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Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism

Michele E. Villalobos[1], **Akiko Mizuno**[1], **Branelle C. Dahl**[1], **Nobuko Kemmotsu**[1], and **Ralph-Axel Müller**[1,2]

[1] Brain Development Imaging Laboratory, Department of Psychology, San Diego State University, San Diego, CA 92120

[2] Department of Cognitive Science, University of California, San Diego, CA 92093

Abstract

Some recent evidence has suggested abnormalities of the dorsal stream and possibly the mirror neuron system in autism, which may be responsible for impairments of joint attention, imitation, and secondarily for language delays. The current study investigates functional connectivity along the dorsal stream in autism, examining interregional blood oxygenation level dependent (BOLD) signal cross-correlation during visuomotor coordination. Eight high-functioning autistic men and 8 handedness and age-matched controls were included. Visually prompted button presses were performed with the preferred hand. For each subject, functional connectivity was computed in terms of BOLD signal correlation with the mean time series in bilateral visual area 17. Our hypothesis of reduced dorsal stream connectivity in autism was only in part confirmed. Functional connectivity with superior parietal areas was not significantly reduced. However, the autism group showed significantly reduced connectivity with bilateral inferior frontal area 44, which is compatible with the hypothesis of mirror neuron defects in autism. More generally, our findings suggest that dorsal stream connectivity in autism may not be fully functional.

Keywords

Autism; functional connectivity; dorsal stream; mirror neurons

Introduction

Functional connectivity MRI (fcMRI) is a technique for the *in vivo* examination of brain areas cooperating during rest or task performance. This technique is based on low-frequency interregional correlations in EEG as well as BOLD T2*-weighted MRI (Biswal, 1995; Koeda, 1995). Although, it cannot establish a causal relationship between brain regional activity, it can demonstrate interactions (Friston, 1996b). Connectivity between homologous regions of the right and left hemispheres has been shown, for example, in motor cortex (Jiang et al., 2004), visual cortex (Lowe, 1998), and auditory cortex (Cordes, 2000). Connectivity between regions with known functional relationships, such as Broca's and Wernicke's areas (Hampson, 2002), has also been demonstrated. The present study applied fcMRI procedures to assess interregional cooperation with primary visual cortex during visuomotor coordination in autism.

Corresponding Author: Ralph-Axel Müller, Ph.D., Department of Psychology, San Diego State University, 6363 Alvarado Ct., #225 E, San Diego, CA 92120-1863, Tel.: (619) 594-5276, Fax: (619) 594-8707, amueller@sciences.sdsu.edu, http://www.sci.sdsu.edu/~amueller/index.html.

Autism is a developmental disorder defined by sensorimotor, cognitive, and sociobehavioral characteristics, with onset before three years of age (Rapin and Katzman, 1998; Tager-Flusberg et al., 2001). Since first described by Kanner (1943), this syndrome has become increasingly prevalent (Charman, 2002), possibly due to changes in public awareness and diagnostic criteria. No single cause has yet been identified. Atypical brain development in autism is considered to be a consequence mostly of genetic factors (Folstein and Rosen-Sheidley, 2001), with additional environmental contributions (Trottier et al., 1999). Many brain regions of suspected abnormality have been reported (Akshoomoff, 2002), though with little consensus (Brambilla et al., 2003; Rumsey, 2000). Major brain structures implicated include frontal (Damasio, 1978; Zilbovicius, 1995), parietal (Courchesne, 1993), and mediotemporal regions (Bachevalier, 1994), as well as cerebellum, basal ganglia, brain stem, and limbic system (Courchesne, 1997; Hashimoto et al., 1995; Rodier, 2002).

Earliest signs of social and communicative impairments, as well as sensorimotor deficits may be detected by one year of age in infants later diagnosed with autism (Osterling, 1994; 2002), suggesting early emerging problems in brain systems that support socio-communicative development (Baron-Cohen, 1999a; b; Dawson, 1996). In addition, abnormalities in motor systems have been suggested as early markers for this disorder (Teitelbaum et al., 1998). Clinical motor impairments associated with anatomical abnormalities in cerebellar and parietal areas have been observed (Haas et al., 1996; Hallett et al., 1993). Functional MRI studies also provide evidence for abnormal motor networks, showing atypically distributed activation in cerebellar (Allen et al., 2004) and frontoparietal areas (Müller et al., 2001) during simple finger movement.

The premise for examining sensorimotor skills is that these provide building blocks for cognitive and social skills. Any deficits in sensorimotor skills may therefore play a potential role in disturbances of higher-order functional systems. Or in neurofunctional terms, defects in early developing brain networks may play a role in the organization of later developing neural systems (Elman et al., 1996).

Socio-communicative deficits are at the core of the autistic symptomatology. It has been argued that such abnormalities may arise from a deficit in the inability to understand the beliefs of others (i.e. ‘theory of mind’; Baron-Cohen et al., 1985). However, this deficit becomes apparent only around the fourth year of age, whereas other autistic signs become evident much earlier in life. This suggests explanations based on developmental precursors of ‘theory of mind’. Precursors may include imitation and the ability to engage in joint attention with others (Charman, 2003; Rogers et al., 2003). These functions are related to recent proposals pertaining to mirror neuron impairment in autism (Gallese, 2003; Williams et al., 2001).

Mirror neurons, which show increases in firing rate associated with internally generated action as well as with corresponding externally observed actions, have been identified in primate prefrontal cortex (area F5; Gallese, 1996; Rizzolatti, 1996). Area F5 in primates is a potential homologue to human area 44 in inferior frontal cortex (Petrides and Pandya, 1994; Von Bonin and Bailey, 1947), an area traditionally believed to be involved in language (Broca’s area). Human imaging studies have reported activation in area 44 during functions corresponding to those of the mirror neuron system, such as action observation and imagery (Binkofski et al., 2000; Buccino, 2001). It has been suggested that mirror neurons may serve as a bridge between higher visual processing, motor planning, and action knowledge (Rizzolatti, 2002). Thus, the mirror neuron system can be considered part of what has been traditionally described as the dorsal stream of visual processing (Ungerleider and Mishkin, 1982). As proposed by Williams and colleagues (2001), defects in the mirror neuron system may be responsible for impairments of imitation (Williams et al., 2004) and joint attention

(Charman, 2003) that are characteristic of autism. Imaging studies in healthy adults have shown that inferior frontal area 44, i.e. the presumed frontal site of mirror neurons, is crucially involved in imitation (Heiser et al., 2003; Iacoboni et al., 1999; Koski et al., 2003; Leslie et al., 2004). Impairments of imitation and joint attention in autism are especially important because they are suspected to contribute to language delay (Rogers et al., 2003).

There is substantial evidence that visual information is processed in two distinct cortical systems (dorsal and ventral streams; Ungerleider and Mishkin, 1982). Originally these two streams were assumed to process distinct types of visual information (spatial versus object vision). The dorsal stream (projecting into posterior and superior parietal cortex) has been related to stimulus motion and localization in visual space, whereas the ventral stream (projecting into the inferior temporal lobe) is in involved in form discrimination and object identification. However, animal and lesion evidence further suggests that the dorsal stream connects to frontal regions and that its functions go beyond the visuospatial ("where") and are instead crucial for visuomotor coordination ("how"; Goodale, 2000), constituting a system of "vision for action" (Goodale and Westwood, 2004).

Few autism studies have explicitly examined dorsal stream function. Spencer and colleagues found abnormally high motion coherence thresholds suggestive of dorsal stream impairment in autistic children (Spencer, 2000). Several fMRI studies (Allen and Courchesne, 2003; Belmonte and Yurgelun-Todd, 2003; Müller et al., 2001; 2003) have indicated abnormal activation patterns during visuomotor and visuospatial tasks in parietal regions of the dorsal stream. Visuospatial impairments have been shown to go along with parietal lobe volume reductions in some autistic individuals (Townsend and Courchesne, 1994; Townsend et al., 2001). Carper and colleagues (2002) also showed that both frontal and parietal white matter is significantly larger in autistic children compared to typically developing children. Postmortem studies on cellular integrity suggest an increase in frontal cortical neuronal density, which may reflect abnormalities in neuronal proliferation, migration and apoptosis in autism (Bailey et al., 1998). Executive impairments observed in several studies further support frontal dysfunction (Hill, 2004; Minshew et al., 1997).

Based on frontal and parietal abnormalities it is therefore reasonable to expect dysfunction of the dorsal stream and possibly the mirror neuron system in autism. The present study examines functional connectivity (i.e., interregional BOLD signal cross-correlation) during visuomotor coordination, with focus on the dorsal stream. Hemodynamic time series throughout the brain were cross-correlated with mean time series in area 17 (primary visual cortex), since in our experiment motor responses were driven by changing visual inputs. A corresponding study limited to activation analyses for visuomotor coordination in autistic individuals was previously published (Müller et al., 2003), showing enhanced variability of fronto-parietal activation loci and abnormal scatter of activation beyond normal premotor and superior parietal sites, invading inferior parietal and prefrontal areas. In the present study, we hypothesized that in autism functional connectivity with area 17 (the first cortical relay of visual stimuli driving motor responses) would be reduced along the dorsal stream, and specifically (a) in superior parietal regions, and (b) in inferior frontal cortex.

METHODS

Subjects

Eight male autistic patients, as defined by the Diagnostic and Statistical Manual of Mental Disorders (1994) and eight age and handedness-matched male controls were studied. Autistic subjects were screened for fragile X (as determined by DNA or chromosomal analyses), psychotropic medication, and history of seizures, seizure-like episodes, or any additional psychiatric or neurological disorders. The following measures were used as

diagnostic criteria: Diagnostic and Statistical Manual of Mental Disorders, the Childhood Autism Rating Scale (CARS; Schopler, 1980) and the Autism Diagnostic Interview-Revised (Lord, 1994). Each patient met all diagnostic criteria for autistic disorder, except for one subject who scored below cutoff on the CARS, but met criteria on the other measures (see Table 1). The Wechsler Adult Intelligence Scale-Revised and Wechsler Intelligence Scale for Children-Revised were used as measures of IQ. All autistic patients were nonretarded (i.e., full scale IQ > 70). Mean nonverbal IQ was in the normal range (92.3; range: 80–112). Control subjects were matched for age, sex and handedness. Two left-handed and one ambidextrous autistic subject were matched with left-handed controls. There were no significant differences in mean age within each group (control: 28.6 years [range 21–43]; autism: 28.1 years [range 15–39]; p=.90).

The Institutional Review Boards of the San Diego Children's Hospital Research Center and the University of California, San Diego approved the study. Written informed consent was obtained from each subject. The 15-year-old autistic patient gave written informed assent, with written consent obtained from a parent.

Magnetic Resonance Imaging

Images were acquired on a 1.5 T GE system using a custom-made head gradient coil. Sagittal and axial localizer scans ensured whole-head coverage and were used to select sagittal slices for echo-planar image (EPI) acquisition.

Manual shimming was performed for reduction of magnetic field inhomogeneities. EPIs were acquired with a single-shot gradient-recalled pulse sequence (interleaved slice acquisition; repetition time [TR] 2.5 sec; echo time [TE] 40 msec; flip angle 90°). The field of view [FOV] was 24 cm, and 19 sagittal slices were acquired with a thickness of 7 mm (1mm gap) and an in-plane resolution of 3.75 mm^2. The times series for each subject contained 98 EPIs. In addition, field maps were acquired for each sagittal slice for correction of EPI distortions. Lastly, one high-resolution structural volume was acquired in the same session, using a 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) pulse sequence (TR 30 msec; TE 5 msec; flip angle 45º; slice thickness 1.2 mm; in-plane resolution $1mm^2$).

Experimental Conditions

Visual stimuli were back-projected on a screen located approximately 12 feet from the subject's head and were viewed through a mirror inside the head coil. Two conditions alternated in 40-second blocks (BABABA). During the first five seconds a fixation cross was displayed. A diagram of a hand that corresponded to the position of the subject's own hand on a four-button press device was displayed with a blue dot appearing every 550 ms on one of the four fingers. Subjects were instructed always to press the corresponding button with their preferred hand. In order to ensure comprehension of the task, subjects practiced this setup briefly immediately before the fMRI session, with digit sequences different from those used in the scanner.

In condition A, a six-digit sequence (e.g. 4-2-3-4-1-3) was repeated 10 times throughout each 40-second block. For each block, a different sequence was used. In condition B, the blue dot flashed only on the index finger and subjects performed corresponding button presses.

Image Preprocessing

In order to correct for distortion of echoplanar images based on magnetic field inhomogeneities, an unwarping algorithm (Reber, 1998) was applied by using phase maps

acquired for each session. The first three time points of each series (usually affected by signal instability) were discarded from further analysis. All image volumes were motion corrected, temporally smoothed with a 3 time point filter (filtered voxel intensity at time point b = 0.15*a + 0.7*b + 0.15*c), spatially normalized, and smoothed with a Gaussian kernel of 6×6×6 mm (full-width half-maximum [FWHM]). Linear trends were removed from the image time series. All preprocessing and analyses were performed in AFNI (Analysis of Functional Neuroimages; Cox, 1996).

Eye Movement

Effects of eye movement were estimated by creating regions of interest over the orbits and extracting the mean time series from a fully preprocessed and detrended functional image set for each subject (cf. Tregellas et al., 2002). This time series was used as an orthogonal regressor for intraindividual statistics (see below).

Functional Connectivity Procedures

These procedures were largely similar to those applied in previous fcMRI studies (Biswal, 1995; Xiong et al., 1999). The initial step was to define the primary visual cortex. For each subject, bilateral area 17 seed volumes were identified on spatially normalized anatomical images. The seed volume was drawn individually on contiguous sagittal slices of each subject's high-resolution structural image to correct for individual morphological variability (Fig. 1A).

A mean time series for bilateral primary visual cortex was computed for each subject. In each subject, mean signal change in area 17 was then cross-correlated with the time series of all other voxels in the brain. Eight orthogonal regressors were used: (a) six for detected head movement along three rotations and three axes, (b) an oculomotor regressor (as described above), and (c) a smoothed and shifted box-car model, which served to remove effects of task-control cycles. Use of these regressors implies that the resultant fcMRI maps were not driven by head or eye movements, nor by the experimental paradigm, but instead by the task-independent BOLD signal change in primary visual cortex (see Discussion). These analyses can therefore be considered *task-independent*, as opposed to analyses that do not remove effects of task-control cycles (*task-embedded* analyses).

Fit coefficients from intraindividual correlation analyses were entered into one-sample t-tests to yield groupwise maps of functional connectivity. In addition, a two-sample t-test was performed in order to examine group differences in functional connectivity. All statistical maps were corrected for multiple comparisons, using Monte-Carlo-type alpha simulations (Poline et al., 1997), for a corrected cluster significance threshold of $p < .05$.

Results

Behavioral Results

Performance was examined in terms of response time and accuracy. The number of incorrect button presses per task block was 12.2 (*SD* = 8.4) or 20.3% in the autism group, compared to 3.4 (*SD* = 4.3) or 5.7% in the control group. Mean response times were also slightly higher (autism: 574.1 msec, *SD*=179.9; controls: 513.9 msec, *SD*=81.0). Group differences were significant for number of errors (t (14) = 2.63, $p < .05$), but not for response time (t (13) = 0.85, p =0.41).

Image Analyses

Analyses of main task effects (digit sequences versus index finger tapping conditions), as described in detail previously (Müller et al., 2003), revealed significant activation clusters in

premotor and superior parietal regions in both groups. However, the control group demonstrated greater task-related effects in the occipital (Brodmann area [BA] 17 and BA 18), right middle frontal (BA 9) and superior parietal areas (BA 7). The autism group showed greater activation in bilateral inferior parietal areas (BA 40), bilateral premotor cortex (BA 6), and left middle and superior frontal gyri (BA 8 and 10).

Clusters showing significant correlation with time series in primary visual cortex ($p < .05$; corr.) are listed in Table 2 and Figure 2. Anatomical identifications are based on (a) overlays onto spatially normalized mean structural MRI for each group, and (b) the atlas by Talairach and Tournoux (1988). Note that no significant differences in either group were observed comparing fcMRI effects for the two experimental conditions described above.

Control group—Significant connectivity clusters were observed in bilateral inferior frontal (BA 44 & 45) and right superior frontal gyri (BA 6). Additional frontal clusters were seen in the bilateral medial frontal gyrus (BA 8), left middle frontal area 9, and the right anterior cingulate gyrus (BA 32). Subcortical connectivity clusters were observed in bilateral thalamus and basal ganglia (with a peak in the right putamen).

Autism group—In the autism group, a large cluster was observed in the left insula and frontal operculum. Only one further frontal cluster was found, in medial portions of area 6 of the left hemisphere. Areas reflecting connectivity along the dorsal stream included bilateral extrastriate cortex (BA 18), right superior parietal area 7, and right precuneus (BA 19 & 39). Subcortical clusters were seen in right thalamus and basal ganglia (putamen). Other areas showing cross-correlation with primary visual cortex were found in the right temporo-occipital junction (BA 39) and middle temporal gyrus (BA 37).

Group comparison—Group analyses revealed overall greater functional connectivity in the control group. Areas showing significantly greater connectivity with primary visual cortex included bilateral inferior frontal areas 44, extending into area 45 on the right and into middle frontal area 9 on the left. Further clusters included right superior frontal gyrus (BA 6 & 8) and the paracentral lobule (area 5). Additional subcortical areas of greater connectivity in the control group were observed in bilateral thalamus and right basal ganglia (with peaks in the pulvinar and the putamen), as well as in the cerebellar vermis. No inverse effects were found, i.e., the autism group did not show significantly greater connectivity than the control group in any brain region.

Discussion

Contrary to our first hypothesis, we did not see significantly reduced connectivity between area 17 and superior parietal areas in our autism sample. The sole significant effect in the vicinity of the superior parietal lobe occurred in area 5 of the paracentral lobule, part of which contains secondary somatosensory cortex. The effect was, however, in the anterior portions of area 5, which is secondary motor cortex and not typically considered a component of the dorsal stream.

Absence of findings in the superior parietal lobe may appear inconsistent with previous studies indicating parietal abnormalities associated with impaired visuospatial attention in autism (Belmonte and Yurgelun-Todd, 2003; Townsend and Courchesne, 1994). Atypical activation patterns in the parietal lobe have also been observed in fMRI studies of visuomotor coordination in autism (Müller et al., 2003; 2001). However, in contrast to the latter activation studies, the present study examined BOLD signal correlation reflecting functional connectivity, with task-related changes being regressed out. Our results may suggest that despite neurofunctional impairment of the parietal lobes in autism, functional

connectivity between primary visual cortex and superior parietal areas may be mostly intact. However, there is some evidence for white matter involvement of the parietal lobes in autism. MRI volumetric studies have shown early overgrowth of parietal white matter in autistic children up to age 4 years (Carper et al., 2002) and abnormally large radiate compartments in parietal white matter in older children (Herbert et al., 2004). Reduced size in posterior subregions of the corpus callosum connecting bilateral parietal lobes (Egaas et al., 1995) would further indicate anomalies of connectivity in the autistic parietal lobe. The absence of significant group differences in parietal areas in our fcMRI study may suggest that these anomalies do not primarily affect connectivity between V1 and parietal lobes. It remains open whether our results may be related to only partial impairment of visuospatial functions in autism with islets of ability, as observed in typically intact or even elevated performance on block design (Shah and Frith, 1993) or the embedded figures test (Jolliffe and Baron-Cohen, 1997).

Consistent with our second hypothesis, functional connectivity between primary visual area 17 and inferior frontal cortex (areas 44 and 45) was significantly reduced in the autism group compared to the control group. Our previously published activation analyses (Müller et al., 2003) showed inferior frontal effects for visuomotor coordination in both control and autism groups. However, these results are not inconsistent. Functional connectivity MRI effects are distinct from activation effects, which are based on comparisons of hemodynamic changes for different conditions. Most initial fcMRI studies (e.g., Biswal, 1995) used time series acquired during rest, i.e., in the absence of task-induced activation. Even though the underlying physiology is not fully understood (see Obrig et al., 2000), fcMRI effects are driven by BOLD signal components at frequencies below 0.1 Hz (Cordes et al., 2000; Lowe et al., 1998), which is below the typical frequency of task trials in activation studies. Furthermore, in our study activation effects were removed with an orthogonal regressor for task-control cycles. Activation results from our study show that inferior frontal cortex does participate in motor responses prompted by visual stimuli in autism. However, our fcMRI results suggest that in the autistic brain efficiency of interregional functional cooperation between cortex processing visual input (area 17) and ventral prefrontal cortex involved in action planning may be reduced.

Reduced functional connectivity between V1 and inferior frontal areas may imply defects in the mirror neuron system and in dorsal stream processing (Williams et al., 2001). As described above inferior frontal cortex is considered the human homologue of brain regions in which mirror neurons have been identified in the monkey (Rizzolatti and Arbib, 1998). Our findings suggest that convergence of dorsal stream afferents and premotor circuits for action plans may not be fully intact in autism. Such defects in the mirror neuron system may be related to impairments in joint attention, and imitation, which may in turn represent elementary deficits leading to language delay (Charman, 2002; Müller, 2005; Rogers et al., 2003). Note that this interpretation is not based on the precise nature of our task, but on the observed patterns of connectivity, which suggest that in autism area 44 (i.e., the presumed site of mirror neurons) is less efficiently connected with visual cortex. It should also be noted that our findings, although consistent with the mirror neuron hypothesis, cannot definitively establish that reduced fcMRI in inferior frontal cortex reflects reduced presence or function of mirror neurons.

Both groups showed subcortical connectivity with primary visual area 17 in thalamus and lentiform nuclei. Such connectivity is expected given these structures' known comprehensive roles in sensorimotor function. Overall however, the control group showed significantly greater functional connectivity in right thalamus and putamen. The putamen is part of a basal ganglia-thalamocortical loop and receives afferents mostly from primary motor and somatosensory cortices (DeLong, 2000). The group effect seen in the putamen is

therefore unlikely to reflect differences in monosynaptic connectivity with V1, but may rather relate to differences in modulatory motor functions of the striatum (Yelnik, 2002).

There is little evidence for defects in early visual processing in autism (Hadjikhani et al., 2004). The thalamic effect seen in our study was located in the medial pulvinar and is unlikely to reflect connectivity along the primary visual pathway, i.e., between lateral geniculate nucleus and V1. Instead, the pulvinar is considered to participate in networks of visuospatial attention (Shipp, 2004). Reduced functional connectivity seen in our study is consistent with evidence for visuospatial impairments in autism (Townsend et al., 1996).

Our fcMRI approach differed sightly from those chosen by most previous studies. We opted against the more conventional use of the resting state (e.g., Biswal, 1995; Xiong et al., 1999). It is known that passive and stimulus-free “rest”, in particular in a noisy and constrained MRI setting, is not a neutral baseline condition, but is instead characterized by distinct activity profiles (Binder et al., 1999; Raichle et al., 2001), which may vary from one individual to the next. Variable response to the scanning environment may be especially problematic in the study of clinical populations because differential response may be systematically linked to a condition such as autism (Kennedy et al., 2004). Use of a well-defined task, as in the present study, provides better control over the cognitive state of individual subjects during scanning. However, in order to ensure that fcMRI effects were not driven by task-related activation, we applied a boxcar corresponding to task control cycles as an orthogonal regressor. Our fcMRI approach can therefore be considered *task-independent*, but at the same time controlled. It is currently not sufficiently known to what extent such embedding in a task domain appropriate for the neural network of interest (here: visuomotor coordination and the dorsal stream) enhances fcMRI effects. Direct comparison of the two visuomotor conditions in our study was not associated with any significant fcMRI effects in either group. Functional connectivity between area 17 and inferior frontal area 44 tended to be greater in the control group (compared to the autism group) when each condition was analyzed separately, but these effects did not reach corrected significance due to greater power limitations. Hampson and colleagues (2002) showed that BOLD signal correlations within perisylvian language networks were similar in a resting and in an activated state (listening to speech), although the latter state yielded greater leftward asymmetry of fcMRI effects (with a seed voxel in Broca’s area on the left). However, contrary to our study, the design in the study by Hampson and colleagues did not permit removal of activation effects, which may have affected asymmetry.

In a recent study on sentence comprehension in autism, Just and colleagues (2004) proposed an underconnectivity hypothesis for autism. While our results are compatible with the model of impaired functional network organization in autism, they suggest that more specific hypotheses are needed to describe network organization in autism. Just and colleagues found reduced BOLD signal cross-correlation in autism for all of the 10 cortical ROI pairs they examined. Among them, reduced connectivity between calcarine fissure and left inferior frontal cortex is compatible with our present findings. However, a global underconnectivity hypothesis for autism appears inconsistent with our finding of mostly retained occipito-parietal connectivity.

In several of our previous fMRI studies of motor control and visuomotor coordination in autism (Müller et al., 2004; 2003; 2001), we observed atypical frontal activation patterns and put forth a working hypothesis of early developing relatively simple sensorimotor functions “crowding out” later emerging polymodal and executive functions in prefrontal cortex. Although our present fcMRI findings do not directly speak to this hypothesis, they are not inconsistent with it. Even assuming that normal mechanisms of activity-driven stabilization and loss of axonal connectivity were at work in autism (Kandel et al., 2000),

abnormal functional organization in ventral prefrontal cortex would likely have secondary adverse effects on occipito-frontal connectivity – as seen in our study – because this circuitry would be functionally less efficient. Recent MRI volumetric findings of early postnatal overgrowth followed by abnormally flat growth rates in frontal and parietal white matter (Carper et al., 2002) further suggests that in the autistic brain interregional connectivity between frontal lobes and posterior cortices may be established precociously and in the absence of normal activity-driven selective mechanism necessary for the establishment of efficient functional networks.

In conclusion, our findings suggest abnormalities in frontal components of the dorsal stream, consistent with the hypothesis of mirror neuron dysfunction in autism, which may be one of probably many neurofunctional defects in autism. Our study complements previous functional imaging studies showing abnormal activation patterns in fronto-parietal networks with evidence on functional connectivity, suggesting abnormal cooperation between primary visual cortex and inferior frontal lobe in autism.

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References

Akshoomoff N, Pierce K, Courchesne E. The neurobiological basis of autism from a developmental perspective. Dev Psychopathol. 2002; 14:613–634. [PubMed: 12349876]

Allen G, Courchesne E. Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an FMRI study of autism. Am J Psychiatry. 2003; 160:262–73. [PubMed: 12562572]

Allen G, Müller RA, Courchesne E. Cerebellar function in autism: fMRI activation during a simple motor task. Biol Psychiatry. 2004; 56:269–278. [PubMed: 15312815]

Bachevalier, J.; Merjanian, PM., editors. The Neurobiology of Autism. Baltimore: John Hopkins, University Press; 1994. The contribution of medial temporal lobe structures in infantile autism: a neurobehavioral study in primates.

Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P. A clinicopathological study of autism. Brain. 1998; 121:889–905. [PubMed: 9619192]

Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a “theory of mind? Cognition. 1985; 21:37–46. [PubMed: 2934210]

Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams S. The amygdala theory of autism. Neuroscience and Behavioral Reviews. 1999a; 24:355–364.

Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer M, Simmons A, Williams S. Social intelligence in the normal and the autistic brain: An fMRI study. Eur J Neurosci. 1999b; 11:1891–1898. [PubMed: 10336657]

Belmonte MK, Yurgelun-Todd DA. Functional anatomy of impaired selective attention and compensatory processing in autism. Brain Res Cogn Brain Res. 2003; 17:651–64. [PubMed: 14561452]

Binder JR, Frost JA, Hammeke TA, Bellgowan PS, Rao SM, Cox RW. Conceptual processing during the conscious resting state. A functional MRI study. J Cogn Neurosci. 1999; 11:80–95. [PubMed: 9950716]

Binkofski F, Amunts K, Stephan KM, Posse S, Schormann T, Freund HJ, Zilles K, Seitz RJ. Broca’s region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. Hum Brain Mapp. 2000; 11:273–85. [PubMed: 11144756]

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in single and multislice echoplanar imaging using resting state fluctuations. Magn Reson Med. 1995; 34:537–541. [PubMed: 8524021]

Brambilla P, Hardan A, di Nemi SU, Perez J, Soares JC, Barale F. Brain anatomy and development in autism: review of structural MRI studies. Brain Res Bull. 2003; 61:557–69. [PubMed: 14519452]

Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, Seitz RJ, Zilles K, Rizzolatti G, Freund H-J. Action observation activates premotor and parietal areas in somatotopic manner: An fMRI study. Eur J Neurosci. 2001; 13:400–404. [PubMed: 11168545]

Carper RA, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage. 2002; 16:1038–51. [PubMed: 12202091]

Charman T. The prevalence of autism spectrum disorders: Recent evidence and future challenges. Eur Child Adolesc Psychiatry. 2002; 11:249–256. [PubMed: 12541002]

Charman T. Why is joint attention a pivotal skill in autism? Philos Trans R Soc Lond B Biol Sci. 2003; 358:315–24. [PubMed: 12639329]

Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, Quigely MA, Meyerand ME. Mapping functionally related regions of brain with functioanl connectivity MR imaging. American Journal of Neuroradiology. 2000; 21:1636–1644. [PubMed: 11039342]

Courchesne E. Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. Curr Opin Neurobiol. 1997; 7:269–278. [PubMed: 9142760]

Courchesne E, Press GA, Yeung-Courchesne R. Parietal lobe abnormalities detected with MR in patients with infantile autism. Am J Roentgenol. 1993; 160:387–393. [PubMed: 8424359]

Cox RW. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 1996; 29:162–173. [PubMed: 8812068]

Damasio AR, Maurer RG. A neurological model for childhood autism. Arch Neurol. 1978; 35:777–786. [PubMed: 718482]

Dawson G. Brief report: Neuropsychology of autism: A report on the state of the science. J Autism Dev Disord. 1996; 26:179–184. [PubMed: 8744481]

DeLong, MR. The basal ganglia. In: Kandel, ER.; Schwartz, JH.; Jessell, TM., editors. Principles of Neural Science. 4. Elsevier; New York: 2000. p. 853-867.

Egaas B, Courchesne E, Saitoh O. Reduced size of corpus callosum in autism. Arch Neurol. 1995; 52:794–801. [PubMed: 7639631]

Elman, JL.; Bates, EA.; Johnson, MH.; Karmiloff-Smith, A.; Parisi, D.; Plunkett, K. Rethinking innateness: A connectionist perspective on development. Cambridge, Mass: MIT Press; 1996.

Folstein SE, Rosen-Sheidley B. Genetics of autism: complex aetiology for a heterogeneous disorder. Nat Rev Genet 2, Nature Reviews Genetics. 2001:943–55.

Friston KJ, Frith CD, Fletcher P, Liddle PF. Functional topography: Multidimensional scaling and functional connectivity in the brain. Cereb Cortex. 1996b; 6:156–164. [PubMed: 8670646]

Gallese V. The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. Psychopathology. 2003; 36:171–80. [PubMed: 14504450]

Gallese V, Faddiga L, Fogaddi, Rizzolatti G. Action recognition in the premotor cortex. Brain. 1996; 119:593–609. [PubMed: 8800951]

Goodale, MA. Perception and action in the human visual system. In: Gazzaniga, M., editor. The new cognitive neurosciences. 2. The MIT Press; 2000. p. 365-77.

Goodale MA, Westwood DA. An evolving view of duplex vision: separate but interacting cortical pathways for perception and action. Curr Opin Neurobiol. 2004; 14:203–11. [PubMed: 15082326]

Haas RH, Townsend J, Courchesne E, Lincoln AJ, Schreibman L, Yeung-Courchesne R. Neurologic abnormalities in infantile autism. J Child Neurol. 1996; 11:84–92. [PubMed: 8881982]

Hadjikhani N, Chabris CF, Joseph RM, Clark J, McGrath L, Aharon I, Feczko E, Tager-Flusberg H, Harris GJ. Early visual cortex organization in autism: an fMRI study. Neuroreport. 2004; 15:267–70. [PubMed: 15076750]

Hallett M, Lebiedowska MK, Thomas SL, Stanhope SJ, Denckla MB, Rumsey J. Locomotion of autistic adults. Arch Neurol. 1993; 50:1304–8. [PubMed: 8257307]

Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC. Detection of functional connectivity using temporal correlations in MR images. Hum Brain Mapp. 2002; 15:247–262. [PubMed: 11835612]

Hashimoto T, Tayama M, Murakawa K, Yoshimoto T, Miyazaki M, Harada M, Kuroda Y. Development of the brainstem and cerebellum in autistic patients. J Autism Dev Disord. 1995; 25:1–18. [PubMed: 7608030]

Heiser M, Iacoboni M, Maeda F, Marcus J, Mazziotta JC. The essential role of Broca's area in imitation. Eur J Neurosci. 2003; 17:1123–8. [PubMed: 12653990]

Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness VS Jr. Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol. 2004; 55:530–40. [PubMed: 15048892]

Hill EL. Executive dysfunction in autism. Trends Cogn Sci. 2004; 8:26–32. [PubMed: 14697400]

Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G. Cortical mechanisms of human imitation. Science. 1999; 286:2526–8. [PubMed: 10617472]

Jiang T, He Y, Zang Y, Weng X. Modulation of functional connectivity during the resting state and the motor task. Hum Brain Mapp. 2004; 22:63–71. [PubMed: 15083527]

Jolliffe T, Baron-Cohen S. Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? J Child Psychol Psychiatry. 1997; 38:527–34. [PubMed: 9255696]

Just MA, Cherkassky VL, Keller TA, Minshew NJ. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain. 2004; 127:1811–1821. [PubMed: 15215213]

Kandel, ER.; Jessell, TM.; Sanes, JR. Sensory experience and the fine tuning of synaptic connections. In: Kandel, ER.; Schwartz, JH.; Jessell, TM., editors. Principles of Neural Science. 4. Elsevier; New York: 2000. p. 1115-30.

Kanner L. Autistic Disturbances of Affective Contact. Nervous Child. 1943; 2:217–250.

Kennedy DP, Redcay E, Courchesne E. Cognition, emotion, and the resting state: an fMRI study of neurofunctional abnormalities in autism. International Meeting for Autism Research. 2004; 44:1.1.4.

Koeda T, Knyazeva M, Nijiokikjien C, Konkman EJ, De Sonneville L, Vildavsky V. The EEG in acallosal children. Coherence values in the resting state: left hemisphere compensatory mechanism. Electroencephalogr Clin Neurophysiol. 1995; 95:397–407. [PubMed: 8536568]

Koski L, Iacoboni M, Dubeau MC, Woods RP, Mazziotta JC. Modulation of cortical activity during different imitative behaviors. J Neurophysiol. 2003; 89:460–71. [PubMed: 12522194]

Leslie KR, Johnson-Frey SH, Grafton ST. Functional imaging of face and hand imitation: towards a motor theory of empathy. Neuroimage. 2004; 21:601–7. [PubMed: 14980562]

Lord C, Rutter M, Le Couteur A. Autism diagnostic interview-revised: A revised version of diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord. 1994; 24:659–685. [PubMed: 7814313]

Lowe MJ, Mock BJ, Sorenson JA. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage. 1998; 7:119–32. [PubMed: 9558644]

Lowe MJ, Mock BJ, Soreson JA. Functional connectivity in single and mutliechoplanar imaging using resting-state fluctuations. Neuroimage. 1998; 7:119–132. [PubMed: 9558644]

Minshew NJ, Goldstein G, Siegel DJ. Neuropsychologic functioning in autism: Profile of a complex information processing disorder. J Int Neuropsychol Soc. 1997; 3:303–316. [PubMed: 9260440]

Müller RA. Neurocognitive studies of language impairment: The 'bottom-up' approach. Applied Psycholinguistics. 2005; 26:65–78.

Müller RA, Cauich C, Rubio MA, Mizuno A, Courchesne E. Abnormal patterns of frontal activity during digit sequence learning in high-functioning autistic patients. Biol Psychiatry. 2004; 56:323–332. [PubMed: 15336514]

Müller RA, Kleinhans N, Kemmotsu N, Pierce K, Courchesne E. Abnormal variability and distribution of functional maps in autism: An fMRI study of visuomotor learning. Am J Psychiatry. 2003; 160:1847–1862. [PubMed: 14514501]

Müller RA, Pierce K, Ambrose JB, Allen G, Courchesne E. Atypical patterns of cerebral motor activation in autism: a functional magnetic resonance study. Biol Psychiatry. 2001; 49:665–676. [PubMed: 11313034]

Obrig H, Neufang M, Wenzel R, Kohl M, Steinbrink J, Einhaupl K, Villringer A. Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults. Neuroimage. 2000; 12:623–39. [PubMed: 11112395]

Osterling J, Dawson G. Early recognition of children with autism: A study of first birthday home videotapes. J Autism Dev Disord. 1994; 24:247–257. [PubMed: 8050980]

Osterling J, Dawson G, Munson J. Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation: A study of first birthday party home videotapes. Development and Psycholpathology. 2002; 14:239–251.

Petrides, M.; Pandya, DN. Comparative architectonic analysis of the human and macque frontal cortex. In: Boller, F.; Grafman, J., editors. Handbook of Neuropsychology. Elsevier Science Ltd; Amsterdam: 1994.

Poline JB, Worsley KJ, Evans AC, Friston KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. Neuroimage. 1997; 5:83–96. [PubMed: 9345540]

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A. 2001; 98:676–82. [PubMed: 11209064]

Rapin I, Katzman R. Neurobiology of autism. Ann Neurol. 1998; 43:7–14. [PubMed: 9450763]

Reber P. Correction of off resonance-related distortion in echo-planar imaging using EPI-based field maps. Magn Reson Med. 1998; 39:328–330. [PubMed: 9469719]

Rizzolatti G, Arbib MA. Language within our grasp [see comments]. Trends Neurosci. 1998; 21:188–94. [PubMed: 9610880]

Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D. Localisation of grasp representations in humans by PET--1: observation vs. execution Exp Brain Res. 1996; 111:246–252.

Rizzolatti G, Fogassi L, Gallese V. Motor and cognitive functions of the ventral premotor cortex. Curr Opin Neurobiol. 2002; 12:149–154. [PubMed: 12015230]

Rodier P. Converging evidence for brain stem injury in autism. Development and Psycholpathology. 2002; 14:537–557.

Rogers SJ, Hepburn SL, Stackhouse T, Wehner E. Imitation performance in toddlers with autism and those with other developmental disorders. J Child Psychol Psychiatry. 2003; 44:763–81. [PubMed: 12831120]

Rumsey JM, Ernst Monique. Functional neuroimaging of autistic disorders. Ment Retardation and Developmental Disabilities Research Reviews. 2000; 6:171–179.

Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: Childhood Autism Rating Scale CARS. J Autism Dev Disord. 1980; 10:91–103. [PubMed: 6927682]

Shah A, Frith U. Why do autistic individuals show superior performance on the block design task? J Child Psychol Psychiatry. 1993; 34:1351–1364. [PubMed: 8294523]

Shipp S. The brain circuitry of attention. Trends Cogn Sci. 2004; 8:223–230. [PubMed: 15120681]

Spencer J, O'Brien J, Riggs K, Braddick O, Atkinson J, Wattam-Bell J. Motion processing in autism: evidence for a dorsal stream deficiency. Neuroreport. 2000; 11:2765–2767. [PubMed: 10976959]

Tager-Flusberg H, Joseph R, Folstein S. Current Directions in research on autism. Mental Retardation and Developmental Disabilities Research Reviews. 2001; 7:21–29. [PubMed: 11241879]

Talairach, J.; Tournoux, P. Co-Planar Stereotaxic Atlas of the Human Brain. Stuttgart: Georg Thieme; 1988.

Teitelbaum P, Teitelbaum O, Nye J, Fryman J, Maurer RG. Movement analysis in infancy may be useful for early diagnosis of autism. Proc Natl Acad Sci U S A. 1998; 95:13982–7. [PubMed: 9811912]

Townsend J, Courchesne E. Parietal damage and narrow "spotlight" spatial attention. J Cogn Neurosci. 1994; 6:220–232.

Townsend J, Harris NH, Courchesne E. Visual attention abnormalities in autism: delayed orienting to location. J Int Neuropsychol Soc. 1996; 2:541–550. [PubMed: 9375158]

Townsend J, Westerfield M, Leaver E, Makeig S, Jung T, Pierce K, Courchesne E. Event-related brain response abnormalities in autism: evidence for impaired cerebello-frontal spatial attention networks. Cognitive Brain Research. 2001; 11:127–45. [PubMed: 11240116]

Tregellas JR, Tanabe JL, Miller DE, Freedman R. Monitoring eye movements during fMRI tasks with echo planar images. Hum Brain Mapp. 2002; 17:237–43. [PubMed: 12395391]

Trottier G, Srivastava L, Walker CD. Etiology of infantile autism: a review of recent advances in genetic and neurobiological research [see comments]. J Psychiatry Neurosci. 1999; 24:103–15. [PubMed: 10212552]

Ungerleider, LG.; Mishkin, M. Two cortical visual systems. In: Ingle, DJ.; Goodale, MA.; Mansfield, RJW., editors. Analysis of visual behavior. MIT Press; Cambridge: 1982. p. 549-586.

Von Bonin, G.; Bailey, P. The Neocortex of Macaca Mulatta. Urbana, IL: University of Illinois Press; 1947.

Williams JH, Whiten A, Singh T. A systematic review of action imitation in autistic spectrum disorders. J Autism Dev Disord. 2004; 34:285–299. [PubMed: 15264497]

Williams JH, Whiten A, Suddendorf T, Perrett DI. Imitation, mirror neurons and autism. Neurosci Biobehav Rev. 2001; 25:287–95. [PubMed: 11445135]

Williams JHG, Whiten A, Suddendorf T, Perret DI. Imitation, mirror neurons and autism. Neuroscience and Behavioral Reviews. 2001; 25:287–295.

Xiong J, Parsons LM, Gao JH, Fox PT. Interregional connectivity to primary motor cortex revealed using MRI resting state images. Hum Brain Mapp. 1999; 8:151–6. [PubMed: 10524607]

Yelnik J. Functional anatomy of the basal ganglia. Mov Disord. 2002; 17(Suppl 3):S15–21. [PubMed: 11948751]

Zilbovicius M, Garreau B, Samson Y, Remy P, Barthelemy C, Syrota A, Lelord G. Delayed maturation of the frontal cortex in childhood autism. Am J Psychiatry. 1995; 152:248–252. [PubMed: 7840359]

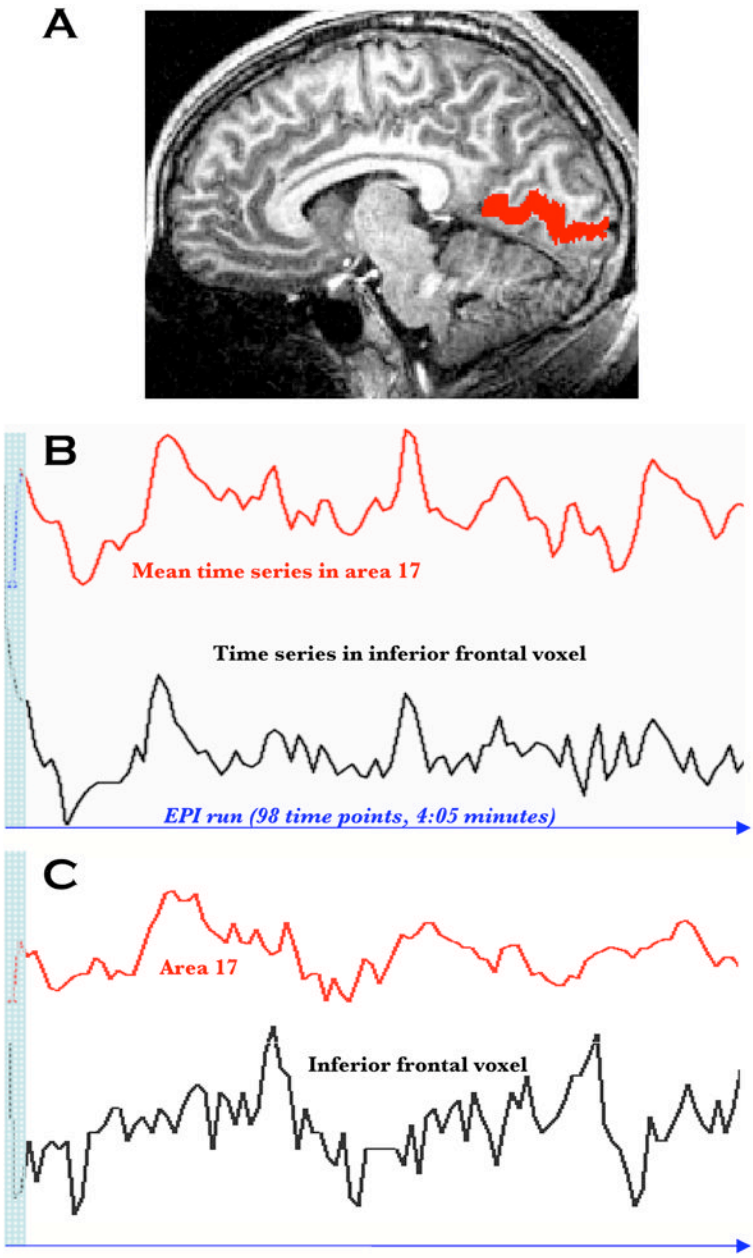

Figure 1.

(A) Area 17, as identified on the high-resolution structural image of an individual control subject. (B) Detrended mean time series for primary visual area 17 (top) and time series for a voxel in left inferior frontal area 44 (bottom) for a control subject. The correlation coefficient for this voxel is r=0.78. The shaded column on the left represents the first 3 time points discarded from analyses (see Methods). (C) Detrended mean time series for primary visual area 17 and time series for a voxel in left inferior frontal area 44 for autism subject # 5. The correlation coefficient for this voxel is r=.19

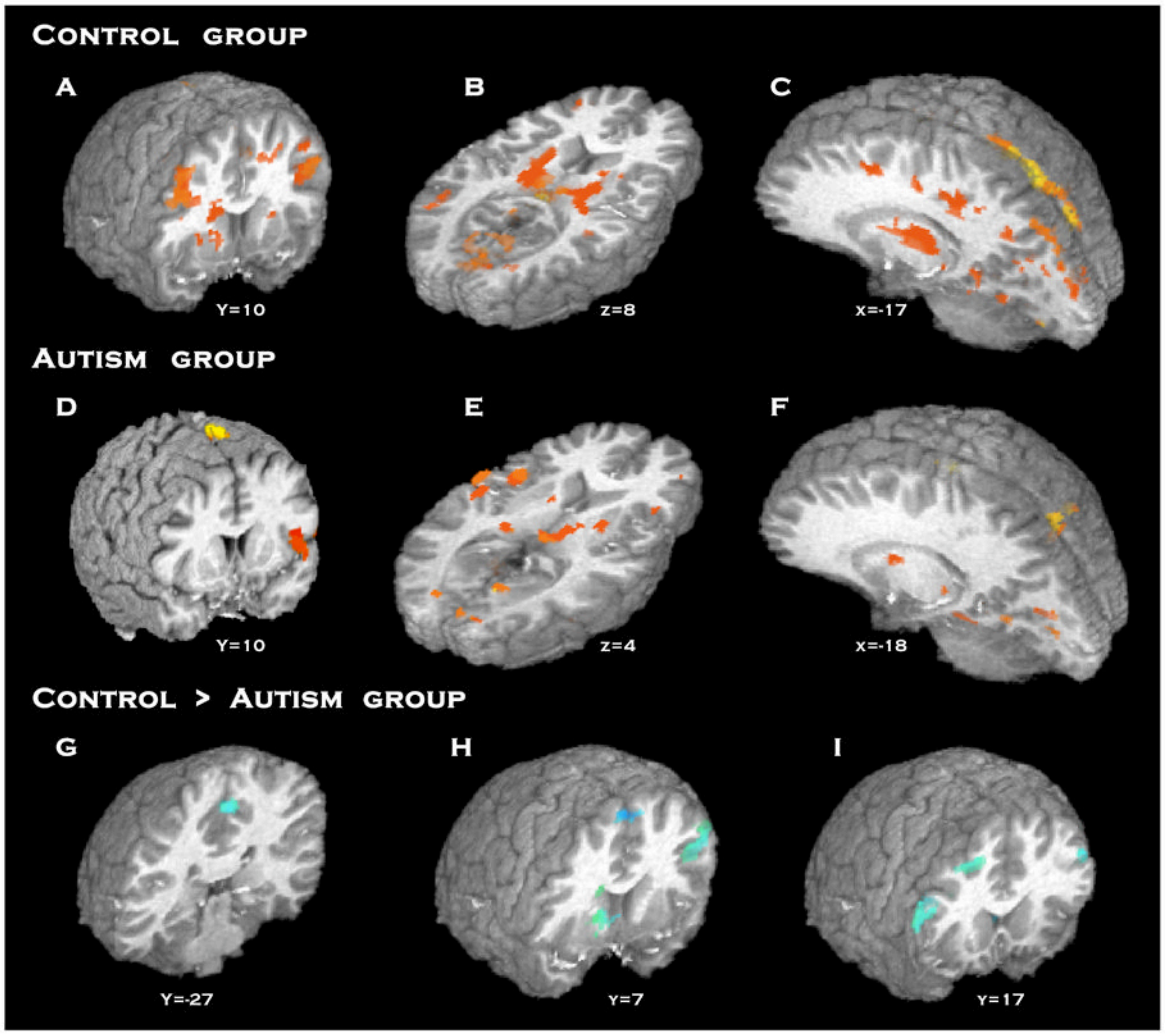

Fig. 2.

Functional connectivity maps for control (A-C) and autism group (D-F) and clusters of significant group differences (Control > Autism; G-J). No inverse effects (Autism > Control) were detected. All shown clusters $p<.05$ (corr.). In the control group, connectivity effects are seen in bilateral inferior frontal and middle frontal gyri (A), bilateral thalamus and basal ganglia, as well as posterior cingulate gyrus (B). Connectivity along the dorsal stream, with effects in superior parietal lobe and precuneus can be seen in (C). In the autism group, comparable effects are partly reduced. No connectivity is detected in right inferior frontal cortex (D), although a cluster in seen in left opercular and insular regions (D-E). Effects in thalamus and basal ganglia show rightward asymmetry (E). Dorsal stream connectivity appears reduced, but superior parietal effects are seen (F). On direct group comparison, signficantly greater connectivity in the control group is found in paracentral regions (G), in left middle and inferior frontal and bilateral superior frontal gyri, as well as in basal ganglia and thalamus (H), and in right inferior frontal gyrus (I).

Table 1

Quantitative diagnostic and psychometric data for autistic individuals

Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Mean**	**(SD)**
Handedness[a]	Right	Right	Ambidextrous	Left	Right	Right	Left	Right		
Age (years)	15	21	23	24	33	35	35	41	28.4	(8.9)
C.A.R.S.[b]	41	39	35.5	31	32.5	23.5	36	30	33.6	(5.6)
ADI-R [c]										
Social	27	28	30	22	25	22	21	24	24.9	(3.2)
Verbal	22	21	16	13	21	16	22	19	18.8	(3.4)
Nonverbal Communication	14	14	14	8	14	8	12	19	12.9	(3.6)
Restricted Interests & Repetitive Behavior	12	7	11	6	7	7	10	6	8.3	(2.4)
Nonverbal IQ	99	81	81	87	80	112	106	92	92.3	(12.3)
Full scale IQ	87	74	79	85	73	103	102	89	86.5	(11.4)

[a] Based on neurological examination

[b] Childhood Autism Rating Scale (Cut-off score for autism: 30)

[c] Autism Diagnostic Interview-Revised (Cut-off scores for autism: Social: 10; Verbal: 8; Nonverbal: 8; Restr. Interests & Rep. Behavior: 3)

Table 2

f significant effects (p<.05, corr.) for three comparisons

Control Group						Autism Group						Control > Autism Group					
		Talairach coordinates						Talairach coordinates						Talairach coordinates			
ml)	Peak *t*	x	y	z	Peak Localization (Brodmann area)	Volume(ml)	Peak *t*	x	y	z	Localization (Brodmann area)	Volume (ml)	Peak *t*	x	y	z	Localization (Brodmann area)
	20.3	1	23	44	B Medial Frontal (8)	640	8.9	−5	−23	70	L Medial Frontal (6)	616	5.6	−3	−27	50	B Paracentral (5)
	20.3	−51	3	40	L Middle Frontal (9)							1640[a]	7.2	−51	5	40	L Middle Frontal (9)
	15.6	−47	9	32	L Inferior Frontal (44)	4392	14.2	−45	7	0	L Insula/Frontal	1640[a]	6.1	−44	10	27	L Inferior Frontal (44)
	17.4	19	35	20	R Anterior Cingulate (32)						Operculum (6/44)	520	5.4	19	19	44	R Superior Frontal (8)
	19.6	7	−5	64	R Superior Frontal (6)							936	6.2	5	7	64	R Superior Frontal (6)
	26.2	53	17	20	R Inferior Frontal (44/45)							1296	7.1	57	17	20	R Inferior Frontal (44/45)
	17.4	−1	−77	40	B Precuneus (7/19)	584	8.0	11	−69	54	R Superior Parietal (7)						
	32.2	−15	−77	44	L Precuneus/Superior Parietal Lobe (7)												
	32.7	−15	−31	44	L Posterior Cingulate (31)												
	17.5	27	−35	38	R Inferior Parietal (40)	528	8.2	27	−69	32	R Angular (39/19)						
	24.1	5	−59	12	R Posterior Cingulate (23)	512	9.4	13	−47	8	R Posterior Cingulate (29/30)						
and Occiptal																	
						1448	10.3	−43	−69	10	L Temporo-occipital junction (39)						
	21.6	49	−31	16	R Superior Temporal (42/22)	1080	9.4	47	−49	−6	R Middle Temporal (37)						
	17.0	19	−77	30	R Cuneus (19)	1384	10.5	19	−49	−8	R Fusiform Gyrus (19/37)						
	20.4	−21	−77	20	L Cuneus (18)	1528	11.5	1	−73	12	B Cuneus (18)						
al																	
	28.1	7	23	4	B Thalamus	1496	14.3	5	−19	4	R Thalamus	592	6.7	5	−21	4	B Thalamus (Pulvinar)

Control Group						Autism Group						Control > Autism Group					
		Talairach coordinates					Talairach coordinates						Talairach coordinates				
nl)	Peak *t*	x	y	z	Peak Localization (Brodmann area)	Volume(ml)	Peak *t*	x	y	z	Localization (Brodmann area)	Volume (ml)	Peak *t*	x	y	z	Localization (Brodmann area)
	28.4	27	−19	8	R Lentiform/Putamen	1520	10.8	27	−3	12	R Lentiform/Putamen	1216	6.8	25	1	2	R Lentiform/Putamen
												496	5.7	−5	−59	0	Cerebellar Vermis

identified in one cluster.

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