Only one study using electroencephalographic recordings showed a decreased coherence in the resting state in participants with autism (Murias et al., 2007).

Using magnetoencephalographic (MEG) recordings, we focus on the study of the collective, global dynamics of brain function in order to gain insight into cognitive processes. We study here phase synchrony between MEG signals that allows for a dynamic examination of the transient coordinated activity in cortical circuits. In particular, phase relations in cellular activity are fundamental for neuronal integration of information. We examined whether brains of individuals with ASD show different synchronization patterns from those of control participants, during cognitive task performance. We propose that the differences in information processing in the brains of children with ASD will be reflected in different patterns of coordinated brain activity. Considering that it is well established that individuals with autism express impaired executive functions (in at least some, if not all, domains of executive functions), we chose two tasks that demand operational executive functions that are related to mental flexibility and cognitive inhibition (Ozonoff and Jensen, 1999; Hill, 2004). We focused on three main cortical areas: frontal, parietal and occipital cortex, considering that neuroimaging studies indicate that parieto-frontal cortices compute sensorimotor transformations (Binkofski et al., 1999). Our results suggest that children with ASD lack the long-range, fronto-parietal coordinated activity that is observed in control children thus supporting current concepts of underconnectivity in the brains of individuals with autism.

2. Materials and methods

2.1. Participants

Sixteen control children (7 females) and 15 children (1 female) with high-functioning autism (Asperger syndrome) participated in the study. Control children without any known neurological disorder were recruited from the community. Due to our clinical staff time limitations, we could not screen control participants, and so we had to rely on the parent's information. The children's parents provided informed consent for the protocol approved by the Hospital for Sick Children Research Ethics Board. Age range was between 7 and 16 years, averages 10.8 ± 3.4 (ASD group) and 11.1 ± 2.6 (controls). Participants met the criteria for ASD based on DSM-IV. Patients were evaluated by the psychologists in our Autism Research Unit or were recruited from the Geneva Centre for Autism and Autism Ontario. Cognitive abilities were measured using the Wechsler Abbreviated Scale of Intelligence (WASI, PsychCorp, 1999). The lowest IQ was 88, with mean of 111.2 ± 15 for the ASD group, and 123 ± 8 for the control group ($p = 0.012$ comparing broth group values, Student t-test). The averages for their verbal IQs were 119.9 ± 8.8 for the control group, and 119.1 ± 8.4 for the ASD group (difference is not statistically significant).

2.2. Magnetoencephalographic recordings

MEG recordings were acquired at 625 Hz sampling rate, DC-100 Hz bandpass, third-order spatial gradient noise cancellation using a CTF Omega 151 channel whole head system (CTF Systems Inc., Port Coquitlam, Canada). Subjects were tested supine inside the magnetically shielded room. The head position relative to the MEG sensors in the helmet was recorded at the start and end of each recording session.

2.3. Executive function tasks

2.3.1. Card sorting task (CST)

We used a computerized card sorting task that measures cognitive flexibility related to frontal lobe functions, in which participants sort different symbols by a specific feature (colour or shape of the symbol). For the purposes of this study, participants were asked to match a target with a reference symbol by their colour or shape. A cue was given indicating whether the rule was to be repeated or changed. Once participants learned the rule, they were required to sort the target by a different rule (by a 'switch' cue). Presentation of the target with a reference symbol was shown to the subject via a video projector and remained on the screen until a response was made or a maximum time of 500 ms, followed by a cue presented for 300 ms. Cue-target interval varied randomly between 1500 ms and 1600 ms. Participants responded using their right and left index fingers indicating the colour or the shape that was matched between the target and reference symbol. Stimuli remained on the screen until a response was given, or else, up to a time limit of 500 ms. Feedback was given in text following each response. Total trials of 100 were recorded within one block, with average task duration time of 8 min (cf., Barcelo et al., 2008).

2.3.2. Stroop colour-word test

The colour Stroop interference paradigm is a commonly used test of inhibition (Stroop, 1935), in which the participant names the colours of the ink in which words are written. It consists of a list of colour words written in congruent colour (e.g., the word "green" written in green colour), and follows with a list in incongruent colour (e.g., the word "green" written in red colour). It is well established that processing the content of the word is more automatic than processing the colour of the word. Therefore, in the incongruent condition, the individual needs to inhibit the response of word naming that competes with the response of colour naming. In our experimental MEG set-up, words were presented to participants via a video projector, and the children's responses were monitored on-line to check for errors. Besides the congruent and incongruent conditions, we also conducted a baseline condition (termed Black-ink in this study) in which participants named the colour words written in black ink, where interference effects were expected to be much lower or absent. Ninety four words were presented for each condition (Black-ink, Congruent-ink, and Incongruent-ink), the time interval between words was 2.5 s.

2.4. Phase synchronization analysis

Visual inspection of the MEG recordings was done during the acquisition and off-line before the analysis, to remove (or repeat the acquisition) segments with artefacts. Recordings were initially band-passed using a FIRLCS filter (Rosenblum et al., 1996) with a band-pass of ± 2 Hz around a "central frequency". In this study, we used four central frequencies, 10, 18, 26 and 32 Hz, thus covering the range 8 to 34 Hz. The reason to choose these frequency bands is that they cover most of the ranges from alpha to lower gamma that have been attributed one way or another to cognition. In addition, due to some limitations with the extraction of the phase using the Hilbert transform and considering our acquisition rate of 625 Hz, phase synchrony was not assessed past 34 Hz. This is due to the recommendation to have about 20 points per characteristic period of the oscillation (see page 367 in Pikovsky et al. (2001)). This band-pass filtering done before the extraction of the oscillation phase removes eye blink artefacts (which appear only in frontal sensors) because these last around 300–400 ms, which is ~2.5–3.3 Hz in terms of frequencies. Since in our study the lowest frequency studied is 10 ± 2 Hz, we can consider that eye blinks are not affecting our results.

On these band-passed signals, the Hilbert Transform was applied and successive values of instantaneous phases were derived from the corresponding analytic signal. These phase series were then analysed

using sliding windows of 1 s. In each window the analysis consisted of extracting the Mean Phase Coherence Statistic as described in reference (Mormann et al., 2000). Briefly, we use the analytic signal approach, employing the Hilbert transform to estimate instantaneous phases and calculate phase locking between two MEG recording channels (sensors), as previously described (Garcia Dominguez et al., 2005, 2007). With noisy data, phase synchronization is defined in a statistical sense: two signals are phase synchronized if the difference between their phases is bounded over a selected time window, that is, if it clusters around a single value (Pikovsky et al., 2001). A measure of this is the circular variance, CV, of the phase differences $\Delta\theta(t)$, or alternatively, the coefficient $R = 1 - CV$, which can also be expressed as:

$$R_{jk} = |\langle \exp\left(i\Delta\theta_{jk}(t)\right)\rangle|$$

Here $|\cdot|$ denotes the norm and $<\cdot>$ the mean value. $\Delta\theta_{jk}(t) = \theta_j(t) - \theta_k(t)$ are the series of phase differences between the analytic signals of series indexed by j and k (each index j and k refer to one signal, that is, one MEG sensor time series) over a given time window T. The value of R varies from 0 to 1, the higher the value the tighter the clustering of the phase differences $\Delta\theta$ about a single mean value; that is, the closer the R-value to 1 the more synchronized the signals.

To estimate the mean synchrony index in the behavioural tasks, averages of the values of the synchronization index R were computed from stimulus presentation to the moment near the individual's response, about 0.45–0.6 s after stimulus presentation in the Stroop task. For the card sorting task (CST), the interval chosen was between 0.6 and 0.7 s after stimulus presentation. The precise time to calculate the average varied slightly from individual to individual because the time to answer was variable and the average of the synchrony index was taken from the time of stimulus presentation to just before the subject's response. For this purpose, the minimum time for each response of the individual rather than the mean of each subject's distribution of reaction times was taken. All trials were used for the analysis, as aforementioned, these were 100 for the CST, and 282 (94×3 conditions) for the Stroop task. The synchronization baseline for the CST was taken to be the synchrony index values when participants were passively looking at presented words on the screen. The "baseline" for the synchrony analysis in the Stroop task was the initial list of words written in black ink. The MEG sensors used to analyse phase synchrony are depicted in Fig. 2. These correspond to five groups, located in the left frontal (LF), right frontal (RF), left parietal (LP), right parietal (RP) and occipital (O) cortices. The synchrony between any of these two regions was then compared, giving us 9 combinations: LF–RF, LF–RP, LF–LP, LF–O, RF–RP, RF–LP, RF–O, P–O, RP–LP, note that the parietal–occipital (P–O) synchrony was evaluated grouping the sensors in the right and left parietal areas. We chose these cortical areas for two main reasons. First, because parieto-frontal cortices compute sensorimotor transformations (Binkofski et al., 1999), and second, to avoid local spurious synchronization due to summation of signals in the MEG sensors (Garcia Dominguez et al., 2007). The average synchrony between any two areas was computed by measuring the synchrony of each signal in one group with all the signals in the other group. That is, for example to evaluate the LF–RF synchrony, the synchrony between signal LF11 and all the 7 signals on the right frontal side was computed, and the same was done for signal LF22, etc. An initial ANOVA test was followed by Student's t-tests that were used to compare synchrony indices between any two groups. To further examine how the synchrony indices could classify individuals within each group, linear discriminant analysis tests (Ripley, 1996) were performed as detailed in the Results section and Table 3.

The complex representation of R, that is $<\exp(i\alpha)>$, where the absolute value operation has been eliminated and $\Delta\theta(t)$ has been substituted by the single parameter α, can be used to provide additional information about the distribution of mean phase differences α. The parameter α is used here because it is the mean cluster phase, as opposed to the time series of phase differences $\Delta\theta(t)$. This parameter is likely to stay around the values of 0 and π whenever the synchronization is caused by volume conduction effects (Garcia Dominguez et al., 2007), or if there were a common source sending synchronous input to the two areas that are investigated. Since this parameter only conveys useful information at high synchronization (high values of R), we map its values using weighted histograms defined on the complex plane. Specifically, the data (the complex R values) were distributed over 20 bins. Inside each bin, instead of performing a raw counting of the number of points, we weighed the points by their corresponding R values and then normalized the result so that the total area sums up to one. The purpose of this weighting is to grant more importance to those α found within synchronized regimes. The results are graphs such as those shown in Fig. 4.

3. Results

3.1. Behavioural results

The evaluation of the performance on both tasks indicates that the participants with autism made more mistakes than the control group overall. In the card sorting task, ASD participants and controls differed significantly in their overall rates of incorrect responses ($29.7 \pm 23.8\%$ *vs* $13.2 \pm 8.5\%$, respectively; $F_{1,23} = 4.7$, $p < 0.04$). The group with ASD committed more perseverative errors than the controls (11.7 ± 8.5 *vs* 5.4 ± 3.8, respectively; $F_{1,23} = 5.1$, $p < 0.035$), and there was also a trend for a larger number of distractions in the ASD group (14.4 ± 11.5 *vs* 7.6 ± 5.5; $p < 0.09$). In the Stroop task, the ASD group committed more errors while naming the colour in the incongruent condition: average of 5 ± 4.8 errors versus 2.68 ± 2.5 errors in the control group, however the difference was not statistically significant ($p = 0.1$). We note that all our participants with ASD were able to read properly and did not present abnormalities in language processing.

3.2. Synchronization analyses during the two tasks within each group: long-range brain coordinated activity in control participants

To assess the brain synchronization characteristics during the performance of the tasks, we chose to focus on three main cortical areas: frontal, parietal and occipital cortices, considering that neuroimaging studies indicate that parieto-frontal cortices compute sensorimotor transformations (Binkofski et al., 1999). These areas are depicted in Fig. 2. Initially, we studied the phase synchrony patterns in the control group, to determine whether some patterns correlated with task performance and to assess possible gender, age, or IQ-derived differences in these patterns. We looked not only at significant increases in synchronization but also at significant desynchronization. While no IQ or age-related synchrony alterations were detected, a gender-specific pattern was noted in the control group, as described below. In the Stroop task, a significant increase in synchrony was noted amongst most of the areas studied in this control group, which correlated with the naming of the colour in the incongruent condition. The baseline for the synchrony analysis in the Stroop task was the initial list of words written all in black ink. In particular, the synchrony between left and right prefrontal (LF–RF) cortex was the most statistically significant (represented in the schematic head of Fig. 2). The results are summarised as a bar graph in Fig. 1, and as a pictorial representation in Fig. 2 (there is no pictorial representation for the ASD group since no significant differences in synchrony were detected). Interestingly, the increase in prefrontal synchrony was observed in all but one control male and in only one of 6 control girls. The increase in synchrony occurred mostly at the frequency range between 16 and 34 Hz, while there was a tendency to desynchronize at 8–12 Hz (explained in Fig. 1A legend). The group with autism did

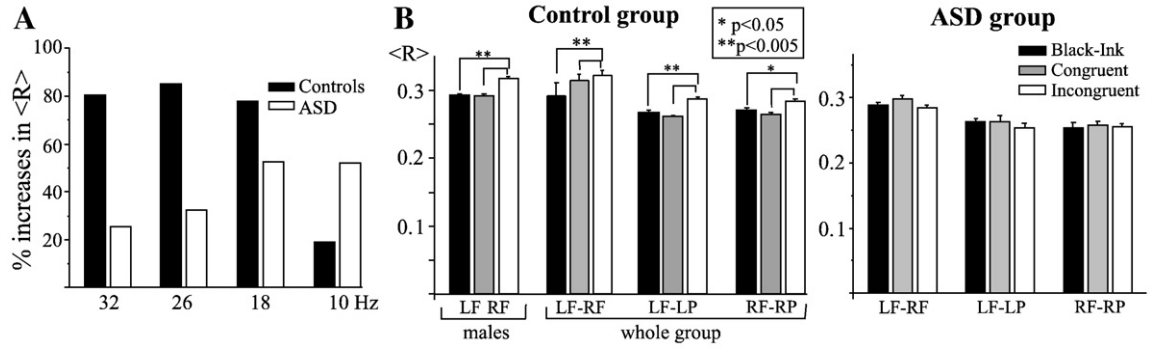

Fig. 1. Synchrony indices (*R*) observed during the performance of the Stroop task. A, the percentage of cases where the average *R* values significantly increased in the incongruent condition compared with the congruent or black-ink condition. The control children (black bars, both males and females) had more frequent increases in synchrony in the frequencies 18 to 32 Hz (central frequencies, as detailed in Materials and methods section: $f \pm 2$ Hz), while there was mostly desynchronization at 10 Hz: ~50% is expected if there was an equal increase–decreased synchronization pattern, hence, about 20% increases in *R* means there was an 80% significant decreases in *R* (desynchronization). Most of the significant changes in *R* values in the ASD group (white bars) were mostly decreases (desynchronization). B, Comparison of *R* values in controls and in the participants with ASD during the three conditions of the task. For clarity, three combinations of cortical areas are shown, left–right frontal (LF–RF, using either all members of the control group or only males), left frontal–left parietal (LF–LP), and right frontal–right parietal (RF–RP), at central frequency 26 Hz. Because girls tended to present less interfrontal synchrony, the *R* values are also presented within the male population only (bars labelled "males"). The pattern is the same for the other combination of areas, but some were not significant as shown in the complete representation of the synchrony in Fig. 2. While the synchronization increased during the incongruent condition (white bars) amongst the controls, no significant changes were detected in the participants with ASD (the same result was observed in the rest of the areas). *$p<0.05$, **$p<0.005$, Student's *t*-test was used to compare one condition with another.

not show any tendency towards synchronization (Fig. 1B, right graph). Indeed, as shown in Fig. 1A, most of the significant changes in synchrony were desynchronization.

In both control and autism groups combined, the significant changes (either increase or decrease) in synchrony was observed in 21.3% of cases when comparing the synchrony indices between the congruent or black versus the incongruent ink condition, but only in 12.7% of the cases in the comparison black and congruent ink (in random data distributions we would expect 5%). This is expected because the major differences should occur between the incongruent condition and the other two, as the black and congruent ink conditions are very similar (the only requirement being to read the word); it is in the incongruent condition when the effort to suppress reading the word is executed.

In the card sorting task, when children had to sort geometric figures as detailed in methods, elevated synchronization relative to baseline (in which participants watched words on the screen) was observed in the control participants in all areas except in the parietal–occipital (Fig. 3B), which could be due to the fact that parieto-occipital interactions may not be specifically recruited during the card sorting

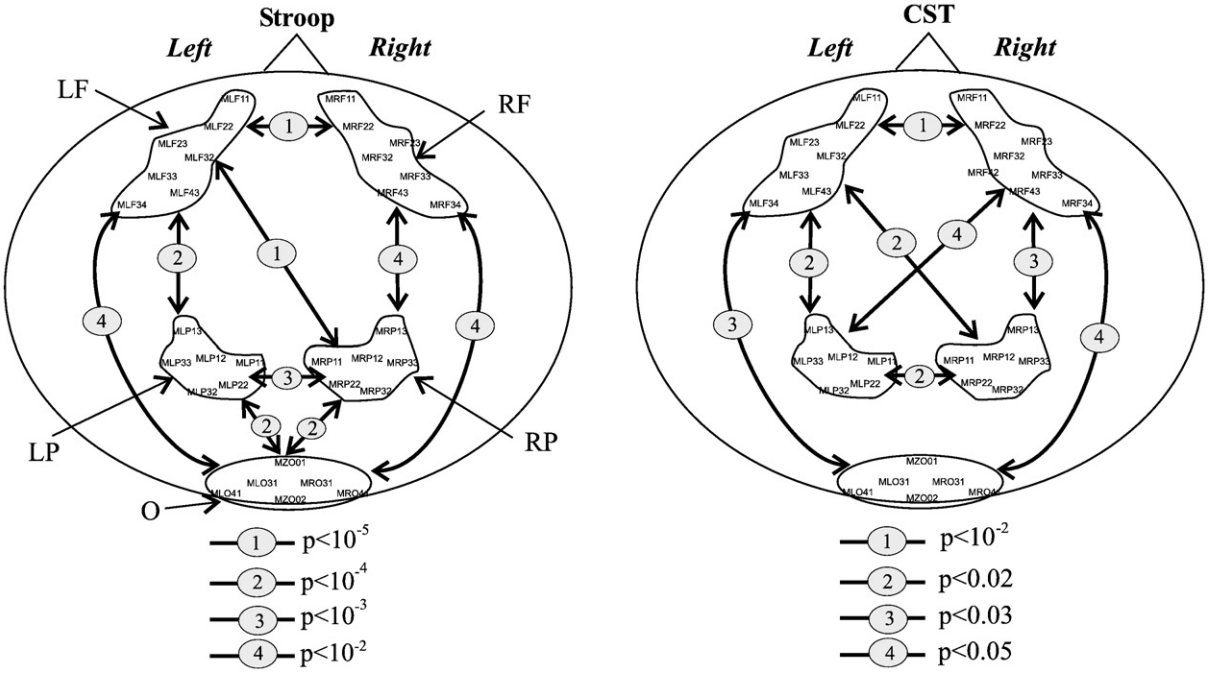

Fig. 2. Schematic representation of the synchronization amongst cortical areas in the control group (considering males and females), during the Stroop (left) and card sorting (CST) tasks, evaluated at 26 and 32 Hz. No pictorial representation for the ASD group can be shown because no significant differences in synchrony were detected. The circled areas show the MEG sensors that were taken for each group, on the left frontal (LF), right frontal (RF), left parietal (LP), right parietal (RP) and occipital (O) cortices. The arrows indicate instances where there was a significant increase in synchronization, comparing the incongruent-ink condition versus the black and congruent-ink conditions for the Stroop task, and comparing baseline versus task performance in the CST. The arrows are numbered according to the significance level. The highest was noted between left and right frontal lobes.

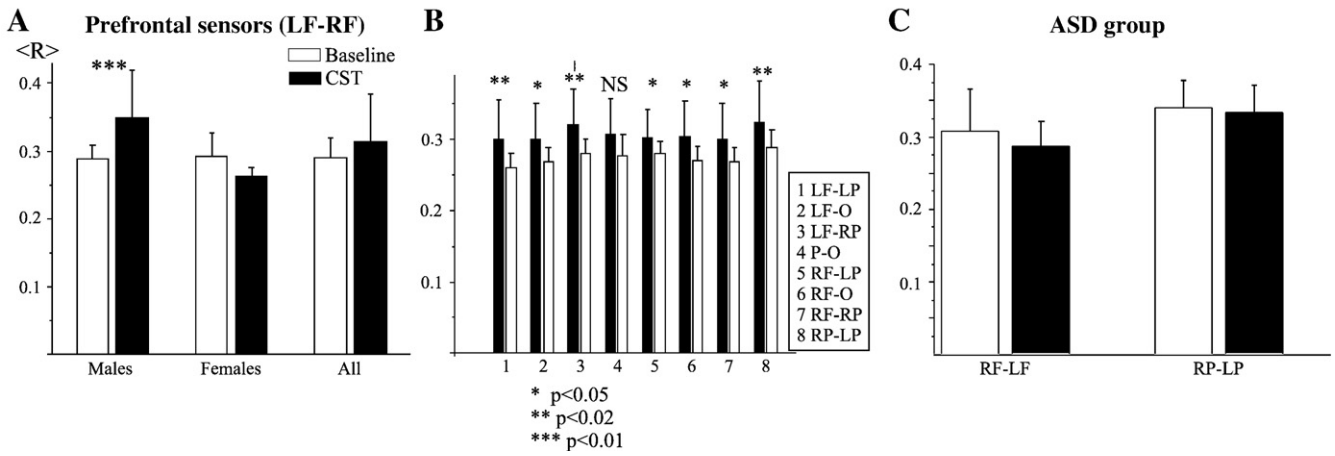

Fig. 3. Synchrony indices (R), computed at 26 and 32 Hz, observed during the card sorting task (CST) compared with baseline. A, average synchrony (<R>) between the left and right frontal lobes in control participants. Note the enhanced synchrony during task performance amongst males, but not in females. Grouping males and females together (bars labelled 'All') results in no significant differences (t-test was done between baseline and CST synchrony values in this case and in the graph in parts B and C). B, increase in R values is observed between all cortical areas chosen (those depicted in Fig. 2); the increase is not significant only in the parieto-occipital combination (P–O, bars number 4). C, In participants with ASD, the average R index does not increase during task performance. Two combinations are shown, right frontal–left frontal and right parietal–left parietal, and results are the same for the other 7 groupings.

task. As noted above in the case of the Stroop task, male control children had very significant enhanced prefrontal synchrony while performing the task, unlike the females (Fig. 3A). No significant increase in synchrony between any two areas was observed in the group with autism (Fig. 3C).

3.3. Group comparisons: lack of long-range synchronization in the ASD group

The main results comparing the synchrony indices (R) between the control and ASD groups are shown in Tables 1 and 2, which present the mean synchrony indices, at 26 and 32 Hz, in each group, for the three conditions in the Stroop task (Table 1) and in the card sorting task (Table 2). We focused on 26 and 32 Hz since those were the frequency ranges in which a more robust increase in phase synchrony was observed in the control group, as detailed in the previous section. The tables show the group comparisons using all children in each group, as well as using only the gender and IQ-matched comparisons ("Gender-IQ matched"). The results are the same, only more pronounced in the matched comparison. This is due to the lack of prefrontal synchronization in the females, thus removing girls from the comparison accentuates the difference amongst the boys. The total IQs were statistically different between groups (see Materials and methods section) because 4 participants in the ASD group had IQ<100; removing these four participants from the group comparison results in IQ averages of 123 ± 8 and 120.1 ± 8 ($p = 0.3$) for the control and ASD groups respectively. However, note that even when these four participants were used in the between-group comparison (Tables 1 and 2, "Complete groups"), the differences in synchronization were still significant, particularly in the incongruent condition for the Stroop task and in the CST task.

Amongst all comparisons that were significantly different, including nine combinations of groups at the four central frequencies in the three conditions (hence $9 \times 4 \times 3 = 108$ comparisons), the mean synchrony index (R) value in controls is larger than that of the ASD group in 52.8% of occasions (57 of 108 possibilities), while the mean R value in ASD group is only larger than the controls in 17.5% of cases (19 of 108 possibilities). The normally observed enhanced synchrony between right and left frontal cortex in the control males did not occur in most of the participants with ASD: there was increase in R values in only 2 of these participants at 26 Hz, and in 2 others at 10 Hz. Note in table 1 that the significance level of the group differences in the incongruent condition is higher (with lower p values), indicating that two groups are more differentiated by this condition associated with higher cognitive demand that requires more mental effort on the part of the participants as aforementioned in previous sections.

Table 2 shows the mean R values at central frequencies 26 and 32 Hz during the card sorting task performance. The control group had significantly higher synchrony in all but one situation: the intraparietal synchrony is higher in the ASD group at 26 Hz, as detailed in the next section. Thus, according to these results, we conclude that the patient group showed, in general, lower cortical synchronized activity than the control group in all tasks.

Linear discriminant analysis (Ripley, 1996) was performed to examine whether the mean values of synchronization indices (9 for each subject, corresponding to the nine group combinations detailed in Materials and methods section) were enough to correctly classify patients and controls within their own class. Table 3 shows the percentage of correct classification for each central frequency and condition in the Stroop task (black, congruent and incongruent ink). As shown, the best significant discrimination was found associated with the synchrony values in the incongruent condition, which could be expected as aforementioned. The classification was based on a leave-one-out cross-validation algorithm (Kohavi, 1995), that is, each single individual is classified using the others as the training data set.

3.4. High synchrony in the parietal cortex in the group with ASD

Elevated values of the synchrony indices were observed between MEG signals covering the right and left parietal cortices in the children with autism, but not in controls. The intraparietal synchrony is largest in 77.5% of possible cases in the ASD group, regardless of task performance, and only in 7.5% in the control group. However, this phenomenon may be age-dependent, because it was not observed in 3 of 6 of the 7–8 years old participants in the ASD group. Note, in Tables 1 and 2, that intraparietal synchrony indices (last row, RP–LP) are larger in the ASD group.

We noted that the mean phase differences amongst signals in the parietal cortex in the children with autism, in those who had high synchronization in this area, were concentrated around 0 degrees (Fig. 4). Since it has been demonstrated that this phenomenon (angles

Table 1
Average synchrony index values, at central frequencies 26 and 32 Hz (±2 Hz), during the Stroop task performance, in the control and ASD group.

	Black ink			Congruent ink			Incongruent ink		
	Control	ASD	*p*	Control	ASD	*p*	Control	ASD	*p*
Complete groups 26 Hz									
LF–LP	0.267	0.262		0.261	0.263		0.286	0.253	***
LF–O	0.270	0.261	*	0.265	0.262		0.283	0.262	***
LF–RP	0.284	0.263	***	0.284	0.263	***	0.304	0.259	***
P–O	0.281	0.281		0.279	0.285		0.298	0.291	
LF–RF	0.293	0.289		0.291	0.297		0.315	0.285	***
RF–LP	0.279	0.256	***	0.274	0.254	***	0.290	0.247	***
RF–O	0.276	0.256	***	0.266	0.259	*	0.283	0.257	***
RF–RP	0.269	0.254	***	0.265	0.258	*	0.283	0.256	***
RP–LP	0.289	0.347	***	0.287	0.349	***	0.305	0.352	***
Complete groups 32 Hz									
LF–LP	0.261	0.265		0.268	0.265		0.279	0.257	***
LF–O	0.264	0.260		0.266	0.260	*	0.277	0.253	***
LF–RP	0.279	0.268	**	0.287	0.265	***	0.302	0.260	***
P–O	0.269	0.280	***	0.276	0.277		0.283	0.278	
LF–RF	0.283	0.283		0.288	0.286		0.304	0.272	***
RF–LP	0.284	0.259	***	0.280	0.260	***	0.288	0.256	***
RF–O	0.274	0.269		0.274	0.264	**	0.283	0.260	***
RF–RP	0.264	0.261		0.267	0.262		0.276	0.252	***
RP–LP	0.282	0.326	***	0.287	0.325	***	0.296	0.321	***
Gender-IQ matched 26 Hz									
LF–LP	0.275	0.263	*	0.262	0.266		0.305	0.251	***
LF–O	0.271	0.262		0.267	0.266		0.298	0.260	***
LF–RP	0.291	0.266	***	0.286	0.269	***	0.321	0.257	***
P–O	0.299	0.288	*	0.291	0.292		0.325	0.291	***
LF–RF	0.288	0.288		0.289	0.297		0.33	0.283	***
RF–LP	0.280	0.251	***	0.271	0.250	***	0.298	0.242	***
RF–O	0.269	0.246	***	0.261	0.254		0.289	0.243	***
RF–RP	0.272	0.254	***	0.267	0.260		0.295	0.253	***
RP–LP	0.303	0.339	***	0.296	0.346	***	0.323	0.343	**
Gender-IQ matched 32 Hz									
LF–LP	0.264	0.276	*	0.275	0.276		0.298	0.261	***
LF–O	0.265	0.273		0.276	0.269		0.294	0.258	***
LF–RP	0.284	0.277		0.300	0.274	***	0.318	0.261	***
P–O	0.275	0.295	***	0.286	0.289		0.301	0.280	***
LF–RF	0.282	0.294	*	0.296	0.298		0.321	0.279	***
RF–LP	0.282	0.263	***	0.280	0.261	***	0.296	0.253	***
RF–O	0.273	0.269		0.274	0.264	*	0.293	0.253	***
RF–RP	0.266	0.270		0.272	0.270		0.29	0.253	***
RP–LP	0.289	0.331	***	0.293	0.333	***	0.306	0.321	*

In the "Complete groups" all participants were used, regardless of sex or IQ. In the "Gender-IQ matched" only males were used (since there were all males except for one in the ASD group). Note the ASD group has higher synchrony only in the case of parietal cortex (last row, RP–LP) regardless of condition. The columns labelled '*p*' denote the significance values comparing the two groups: $*p<0.05$, $**p<0.005$, $***p<0.0005$.

Table 2
Average synchrony index values, at central frequencies 26 and 32 Hz, during the card sorting task performance, in the control and ASD group.

	26 Hz			32 Hz		
	Control	ASD	*p*	Control	ASD	*p*
Complete groups						
LF–LP	0.304	0.268	**	0.311	0.266	**
LF–O	0.302	0.265	**	0.310	0.262	**
LF–RP	0.320	0.273	**	0.333	0.275	**
P–O	0.312	0.284	**	0.316	0.286	**
LF–RF	0.326	0.293	**	0.331	0.278	**
RF–LP	0.301	0.253	**	0.313	0.264	**
RF–O	0.299	0.266	**	0.313	0.270	**
RF–RP	0.299	0.266	**	0.316	0.262	**
RP–LP	0.322	0.342	*	0.339	0.320	*
Gender-IQ matched						
LF–LP	0.309	0.268	***	0.312	0.269	***
LF–O	0.301	0.265	***	0.309	0.266	***
LF–RP	0.323	0.274	***	0.331	0.278	***
P–O	0.311	0.283	***	0.313	0.279	***
LF–RF	0.323	0.284	***	0.328	0.279	***
RF–LP	0.299	0.253	***	0.310	0.268	***
RF–O	0.305	0.262	***	0.312	0.271	***
RF–RP	0.298	0.263	***	0.308	0.263	***
RP–LP	0.328	0.332		0.349	0.31	*

Same comparisons as in Table 1 ("Complete groups" and "Gender-IQ matched"). As in the cases shown in Table 1, higher synchrony occurs in the control group, except for the intraparietal (RP–LP) at 26±2 Hz. The columns labelled '*p*' denote the significance values comparing the two groups: $*p<0.005$, $**p<0.0005$.

around 0) could be due to summation of signals in the MEG sensors, particularly when a few high amplitude signals are present (Garcia Dominguez et al., 2007), we then examined the amplitude signals in the areas studied. After comparing the amplitudes of the MEG signals in frontal, temporal, occipital and parietal sensors not only were there no differences in the amplitudes, but also the signals in the parietal sensors had, normally, lower amplitudes than those of the others. To assess amplitude differences, the average of the maxima and their standard deviations in each time series was evaluated. In addition, considering that the chance of superposition is small if sensors are distant, it is unlikely that source superposition is taking place in our case. As expected, in the few young children who did not show the highest synchrony between the parietal cortices, the angles varied more (Fig. 4). If the elevated synchrony was due to direct intraparietal communication, we would expect to see angles different from 0, since there must be transmission delays between the right and left sensors we chose (depicted in Fig. 2). The angles around 0 strongly suggest that there is a common input that is arriving at the same time to all areas of the parietal cortex.

4. Discussion

We addressed the hypothesis that the patterns of coordinated activity, measured as phase synchronization, in the neocortex of autistic brains will be different from those found in control participants. The observations presented above indicate that children with autism do not express the increase in brain coordinated activity observed in control children during the performance of tasks that probe executive function, while they show higher intraparietal synchrony regardless of task operation. Since it is known that patients with autism are somehow impaired in executive functioning, we chose two tasks that demand operational executive functions and are considered tests of behavioural flexibility (Hill, 2004; Ozonoff and Jensen, 1999). In our analysis, we did not separate correct from incorrect responses, first, because in the control group there were few

Table 3
Percentage of correct classification (classifying children with ASD and controls within their own class) using linear discriminant analysis for each central frequency and condition in the Stroop task.

		Black ink	Congruent ink	Incongruent ink
10 Hz	ASD group	71	43	57
	Control group	43	43	71
18 Hz	ASD	57	71	100
	Control	100	71	100
26 Hz	ASD	57	71	100
	Control	57	71	100
32 Hz	ASD	57	71	100
	Control	86	57	71

The independent variables used in the classification were the nine *R* values resulting from the 9 comparisons between groups (see Materials and methods section for the nine groupings, or Tables 1 and 2). Values closer to 100 indicate a good separation between control and patients based on the aforementioned synchronization values for specific tasks and frequencies. Fifty is the expected percentage under a blind classification.

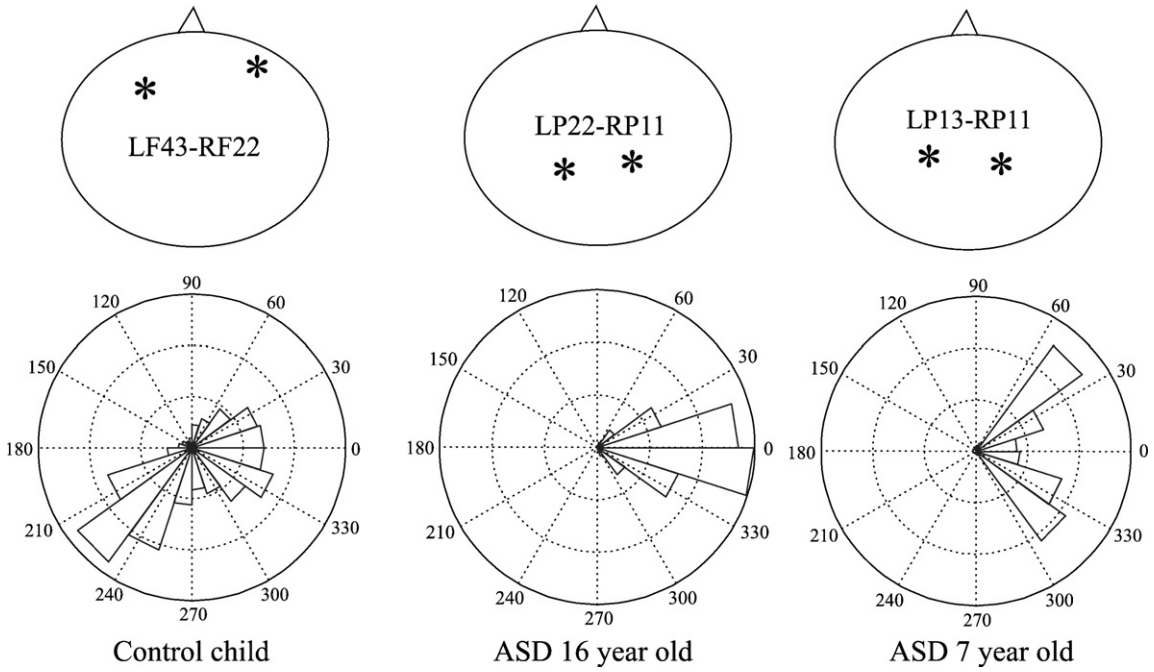

Fig. 4. Polar depictions of the phase difference angles observed in some interactions between right and left areas (evaluated at central frequency 26 Hz). The angles have been weighted with the *R* values, so that the angles associated with high synchrony are prominent in the graphs. The first graph shows those corresponding to a control child (between MEG sensors LF43 and RF22, located over the left and right frontal cortices, respectively), while the other two correspond to participants with ASD (between right and left parietal sensors). Note that the angles in the third graph, corresponding to a 7 year old child with ASD who did not show high intraparietal synchrony, are not clustered around 0, like those of the middle graph (from a 16 year old child with ASD and high intraparietal synchrony). Clustering around 0° could indicate either summation of signals at the MEG sensors due to high-amplitude signals, or that the two areas are receiving a common input from a third connected to both.

errors, and second because we are trying to address relative differences in information processing as described via phase synchronization statistics, therefore, the more the behavioural differences, the better for our purpose.

Within the context of current concepts in cognition, our results support the concept that transient dynamical states in specific neuronal networks contribute to information processing (Kelso, 1995; Friston, 2001; Varela et al., 2001; Baars et al., 2003; Lamme, 2003), and emphasize the importance of coordinated activity between separate cortical regions. We studied phase synchrony of MEG signals because this allows for a dynamic examination of the transient coordinated activity in cortical circuits. A shortcoming of MEG recordings is that we can only study cortical activity. However, linking this type of study to those using neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) that allows a full brain analysis of activity, can illuminate important features of brain cognitive processes despite the different time scales of the techniques. Thus, recent neuroimaging evidence supports the concept of reduced brain functional connectivity in patients with autism in visuomotor performance (Villalobos et al., 2005) and sentence comprehension (Just et al., 2004). More extensive task-related activations between frontal areas were detected in control participants but not in those with autism, in an fMRI study using the embedded figures task (Ring et al., 1999). Additionally, underconnectivity in inhibition networks of the frontal–parietal networks has been documented (Kana et al., 2007) as well as less connectivity in the baseline resting state cortical networks (Cherkassky et al., 2006; Murias et al., 2007). Similar studies of synchronization in other neurological conditions have found lower long distance interaction in fronto-temporal-parietal networks in Alzheimer's disease (Stam et al., 2006). Supporting our observations is another study with autistic patients that showed abnormalities in cortical activation sequences, thus suggesting differences in coordination dynamics, during imitation of facial expressions in autism (Nishitani et al., 2004). The neuroanatomical observations of smaller and more abundant minicolumns in autistic neocortices (Casanova et al., 2002), as well as local decreases of grey matter thickness (Abell et al., 1999), provide anatomical support for the idea of alterations in coordinated brain activity. Additional neuroanatomical findings in individuals with autism that may explain the observed disruption of long-range coordinated activity are the white matter enlargement in autism affecting cortico-cortical connections (Herbert et al., 2004) and a delayed maturation of frontal cortices (Zilbovicius et al., 1995). Parietal lobe abnormalities have also been noted: grey matter reduction (McAlonan et al., 2005), enlargement (Ashtari et al., 2007) or cortical volume loss (Courchesne et al., 1993). These abnormalities may explain the reason for the high intraparietal synchronization we noted in the group with ASD. However, noting that the phase difference angles were mostly centred around 0, we favour the suggestion that there is a common input to the parietal cortex from other cortical or subcortical areas, resulting in the high synchrony in this area. In this regard, it is important to note that MEG recordings, just like EEG, provide mostly synaptic activity, rather than cell firing. Hence, assessing synchronization in these types of recordings is studying the correlation between synaptic activities.

Considering the similar synchrony pattern (more specifically, lack of brain coherence in adult individuals with autism) during the resting state reported by Murias et al. (2007), we are tempted to conclude that the less brain coordinated activity in autism could be a general phenomenon, and not associated to one particular task, for it seems to be present already at rest. Hence, if we call “background activity”, or noise, the recordings performed at rest, then it can be said that we may be measuring the task-specific activity but perhaps superimposed on the background activity. This is in line with current views of task-specific event-related brain responses as transient perturbations of the “default state” of background EEG activity which cannot be simply regarded as “background noise” (Buzsaki and Draguhn, 2004).

The more significant enhanced prefrontal synchrony in controls during these tasks can be expected by considering the established role

of the frontal cortices in cognitive demands in general and in executive functions in particular (Duncan and Owen, 2000; Miller et al., 2001; Fuster, 2003), as well as by the neurological observations in patients with lesions of dorsolateral frontal cortex in that they show impaired performance in the Wisconsin Card Sorting task (Milner, 1963; Barcelo and Knight, 2002). This has been attributed, in part, to less attentional control exerted by prefrontal lobes in these pathologies (Stemme et al., 2007). Supporting previous observations obtained with amplitude analysis of MEG signals (Wang et al., 2001), we found an increased synchronization in fronto-parietal networks, in control children, during task performance. Those previous studies found increases in frontal activity 200–400 ms after stimulus presentation. Neuroimaging studies using PET and fMRI in the Stroop task demonstrate higher activation in fronto-parietal networks (Adleman et al., 2002), and particularly increased activity in the right prefrontal and bilateral parietal and occipital regions is common to many studies (see Fig. 3 in Peterson et al. (1999)). Reciprocal fronto-parietal connections, not only intra but also interhemispheric, have been anatomically described (Cavada and Goldman-Rakic, 1989), and neuroimaging evidence indicates that parieto-frontal cortices compute sensorimotor transformations (Binkofski et al., 1999). Thus, it is not surprising that there is an enhancement of synchrony amongst most of these areas in the performance of our tasks by the control participants. Disruption of prefrontal neural networks associated with errors in card sorting tasks has been detected using event-related potentials (Barcelo, 1999). One factor that may contribute, in part, to some of these observations is a difference in attentional processes, as attention is fundamental for these tasks and predominant activation has been noted in fronto-parietal regions (Lawrence et al., 2003).

With respect to our chosen tasks, it is well documented that individuals with autism show impairment in card sorting tasks, in general because they tend to persevere: they do not show the mental flexibility needed to adapt to the new rule and they persist using the old rule (Ozonoff and Jensen, 1999; Ozonoff, 1995). It is also known that patients with prefrontal cortex lesions persevere on sorting the cards by the initial rule. However, some studies have found no impairment in the Stroop colour word task in autism (Ozonoff and Jensen, 1999; Bryson, 1983). In our study, while the participants with ASD made more naming errors during the incongruent condition, the difference was not statistically significant. Although increasing the sample size may bring about significance, this is not fundamental for the interpretation of the results, as we are searching for biophysical differences underlying the cognitive effort. Regarding the WCC theory mentioned in the introduction, we should note that some psychological studies did not find support for the WCC concept (Brian and Bryson, 1996; Klin and Jones, 2006), and the universality of a local processing bias in autism continues to be debated (Behrmann et al., 2006). While the average IQ was lower in the ASD group, it should be considered that we are looking at the biophysical signatures of different style of information processing which will also be reflected in different IQs, and other possible results in other tests. Thus, in principle and for this type of study, IQ matching is not essential. In any case, no IQ-related changes in synchronization were noted in the control group.

We now address some limitations and shortcomings in our study, and in general in this type of research. First, the intrinsic variability in the subjects, starting with the distinct ages and behavioural dispositions, complicate matters when attempting to correlate biophysical signatures of brain activity with behavioural responses. Our study had a relatively wide age range, however age-related changes in synchrony correlated with the tasks were not found in the control group (since the ASD group had none to start with). Particularly, alpha frequencies are known to change with age, and perhaps if many more subjects were studied, at different ages, some subtle alterations in synchrony could be detected. However, the fact that alpha frequencies change the *power* with age does not necessarily mean that their *synchrony* is changed. Our main results, in any case, are reported at frequencies above alpha (26–32 Hz). The recording and analytical methods have also limitations, in that phase synchrony is estimated from the sensor space, rather than the neural sources. We, and others, are currently trying to improve the analysis by recovering the time series from the neural sources; some methods are about to be published (Amor et al., 2009). We use phase synchrony which is similar to the estimation of coherence with the important difference that coherence analysis does not distinguish between phase and amplitude dynamics. The fact that we obtained similar results as those of Murias et al. (2007) who used coherence, indicates that, while different, in general and for many applications, these analytical methods provide comparable information.

In summary, our observations highlight the distributed nature of cortical information processing in the performance of executive functions, and indicate that the brain coordination dynamics of individuals with ASD is different from that of a control population. Future studies using perceptual tasks, in which individuals with ASD perform differently, may reveal further intricacies of information processing of these individuals.

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