Available online at www.sciencedirect.com
SCIENCE DIRECT
Cognitive Brain Research 17 (2003) 651–664
COGNITIVE BRAIN RESEARCH
www.elsevier.com/locate/cogbrainres

Research report

Functional anatomy of impaired selective attention and compensatory processing in autism

Matthew K. Belmonte[a,*], Deborah A. Yurgelun-Todd[a,b]

[a]*Cognitive Neuroimaging Laboratory, McLean Hospital, Belmont, MA 02478-1048, USA*
[b]*Harvard Medical School, 25 Shattuck Street, Boston, MA 02115-6092, USA*

Accepted 12 June 2003

Abstract

In autism, physiological indices of selective attention have been shown to be abnormal even in situations where behaviour is intact. This divergence between behaviour and physiology suggests the action of some compensatory process of attention, one which may hold clues to the aetiology of autism's characteristic cognitive phenotype. Six subjects with autism spectrum disorders and six normal control subjects were studied with functional magnetic resonance imaging while performing a bilateral visual spatial attention task. In normal subjects, the task evoked activation in a network of cortical regions including the superior parietal lobe ($P<0.001$), left middle temporal gyrus ($P=0.002$), left inferior ($P<0.001$) and middle ($P<0.02$) frontal gyri, and medial frontal gyrus ($P<0.02$). Autistic subjects, in contrast, showed activation in the bilateral ventral occipital cortex ($P<0.03$) and striate cortex ($P<0.05$). Within the task condition, a region-of-interest comparison of attend-left versus attend-right conditions indicated that modulation of activation in the autistic brain as a function of the lateral focus of spatial attention was abnormally decreased in the left ventral occipital cortex ($P<0.03$), abnormally increased in the left intraparietal sulcus ($P<0.01$), and abnormally variable in the superior parietal lobe ($P<0.03$). These results are discussed in terms of a model of autism in which a pervasive defect of neural and synaptic development produces over-connected neural systems prone to noise and crosstalk, resulting in hyper-arousal and reduced selectivity. These low-level attentional traits may be the developmental basis for higher-order cognitive styles such as weak central coherence.

Theme: Disorders of the nervous system

Topic: Developmental disorders

Keywords: Autism; Visual attention; Arousal; fMRI; Parietal; Intraparietal sulcus

1. Introduction

Autism has been construed variously as a disorder involving fundamental deficits in central coherence [36], executive function [68], and theory of mind [6]. While very significant cognitive abnormalities are present in all these domains, their relative primacy in the developmental syndrome of autism remains undetermined. Many of the cognitive traits characteristic of autism may develop as consequences of fundamental abnormalities, or even as compensatory strategies for such abnormalities. Physiological studies of more elementary processes may thus provide a foundation for understanding higher-level deficits in developmental terms [63].

A recurring theme in analyses of autistic cognition is a difficulty updating the scope and focus of attention [14]. Behavioural studies suggest that this operational rigidity may stem from an inability to reorient attention rapidly. An autistic deficit in rapid shifting of attention has been observed in cases of shifts between sensory modalities [29], between spatial locations [88,89,80,82,81,44], and between object features [30,71]. Related to this theme of inefficient selective attention are findings of impairment in engaging visual attention in the presence of distractors

*Corresponding author. Present address: Autism Research Centre, Developmental Psychiatry, Douglas House, 18b Trumpington Road, Cambridge CB2 2AH, UK. Tel.: +44-7986-422-338; fax: +44-1223-333-564.

E-mail addresses: belmonte@mit.edu (M.K. Belmonte), http://www.mit.edu/~belmonte (M.K. Belmonte), ytodd@mclean.harvard.edu (D.A. Yurgelun-Todd).

0926-6410/03/$ – see front matter
doi:10.1016/S0926-6410(03)00189-7

[13], and, in patients with pervasive developmental disorder, a deficit in dividing attention between auditory and visual channels and between visual attributes [19].

These behavioural observations of autism are complemented by neurophysiological results which reveal that even when people with autism produce normal behavioural output, they tend to do so by abnormal physiological means. Frontal negativities associated with sustained attention are reduced or absent in the autistic brain [28,21], the frontal late positive component to peripheral visual stimuli is delayed [83], and the visual P3b is highly variable [28] with a somewhat low average amplitude [67,21,87,83]. Abnormality in the allocation of spatial attention manifests from the very earliest attention-sensitive stages of processing: whereas normally the distance of a stimulus from the spatial focus of attention is indexed by a smooth decrease in P1 amplitude, the P1 in autism decreases with distance either precipitously or not at all [79].

In addition to these failures of normal modulation, neural systems in the autistic brain are often inappropriately activated. The visual N2 to novel stimuli is larger when a person with autism is performing a task than when (s)he is passively observing, even when these novel stimuli are not relevant to the task in question [49]. This inappropriate activation occurs across modalities, also: when a response is required to an auditory stimulus, autistic children manifest an enhanced P3 at occipital sites overlying visual processing areas [50]. During shifts of attention between hemifields, the normal, spatiotopically selective augmentation of the visual steady-state evoked potential is absent, and instead both hemispheres activate indiscriminately in response to any demand to shift attention [9]. In general, perceptual filtering in autism seems to occur in an all-or-none manner, with little specificity for the location of the stimulus, for the behavioural relevance of the stimulus, or even for the sensory modality in which the stimulus appears. Autistic attention, it seems, is founded more on the coarse control of general arousal than on selective activation of specific perceptual systems.

As people with autism are prone to excessive motor activity and anxiety, movement artefacts and performance difficulties have limited the population on which functional magnetic resonance imaging (fMRI) can be performed successfully. Most studies have been restricted to subjects in small numbers (often six or seven) in often heterogeneous groups combining individuals with high-functioning autism and those with Asperger syndrome. Despite these limitations, fMRI has produced consistent support for the hypothesis of inappropriately intense and inappropriately distributed sensory activation, across a variety of tasks. These results include abnormally high activity in ventral occipital visual areas during performance of the Embedded Figures Test, even while prefrontal and parietal activations are abnormally low [72]; heightened activity during face processing in peristriate cortex [32], inferior temporal gyrus [75], and other areas outside the fusiform 'face area' [70] while fusiform activity is abnormally low; heightened activity in the superior temporal gyrus during inference of mental state from pictures of eyes, while prefrontal and medial temporal activations are abnormally low [7]; decreased connectivity between extrastriate visual areas and prefrontal and temporal areas associated with inference of mental state, while prefrontal and temporal activations are again abnormally low [20]; and, during motor tasks, a lack of deactivation of early visual areas [63] and oddly distributed patterns of activation throughout the Rolandic cortex [63] and cerebellum [2].

At least as important as this hyperactivation and abnormal patterning of primary perceptual processes is the accompanying hypoactivation in regions that normally subserve more complex cognitive processes: a wide range of tasks from Embedded Figures to face perception evokes unusually low activations in regions that normally integrate individual features or manage subordinate processes. This apparent impairment in complex cognitive processing suggests a failure of top-down attentional control, and behavioural observations of autism are consistent with such a view. An investigation of autism in terms of Mirsky et al.'s [61] factor analysis of attention demonstrates that autistic impairments load on the Focus-Execute and Shift components—elements of attention that involve flexibility in the application of cognitive and psychomotor processes [40]. This impairment in top-down control is evident even in the domain of eye movements, where people with autism show failures of inhibition in anti-saccade and delayed-saccade tasks in the context of normal performance in a pro-saccade task [60], and reduced dorsolateral prefrontal and posterior cingulate activity in a comparison of the delayed-saccade condition to the pro-saccade condition [54]. Although clear physiological and behavioural evidence exists both for abnormalities of top-down attentional control and for abnormalities of perceptual processing, the developmental relationship between these two domains of impairment remains an open question. The maturation of top-down processes may be influenced by abnormal perceptual inputs, and conversely, perturbations in perceptual systems may be induced by abnormal top-down control.

Remarkably, despite all these persistent abnormalities in the physiology of attention and perception, in many attention tasks that do not involve rapid shifting people with autism perform at normal or near-normal levels [29,9]. This divergence between behaviour and physiology indicates the operation of some compensatory process. The physiological evidence of high general arousal combined with low selectivity suggests that this compensatory process operates at a higher stage of processing, belatedly sorting out relevant stimuli from an indiscriminately amplified background. Electroencephalography [56,41,62,8] and functional imaging [69,25,45,46,

84,86,85,57,48] have pinpointed an effect of early visual selection in ventral occipital cortex, and two fMRI studies suggest that intraparietal cortex mediates a complementary process in which irrelevant distractors that have passed through earlier filtering are actively inhibited [90,11].

Our examination of these phenomena involves observing the effect of unilaterally directed attention on brain activation driven by bilateral rapid serial presentation of visual stimuli. If indeed autism involves a failure of early selectivity, one could expect not only an absent effect of left-directed versus right-directed attention in ventral occipital visual areas, but also a heightened effect in intraparietal cortex, as this higher-level process becomes overloaded with demands to suppress stimuli from the irrelevant hemifield. In order to test this hypothesis, we applied fMRI (1) to map the specific loci of attention-related activations within ventral occipital and intraparietal cortices in individual subjects and (2) within these individually identified loci, to quantify the effect of left-hemifield versus right-hemifield foci of attention on the level of brain activation. Superior parietal lobule, a region known to be involved in visual spatial attention, was also included for purposes of comparison.

Because of individual variability in the detailed anatomy of intraparietal sulcus [64,11] and because of the small number of high-functioning, compliant subjects available, in our attention comparison we have purposely avoided analytical techniques based on blurring the data and warping onto a standard reference brain. The within-subjects region-of-interest approach that we apply has been suggested by several authors as a way of dealing with anatomical variations between individuals [66,24,90,11] and between groups of patients and controls [75,70,63,16,1]. Our statistical methods are tailored to this approach of detailed within-subjects analysis of a small sample: our technique of permutation testing is more powerful than the analogous parametric techniques [10] and is particularly suited to the problem of detecting differences between small groups of subjects [65]. Other fMRI studies on groups as small as six subjects with autism [72,7,70] have yielded significant results.

2. Methods

2.1. Subjects

Eight right-handed, non-retarded adults with clinical diagnoses of autism spectrum disorders were recruited. Of these, one male was eliminated due to difficulty maintaining fixation, and one female was eliminated due to difficulty performing the experimental task. The remaining five males (ages 26 to 50 years) and one female (age 24 years) all met DSM-IV [3] and ADI-R algorithm [53] criteria for autism. The female subject was taking buspirone and paroxetine, and was scanned before her morning dose. None of the other subjects were taking any medication. Subjects had no history of central nervous system (CNS) trauma, and all anatomical scans were read as normal. Subject characteristics are detailed in Table 1.

The autism group was compared to six participants from a parallel study of normal subjects [11] matched for sex and handedness [ages 26.6 (female), 23.4, 24.6, 25.4, 27.7, 35.5 years, mean 27.2 years, S.D. 4.4]. Due to difficulties in recruiting high-functioning adults with autism, exact age-matching with the previously recruited normal subjects was not possible. However, data from the complete group of eleven subjects in the normal study indicate no relationship between age and levels of brain activation in the current experimental paradigm ($P \geq 0.45$ for main effect of age and for all interactions). The normal subjects from this parallel study were selected so as to give the greatest possible overlap of age ranges within the two sex-matched groups.

Stimuli, behavioural recording, and scanning parameters were identical to those used in the aforementioned normal study. Within-subjects analyses for autism patients and for controls used methods based on that study; normal subjects

Table 1
Age, sex, ADI-R scores, and clinical diagnoses for the autism group

Subject	Age (years)	Sex	ADI-R social	ADI-R communication	ADI-R restricted & repetitive	Clinical diagnosis
1*	24.1	Female	24	17	5	Autism
2*	50.4	Male	16	12	5	Autism
3*	29.8	Male	19	19	10	Autism
4	37.6	Male	23	16	8	Asperger syndrome
5	26.9	Male	27	12	10	Asperger syndrome
6	27.7	Male	26	12	4	PDD-NOS
Mean	32.7		22.5	14.7	7.0	
S.D.	9.8		4.2	3.1	2.7	

Although all subjects in this group met DSM-IV and ADI-R criteria for autism based on their developmental histories, their current clinical diagnoses varied. Subjects with a clinical diagnosis of autism are highlighted with asterisks.

were re-analysed alongside autism patients using an updated software implementation. The experimental protocol was approved by the McLean Hospital Institutional Review Board. Informed consent was obtained from each subject, and subjects were paid for their time.

2.2. Stimuli and task

Video was back-projected onto a screen fastened to the front of the head coil, made visible to the subject by a mirror. The experiment comprised 10 trials, each of which consisted of a 60-s task period flanked by two 30-s fixation periods. During the fixation periods the display was dark except for a fixation cross which remained present throughout each trial. During the task periods, coloured squares subtending 1.8° were displayed against a dark background in the left and right upper quadrants, centred 5° lateral and 3° superior to the fixation cross. In each of these two locations, stimuli appeared for 56 ms and were separated from each other by a further 56 ms, giving a presentation rate of 9 stimuli/s. The offset of a stimulus on the left coincided with the onset of a stimulus on the right, and vice versa. Target squares were red; non-target squares were green. In each location, targets occurred with probability 0.0006 for each 112 ms period during the first 18 s of each trial (one target over the 10 trials) and with probability 0.007 during the remaining 42 s of each trial (27 targets over the 10 trials). The average interval between targets was 16 s.

Subjects were instructed to maintain fixation at the centre of the display throughout each trial, and to begin each trial by attending covertly to one of the two stimulus locations and ignoring the other. This starting location was counter-balanced across trials. On detecting a target stimulus in the attended location, subjects had to respond by shifting attention covertly to the opposite location, and by moving the index finger of the dominant hand in the direction of this shift. The rest of the trial then proceeded in the same manner, attending at the new (previously ignored) location and ignoring the old (previously attended). Attention thus alternated between the two spatially separated streams of rapid serial visual stimuli, shifting from one stream to the other on detection of each attended target. Essentially, this task consisted of two oddball paradigms, presented side by side and alternately attended.

As our interest lay not in psychophysical measures of ability to direct attention but in the neurophysiological effects associated with successful direction of attention, the task was designed so that most subjects would perform at or near ceiling. Before entering the scanner, subjects practised the task until they felt comfortable with it. Once in the scanner, subjects were permitted to rest for up to 3 min between trials in order to avoid visual fatigue and to relieve anxiety.

2.3. Behavioural recording

Fixation was monitored using an infrared eye tracking system (ISCAN, Burlington, MA, USA). Infrared illumination of the eye was supplied by an array of LEDs mounted on the head coil and arranged so as to minimise the external magnetic field due to current flow. The eye image was recorded by an infrared camera mounted at the rear of the magnet bore, and transmitted to a computer outside the scanner room for analysis. The eye tracker was calibrated at the beginning of each scanning session, and recalibrated as necessary between trials. Excursions of 1.25° (25% of the distance from fixation to the target location) or more were designated as breaks in fixation. (Noise in the tracking system prevented reliable detection of saccades less than 1.25° in amplitude).

In order to avoid magnetic transients associated with electrical switching, an optical signalling device was constructed to transduce behavioural data. A high-output red LED (Radio Shack #276-086A, 5 cd at 660 nm peak) was mounted at the top of a wooden enclosure, powered from an external supply via a twisted-pair cable so as to minimise external magnetic field. Two strands of DB-1000 1 mm plastic optical fibre were mounted in holes drilled at the bottom of this enclosure, so as to be illuminated or shaded depending on whether the subject's finger was positioned at the enclosure's left or right side. Outside the scanner room, a fast-acting Type 7H cadmium selenide photocell (Mouser Electronics #621-CL707H) in parallel with a 100 MΩ resistor transduced the resulting optical signal into a standard personal computer (PC) game port, which was sampled at 18 s^{-1}.

2.4. Scanning

During each 120-s trial, 40 single-shot echo-planar images (TR=3 s, effective TE=40 ms, flip angle 90°) were collected in each of 19 to 21 coronal slices spanning the entire head volume and oriented perpendicular to the midsagittal line between the anterior and posterior commissures. Images were 7 mm thick and spaced 1 mm apart, with a 20 cm square field of view in a 64×64 matrix for an in-plane resolution of 3.125 mm, and were acquired on a General Electric Signa 1.5T system with a standard birdcage head coil. Scanning was synchronised to the onset of stimulation by using a trigger pulse from the scanner to cue stimulus delivery. Following the functional scan, T1-weighted (TR=500 ms, TE=8 ms) and high-resolution echo-planar (spin-echo, TR=3s, TE=80 ms) images were acquired in 256×256 matrices, in the same planes and with the same field of view as the functional images.

2.5. Analysis

Response latencies for correctly detected targets in the

left and right hemifields were analysed using a 2×2 (group by hemifield) analysis of variance. Again, since the design was intended to produce performance at or near ceiling, latencies for misses and false alarms were too few to be usefully analysed.

Functional images were corrected for head motion using decoupled automated rotational and translational motion correction [55], a method that uses a *k*-space representation of the images to separate rotational and translational (*k*-space phase) components. Linear trend and baseline offset were removed from each trial separately. A thresholding method was applied to temporally averaged, motion-corrected functional images to classify voxels as brain or non-brain, and these automatically generated classifications were then manually examined and retouched. An ideal waveform was constructed, 1 for time points within each of the task periods and 0 for time points within each of the fixation periods. The first point within each of these periods was excluded to allow for haemodynamic lag. In addition, all points within and immediately following breaks in fixation were excluded. The permutation test [10] component of the AFNI software package [31] was used to generate two-tailed probabilities for task-related activation of each brain voxel.

SPM99 [34] was used to compute spatial transformations that normalised each subject's echo-planar images onto a template brain. The probability maps computed by AFNI for the analysis of task versus fixation were then imported into SPM99 as SPM{*z*}s, spatially smoothed, and subjected to the identical spatial transformations. A voxelwise *t*-test was applied over this set of spatially normalised individual maps, producing an SPM{*t*} representing group activations. Tail probabilities for clusters of active voxels were then computed with reference to the distribution of expected cluster sizes [35], for each group separately and for the comparison between groups.

As a separate analysis, within each individual data set and without blurring or spatial normalisation, probability maps from the task-versus-fixation comparison were used in combination with each subject's anatomical images to draw individualised regions of interest for a left-hemifield-versus-right-hemifield attention comparison. The three regions of interest in each hemisphere consisted of five voxels in ventral occipital cortex in the neighbourhood of the middle occipitotemporal gyrus, four voxels just superior to the fundus of the intraparietal sulcus, and four voxels in the superior parietal cortex. Despite variation across subjects in the extent of activation, sizes of these regions were held constant across subjects so as to ensure comparability of error variances in the subsequent analysis of variance [12]. In cases in which activations were of insufficient extent to furnish the desired number of voxels, sub-threshold tail probabilities and local anatomical features were used to guide the placement of regions. These regions were drawn on a single slice or on adjacent slices whose anterior–posterior Talairach coordinate was approximately −70 mm. Regions of interest for all subjects are illustrated in Fig. 1.

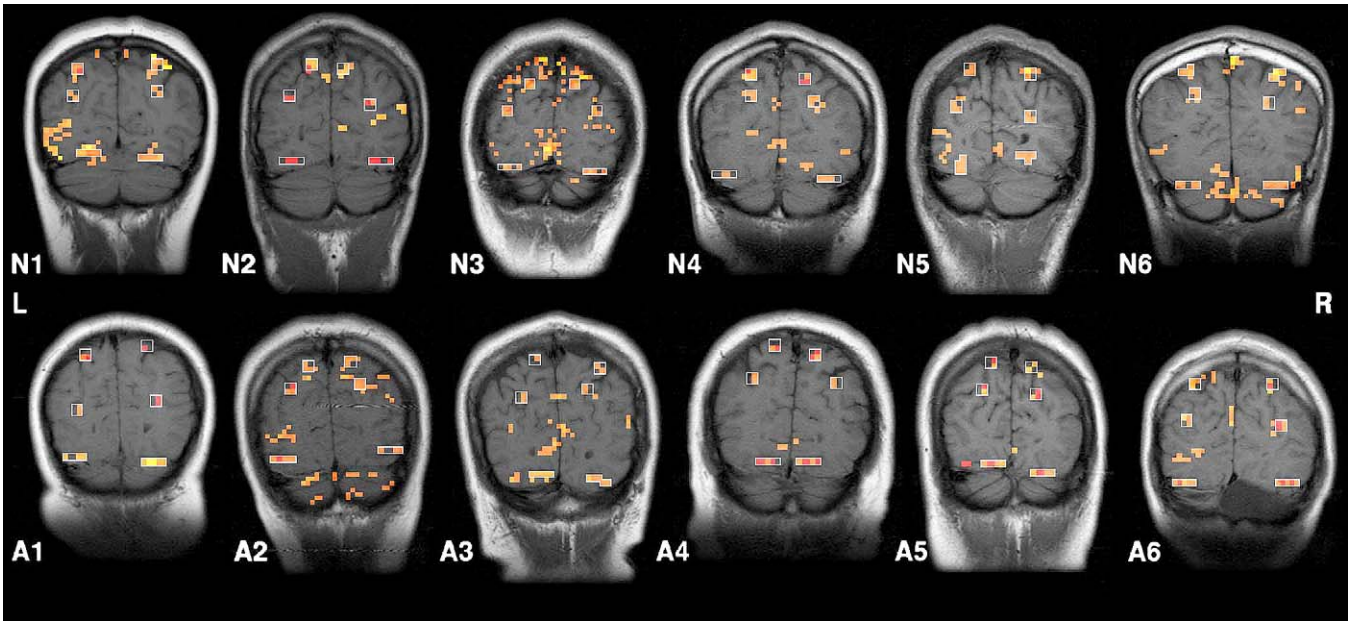

Fig. 1. Attentional regions of interest for normal (top) and autistic (bottom) subjects. In each case, functional regions of interest for the attention comparison were drawn in the contiguous areas that were most strongly activated in the task-versus-fixation comparison, within the bounds of the individual anatomical areas of interest. Note the variations in individual gyral and sulcal anatomy, especially in the intraparietal region. In subjects A1, A3, A5, and N5, some regions mapped to adjacent slices; for the purpose of this illustration these have been projected onto a single slice.

For the attention comparison, behavioural data from each subject were used to define a second ideal waveform that described the direction of attention as a function of time, within the task periods only. In order to account for haemodynamic delay the first point in each task period was excluded from this waveform, as was the first point following each shift of attention. In addition, all points during breaks in fixation were excluded. In cases of missed targets or false alarms, points were excluded backwards in time to the previous correct response or to the beginning of the task period, and forward in time to the next correct response or to the end of the task period. The points remaining after these exclusions were assigned a value of 1 for leftward attention, or 0 for rightward attention. Because this second ideal waveform was defined only within the task periods, this attention comparison was independent of the earlier comparison of task versus fixation.

The regression coefficient between the attention waveform and the fMRI time series was transformed to a *z*-score at each voxel, forming an SPM{*z*}. *z*-Scores from this map were then averaged within each region of interest, to form a *z*-score reflecting the degree of attention-related activity in the group of selected voxels as a whole. Since the ideal waveform was arbitrarily chosen to be positive for leftward attention and zero for rightward attention, a positive regional *z*-score denotes correlation with leftward attention while a negative regional *z*-score denotes correlation with rightward attention. Regional *z*-scores were subjected to a $2 \times 2 \times 3$ (group by hemisphere by region-of-interest) analysis of variance, including age as a covariate. Post hoc *t*-tests were applied as indicated by *F* values from this analysis.

3. Results

Behavioural data, detailed in Table 2, show that normal subjects and most subjects with autism had little difficulty performing the task. Only one subject, in the autism group, accomplished fewer than 13 of the 14 nominal target detections in each location. The average accuracy, calculated as the ratio between the number of correctly detected targets and the total number of detection opportunities, was over 90% for both groups. In terms of response latency, both groups had a slight right hemifield advantage which was not significant [$F(1,20)=0.09$, $P=0.77$], and the autism group responded slightly more slowly but not significantly so [$F(1,20)=0.22$, $P=0.64$].

Talairach coordinates [78] and statistics of activated foci in the whole-brain comparison of task versus fixation are detailed in Table 3. In normal subjects, the task strongly activated a network of cortical regions comprising the left superior parietal lobe, left middle temporal gyrus, left inferior and middle frontal gyri, bilateral premotor cortex, and medial frontal gyrus. In addition, the right superior parietal lobe in the normal group was significantly activated in comparison with the autism group. Pooled activations in subjects with autism were weaker and largely confined to the bilateral ventral occipital cortex and striate cortex, though there was a trend ($P=0.059$) towards activation in the left orbitofrontal cortex. Surface views of these pooled activations for each subject group are shown in Fig. 2.

Talairach coordinates for each region of interest in the attention comparison are given in Table 4. fMRI time series for each region, averaged within each subject group,

Table 2
Numbers of hits, misses, and false alarms, accuracy ratios [hits/(hits + misses)], and response latencies, for targets in each hemifield, for the autistic (top) and normal (bottom) groups

Subject	Left targets						Right targets					
	Hit	Miss	FA	Accuracy (%)	Latency (ms)	S.D. (ms)	Hit	Miss	FA	Accuracy (%)	Latency (ms)	S.D. (ms)
A1	13	0	2	100	578	89	14	0	0	100	683	105
A2	4	4	2	50	1342	200	3	9	3	25	1108	365
A3	14	0	0	100	571	171	14	0	1	100	506	53
A4	14	0	2	100	557	96	15	0	1	100	562	76
A5	14	0	2	100	639	173	13	0	1	100	601	103
A6	13	0	0	100	578	32	13	0	1	100	729	207
Average				92	711	310				88	698	216
N1	14	0	0	100	735	265	14	0	0	100	676	79
N2	14	0	0	100	950	279	14	0	0	100	742	108
N3	14	0	1	100	579	89	14	0	0	100	583	92
N4	13	1	1	93	582	57	15	1	0	94	653	107
N5	14	0	0	100	702	89	14	0	0	100	624	74
N6	14	0	0	100	554	52	14	0	0	100	598	85
Average				99	684	150				99	646	58

As the task was designed so that most of the subjects performed at ceiling, d'-scores are not given.

Table 3
Talairach coordinates, *t*-scores, maximum *z*-scores, extents, and tail probabilities for activated foci in the normal group, in the autism group, and for the comparison between groups

Region	Coordinates			*t*	z_{max}	mm^3	*P*
Normal							
L SPL	−28	−56	60	6.58	3.23	376	0.000
L MTG	−64	−64	6	4.40	2.70	208	0.002
R premotor	46	−2	58	4.40	2.70	240	0.001
L premotor	−36	4	58	5.05	2.88	272	0.000
L IFG	−44	16	−8	3.58	2.41	280	0.000
L MFG	−28	66	22	3.05	2.19	160	0.014
MedFG	4	12	54	4.10	2.60	112	0.014
Autistic							
Striate	−8	−74	16	6.74	3.27	168	0.044
L vO	−33	−76	−18	3.61	2.42	224	0.022
R vO	28	−76	−19	3.52	2.39	224	0.022
L OFC	−30	34	−12	3.52	2.39	144	0.059
Comparison							
L SPL	−32	−56	60	4.48	3.24	944	0.000
R SPL	28	−66	52	3.39	2.70	504	0.003
L MTG	−62	−66	2	4.53	3.27	952	0.000
L PoCG	−48	−32	60	3.41	2.72	504	0.003
R premotor	46	−2	60	3.64	2.84	608	0.002
L IFG	−50	10	−8	3.61	2.82	896	0.000
L MFG	−28	56	26	3.08	2.52	448	0.006
L MFG	−46	48	12	2.75	2.32	336	0.010
MedFG	0	14	54	3.40	2.71	552	0.002

are shown in Fig. 3, and *z*-scores are detailed in Table 5. The analysis of variance showed a main effect of group, reflecting a tendency of many areas of the autistic brain to activate more when attending left than when attending right [$F(1,59)=4.76$, $P=0.033$]. In addition, a group×hemisphere×region-of-interest effect reflected group differences in patterns of regional activation [$F(2,59)=4.17$, $P=0.020$]. Post hoc *t*-tests revealed group differences in the left ventral occipital cortex, which was relatively activated during left attention in the autistic brain but during right attention in the normal brain [$t(10)=2.55$, $P=0.029$], and in the left intraparietal sulcus, which was activated during left attention in both groups but more highly so in the case of the autistic group [$t(10)=3.29$, $P=0.008$].

Notably, the three largest *z*-scores in the left ventral occipital cortex came from the three subjects (A1, A2, A3) with clinical diagnoses of autism. The two males with clinical diagnoses of autism (A2, A3) also generated the two greatest right intraparietal activations during right attention as compared to left attention. The right ventral occipital cortex was significantly [folded $F(5,5)=10.33$, $P=0.023$] more variable in the autism group than in normals: in the two subjects with clinical diagnoses of Asperger syndrome (A4, A5), it activated more for right attention than for left attention. Although no significant group effects were seen in the superior parietal region, the right superior parietal region was significantly more variable in the autistic group [folded $F(5,5)=9.06$, $P=0.030$], with three subjects having large positive (i.e., left-attention) *z*-scores.

4. Discussion

In a task demanding sustained, covert attention to lateral locations in the visual field, the autistic brain activated ventral occipital and striate regions instead of the normal network of superior parietal, middle temporal, dorsolateral prefrontal, premotor, and medial frontal cortices. In a further analysis of the effect of attention within individually mapped functional brain regions, the normal tendency to activate the left ventral occipital cortex while attending to the right hemifield was reversed, and the normal tendency to activate the left intraparietal sulcus while suppressing the right hemifield was augmented. In general, the autistic brain tended to be more active while attending to the left hemifield than while attending to the right. The data also suggested a possible relationship between neurophysiology and clinical behavioural features: the three subjects with clinical diagnoses of autism had particularly large reversed (i.e., left-attention) activations in the left ventral occipital cortex, and the two males within this subgroup had the most augmented right-attention activations in the right intraparietal sulcus.

As our experimental task has much in common with the

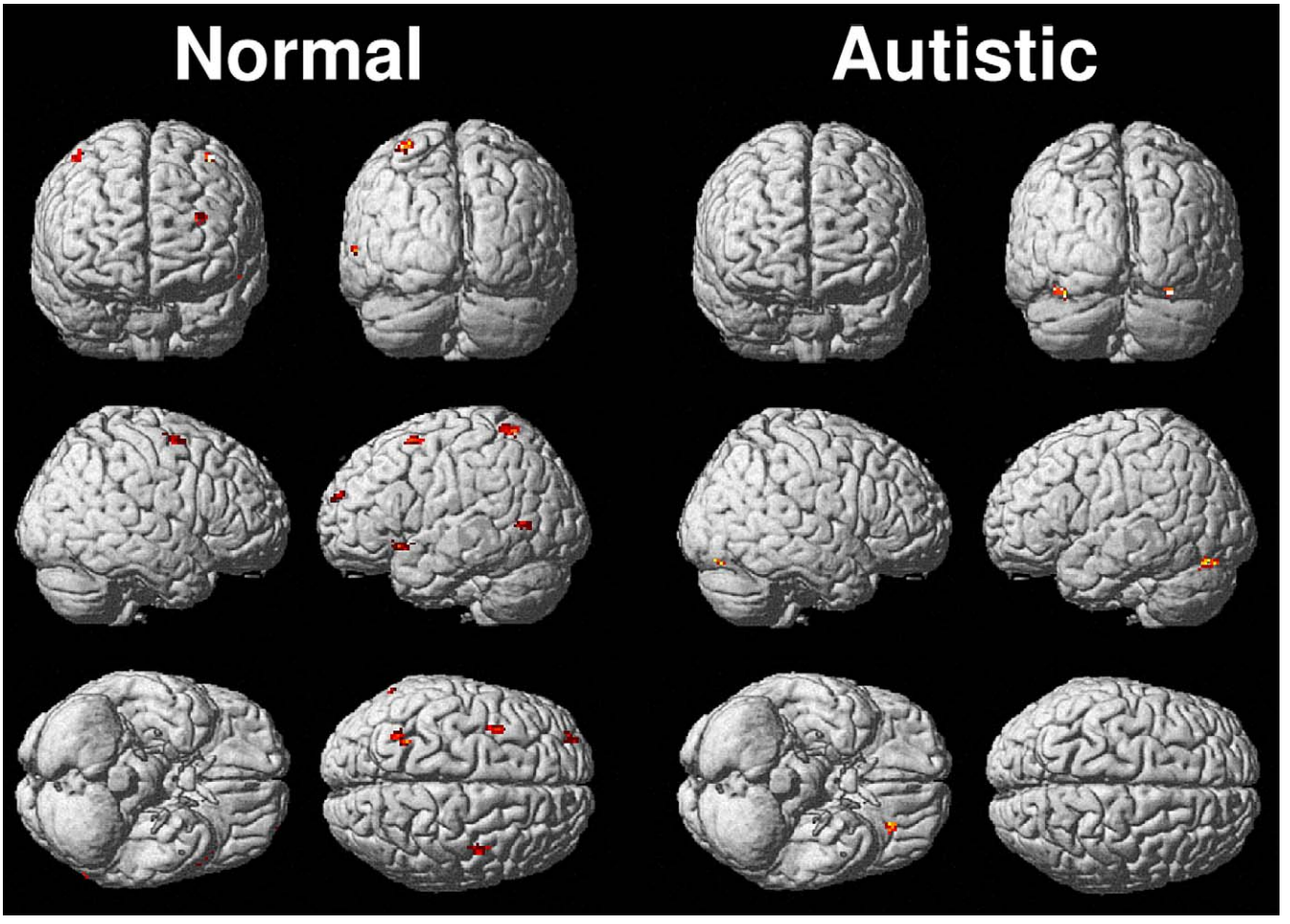

Fig. 2. Surface views of significant activated clusters of voxels for normal (left) and autistic (right) subjects. While normal subjects activated a network of cortical regions including the left superior parietal lobe, left middle temporal gyrus, left inferior and middle frontal gyri, bilateral premotor cortex, and medial frontal gyrus, subjects with autism activated bilateral ventral occipital cortex.

classic oddball paradigm, results of our comparison between task and fixation may be expected to bear some similarity to the results of fMRI studies of oddball tasks. Indeed, our results show a pattern in which visual modality-specific oddball regions were significantly activated in the autism group, whilst modality-independent oddball regions were significantly activated in the normal group. In particular, the striate and extrastriate occipital activations in the autism group correspond to the modality-specific loci in fMRI studies of visual versus auditory oddball targets [91,77,52], and in the normal group the middle temporal, dorsolateral prefrontal, medial frontal, and premotor loci are a subset of the modality-independent loci common to visual oddball tasks [58,22,4] and oddball tasks in general [91,77,52]. Unlike most of these studies of oddball tasks, the current study did not find activations localised to insula, thalamus, or supramarginal gyrus, and the active regions that were identified were predominantly left-lateralised. This lack of complete overlap with previous results may stem from several methodological differences. First, our analysis compared task blocks to fixation blocks rather than target events to non-target events, and as a result was more sensitive to brain regions involved in the task in general rather than those involved specifically in evaluating targets. Second, our small number of subjects no doubt compounded the effects of spatial blurring and whole-brain spatial normalisation to decrease the sensitivity of our analysis. Third, the demands of our task differed from those of the oddball tasks used in these previous fMRI studies: in our paradigm, target stimuli differed from

Table 4
Talairach coordinates (mean±S.D.) for regions of interest derived from the task-versus-fixation comparison, for autistic and normal subjects separately

	Normal	Autistic
L vO	(−28±3, −69±6, −15±8)	(−26±14, −76±4, −18±6)
R vO	(27±7, −69±6, −13±10)	(28±10, −76±4, −19±8)
L IPS	(−33±5, −69±6, 29±7)	(−30±7, −77±3, 25±9)
R IPS	(25±4, −69±6, 26±9)	(25±7, −77±3, 26±8)
L SPL	(−28±11, −69±6, 50±2)	(−21±9, −74±6, 50±6)
R SPL	(25±14, −69±6, 49±3)	(21±7, −74±6, 49±5)

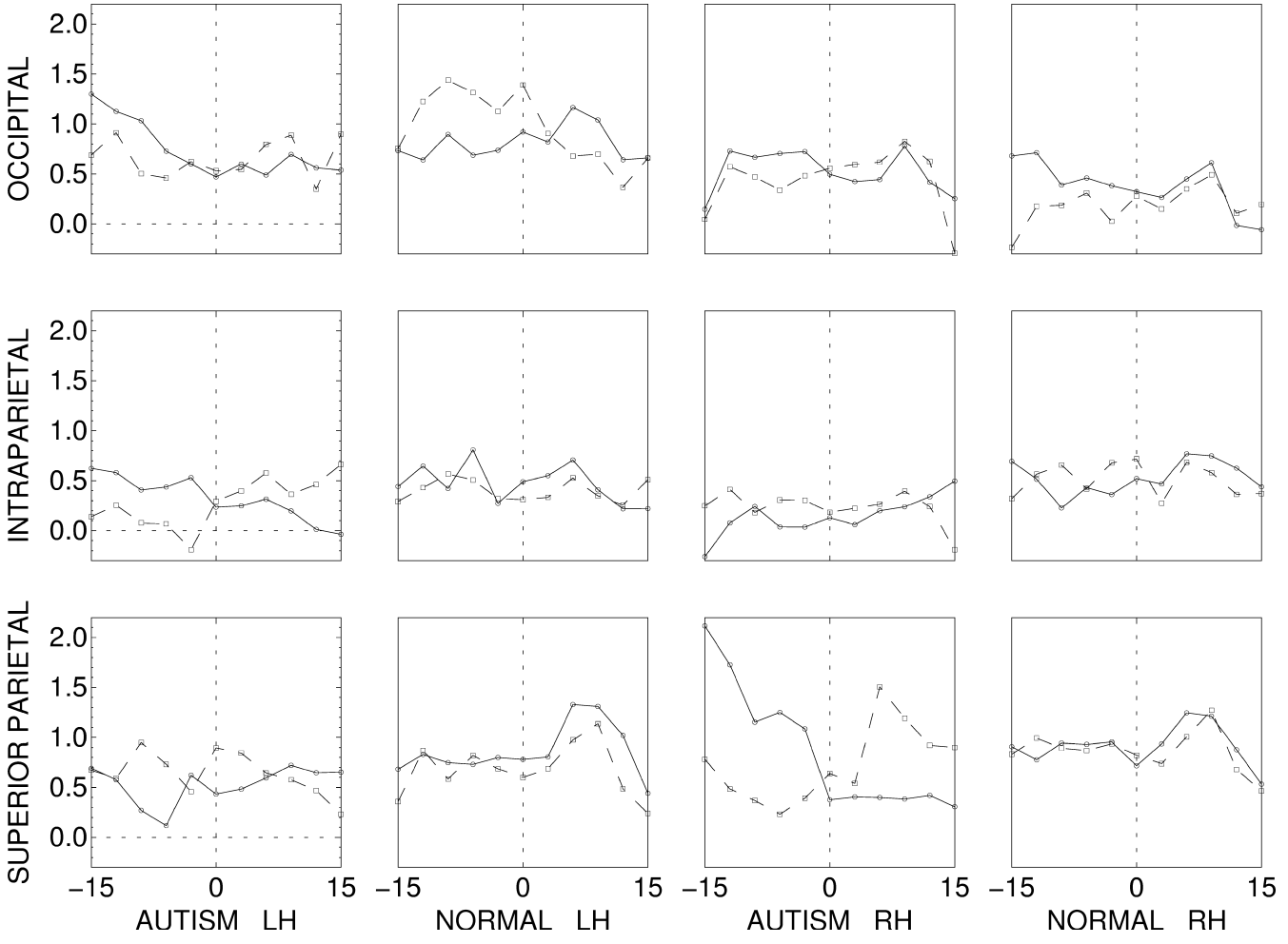

Fig. 3. Grand averages of fMRI time series from left (left two columns) and right (right two columns) hemispheres, for shifts from left visual field to right visual field (solid line) and from right visual field to left visual field (broken line). The horizontal axis is seconds from the time of an attention shift; the vertical axis is percent above the baseline signal recorded during the fixation periods. Time series were averaged from 6 s following the preceding shift or the beginning of the task period, up to the time of the next shift or the end of the task period. Note in the left hemisphere the autistic lack of attentional modulation in ventral occipital cortex, (top left), and heightened modulation in intraparietal cortex (middle left). A large average difference in the superior parietal cortex (bottom right) arose from only three of the six subjects in the autism group and was therefore not statistically significant.

non-targets in colour rather than form, and in addition, a continuous stream of distractors was present at an unattended location.

In the attention comparison, our particular regions of interest were chosen in order to examine the effects of these two spatially separated streams of attended and suppressed stimuli, and the region-of-interest approach in general was applied in order to avoid the deleterious effects of blurring and normalisation—effects that are particularly problematic in some of the brain areas of interest. In ventral occipital cortex, the effect of selective attention is relatively easy to discern statistically since the sensory signals driving it are strong and the anatomical variability across subjects is low. The same cannot be said, however, for the effect in intraparietal sulcus. Within individuals, this attention effect is subtle, reaching significance in a few of the autism subjects but in none of the normal controls. This subtlety of the underlying signal within subjects is exacerbated by anatomical variation between subjects: in a full 30% of the normal population, the intraparietal sulcus follows an unpredictable, zigzag course through the parietal lobe, sending off varying numbers of small rami as it descends toward the transverse occipital sulcus [64]. Spatial averaging in coordinate systems based on global landmarks would therefore tend to eliminate localised, weak activations. In light of this high degree of normal variation in parietal anatomy, several authors [66,24,90,11] have noted the necessity of examining functional anatomy within individuals rather than in a spatial average of individual brains.

In patient populations, and particularly in autism where cerebral anatomic abnormalities have been identified, the weakening of statistical power inherent in whole-brain spatial averaging can only be magnified [75,70,63,16,1]. Given the weakness of the underlying BOLD signal and the variability of the relevant anatomical features both

Table 5
z-Scores from the comparison of left attention (positive *z*) to right attention (negative *z*) in ventral occipital cortex, intraparietal sulcus, and superior parietal lobe for the autistic (top) and normal (bottom) groups

Subject	L vO	R vO	L IPS	R IPS	L SPL	R SPL
A1	+1.70	+0.50	+0.92	+0.14	+1.51	+2.34
A2	+2.19	+1.34	+0.82	−1.58	+1.09	−0.89
A3	+1.43	+1.20	+0.59	−1.08	−0.28	+1.27
A4	+0.45	−0.59	+0.94	+0.00	+0.13	−0.21
A5	−1.41	−1.34	+0.50	−0.11	−0.73	−0.87
A6	+0.40	+0.93	+1.07	−0.70	−0.70	+1.93
Average	+0.79	+0.34	+0.81	−0.55	+0.17	+0.59
S.D.	1.29	1.08	0.22	0.68	0.94	1.43
N1	−1.52	+0.54	−0.16	−0.71	−0.79	−0.41
N2	−0.80	+1.17	−0.19	+0.30	+0.04	+0.21
N3	−1.60	+0.71	+0.31	−0.27	−0.33	−0.13
N4	−1.43	+0.38	+0.28	−0.51	−0.08	−1.04
N5	−1.55	+1.00	+0.50	−0.67	+0.04	+0.17
N6	+1.17	+1.17	+0.71	−0.63	+0.83	+0.07
Average	−0.96	+0.83	+0.24	−0.41	−0.05	−0.19
S.D.	1.08	0.34	0.36	0.39	0.53	0.48

within and possibly between groups, our strategy of within-subjects functional mapping and individual permutation testing followed by groupwise parametric testing is very important in revealing the effect that we have demonstrated. Permutation testing is particularly powerful in situations such as this, where the number of subjects available is small and where anatomical variation demands within-subject statistical analysis [65].

In the comparison of task to fixation, the finding of heightened ventral occipital activation and lowered prefrontal, parietal, and temporal activation in autism as compared to controls is consistent with the theme of abnormally heightened early sensory activation that has emerged from several fMRI studies of autism. In the further comparison of attention conditions within the task, the findings of generally increased activation during attention to the left hemifield and an absent effect of spatial attention in ventral visual areas are consistent with earlier quantitative electroencephalographic findings [9]. The heightened activity in intraparietal cortex is a new finding, and helps to sketch the outlines of abnormal information flow in autistic perception. We propose that this pattern of information flow is characterised by three elements: (1) hyper-arousal, that is, primary sensory processing that is abnormally intense [72,7,32,75,70] and abnormally generalised across anatomical regions and functional systems [49,50,9], and (2) impaired early selection of relevant stimuli [79,9], leading to (3) overloading of higher-order processes, such as the suppressive process identified in the current study.

What physiological causes and effects might explain and relate these three elements? A recent neuropathologic study [17,18] identified in postmortem autistic brains a reduction in the size of cortical minicolumns and an increase in cell dispersion within minicolumns. The authors speculated that a resulting increase in the total number of minicolumns would lead to overconnected and insufficiently inhibited neural networks, with consequent reductions in information content, signal-to-noise, and discriminability of competing inputs—in other words, hyper-arousal and impaired selection. This hyperconnectivity may be akin to that induced by a failure of synaptic pruning in Fragile X [42], a syndrome that shares many cognitive characteristics with autism [33]. Indeed, quantitative MRI anatomical studies have revealed a pattern of early brain overgrowth in autism [15,27,16,76,5], a finding that may be the gross manifestation of such a failure.

The flood of input generated by over-aroused, underselective primary processing would from the earliest months of infancy overload nascent higher-order cognitive processes—processes whose development may be independently sabotaged by the same neuropathology that affects primary regions. Faced with this bottleneck in higher-order cognition, the developing and plastic brain would likely evolve a cognitive style that emphasises low-level features and eschews reliance on global patterns [43]—in other words, weak central coherence. Weak coherence in turn may impair the use of contextual information in complex perceptual and executive tasks [38], including theory-of-mind tasks [74], impede the development of joint attention and shared affect [51,73], and perturb or prevent the activity-dependent development [26,1] of specialised modules for such tasks as theory-of-mind, face processing, and language. This failure to use context and to implement a theory of mind may result in a style of unsupervised learning founded on statistical associations rather than learning that is directed by the intentionality of others [37], and to a preference for ritualised, scripted, and repeatable interactions.

We have considered autistic cognition in terms of a

bottom-up developmental influence of low-level attentional processing on higher-order cognitive processing. However, top-down influences are also possible, and indeed these may seem a more parsimonious explanation of autistic deficits in late stages of information processing affecting memory, language, and reasoning [59]. In this view, hyperactivation of primary perceptual systems may arise as a consequence of a more fundamental deficit in complex information processing. Functional imaging of the adult autistic brain, though more practical than imaging of autistic children, cannot distinguish between a bottom-up developmental chain of dysfunction, a top-down chain, or multiple simultaneous loci of dysfunction.

We have interpreted our intraparietal result in terms of the active suppression of unattended stimuli. An alternative interpretation is that intraparietal activation reflects oculomotor activity in response to stimuli in the unattended hemifield. Although in the present study gross eye movements were identified and rejected, subjects still could have made subtle deviations in eye position below the resolution limit of our eye tracker. More significantly, oculomotor-related activation in intraparietal sulcus could have arisen even in the absence of actual eye movements, due to planning of unexecuted reflexive saccades [39] and/or inhibition of reflexive saccades [23]. Although recent results in non-spatial tasks suggest that the role of intraparietal sulcus is more general than simple saccade preparation [90], in paradigms that include a spatial component it is difficult to factor out the role of oculomotor planning and inhibition. This question of distractor suppression versus saccadic activity can be addressed more specifically in future studies using tasks of non-spatial selective attention.

Anxiety is always a potential confound in experimental studies of autism, since people with autism are so prone to anxiety in novel circumstances and in situations that demand rapid or accurate performance. Attempts were made to reduce levels of anxiety by offering subjects ample opportunity to practise the task before entering the scanner, and by allowing a variable rest period rather than a strictly timed one. Although this variable rest period between trials may itself have posed a confound, in our estimation the anxiety which these breaks helped to alleviate would have posed an even greater obstacle to comparison of the two groups.

Although our method of individual functional mapping solves the problem of individual variation in functional anatomy, it introduces an assumption that the regions identified in each subject group are functionally comparable. While it seems likely that regions bearing similar relationships to local landmarks and similar functional correlations with the task subserve similar processes, purely correlational methods such as functional imaging cannot guarantee this. When the locations of our regions of interest were transformed to Talairach space (Table 4), the coordinates in autistic brains seemed posteriorly shifted by 5 mm to 8 mm relative to normal. Our 8 mm interval between the centres of neighbouring coronal slices makes it impossible to determine whether this apparent shift is a genuine phenomenon, especially given only six subjects with autism. If this posterior shift is real, it may be a byproduct of abnormality in distant structures that has perturbed the positions of global landmarks. Such a perturbation might, for instance, occur as an indirect effect of developmental overgrowth of the anterior cerebrum.

Sensitive statistical methods can, of course, be a double-edged sword; an increase in statistical power can come hand in hand with increased susceptibility to Type 1 error. Our strategy of computing z-scores for each individual subject and then computing a second, group statistic over these individual statistics implements a mixed-effects (often referred to as 'random-effects') statistical model [47]. Although mixed-effects analysis does prevent perturbation of the statistical result by one or a few individuals who are atypical of the rest of the sample, it cannot guard against the possibility that the sample as a whole is atypical of the population. The circumstances of the current study admit at least two possible types of sample bias: a chance bias in random sampling, and a systematic bias to due selection of only high-functioning cases. In the former case, the small size of the the experimental sample increases the risk that this sample is not representative of the population from which it has been drawn. In the latter case, findings may be peculiar to high-functioning people with autism. It may especially be the case that compensatory cognitive strategies and other secondary phenomena differ in high-functioning and 'low-functioning' subpopulations. Further work that includes larger samples and more directly addresses autism's developmental aspect will be of value in examining these possible biases.

We have presented physiological evidence for impaired early selection of relevant stimuli and for compensatory suppression of irrelevant stimuli in adults with autism spectrum disorders. We have also outlined a sequence of physiological and cognitive dysfunctions by which hyperarousal and impaired selection may produce weak central coherence and other higher-order cognitive patterns typical of autism. Our findings, though statistically robust within our sample, are based on a small number of adult subjects with heterogeneous diagnoses within the autism spectrum. Future work would benefit from younger, larger, and separate samples of autism, Asperger syndrome, and also 'unaffected' sibs who have features of the broader autism phenotype. Contrasting across all these sub-populations the relationships between elementary abnormalities of attention and higher-order abnormalities of cognition could highlight the junctures at which cognitive development goes awry. Discovering the maturational windows at which a mild proto-deficit becomes magnified into the full syndrome of autism would be a key step towards the development of targeted interventions.

Acknowledgements

This work was supported by a grant from the National Alliance for Autism Research. In addition, a portion of the data analysis and writing was conducted while M.K.B. was supported by a grant from Cure Autism Now. We thank Margaret Bauman, David Beversdorf, and Deborah Fein for subject referrals, David Beversdorf for sharing ADI-R scores of four of the subjects, and most of all our subjects for giving so much of their time.

References

[1] N. Akshoomoff, K. Pierce, E. Courchesne, The neurobiological basis of autism from a developmental perspective, Dev. Psychopathol. 14 (2002) 613–634.
[2] G. Allen, E. Courchesne, Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism, Am. J. Psychiatry 160 (2003) 262–273.
[3] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, American Psychiatric Association, Washington, DC, 1994.
[4] B.A. Ardekani, S.J. Choi, G.-A. Hossein-Zadeh, B. Porjesz, J.L. Tanabe, K.O. Lim, R. Bilder, J.A. Helpern, H. Begleiter, Functional magnetic resonance imaging of brain activity in the visual oddball task, Cogn. Brain Res. 14 (2002) 347–356.
[5] E.H. Aylward, N.J. Minshew, K. Field, B.F. Sparks, N. Singh, Effects of age on brain volume and head circumference in autism, Neurology 59 (2002) 175–183.
[6] S. Baron-Cohen, A.M. Leslie, U. Frith, Does the autistic child have a 'theory of mind'?, Cognition 21 (1985) 37–46.
[7] S. Baron-Cohen, H.A. Ring, S. Wheelwright, E.T. Bullmore, M.J. Brammer, A. Simmons, S.C.R. Williams, Social intelligence in the normal and autistic brain: an fMRI study, Eur. J. Neurosci. 11 (1999) 1891–1898.
[8] M.K. Belmonte, Shifts of visual spatial attention modulate a steady-state visual evoked potential, Cogn. Brain. Res. 6 (1998) 295–307.
[9] M.K. Belmonte, Abnormal attention in autism shown by steady-state visual evoked potentials, Autism 4 (2000) 269–285.
[10] M.K. Belmonte, D.A. Yurgelun-Todd, Permutation testing made practical for functional magnetic resonance image analysis, IEEE Trans. Med. Imaging 20 (2001) 243–248.
[11] M.K. Belmonte, D.A. Yurgelun-Todd, Anatomic dissociation of selective and suppressive processes in visual attention, NeuroImage 19 (2003) 180–189.
[12] V. Bosch, Statistical analysis of multi-subject fMRI data: assessment of focal activations, J. Magn. Reson. Imaging 11 (2000) 61–64.
[13] J.A. Burack, Selective attention deficits in persons with autism: preliminary evidence of an inefficient attentional lens, J. Abnorm. Psychol. 103 (1994) 535–543.
[14] J.A. Burack, J.T. Enns, J.E.A. Stauder, L. Mottron, B. Randolph, Attention and autism: behavioral and electrophysiological evidence, in: D.J. Cohen, F.R. Volkmar (Eds.), Handbook of Autism and Pervasive Developmental Disorders, 2nd Edition, Wiley, New York, 1997, pp. 226–247.
[15] R.A. Carper, E. Courchesne, Inverse correlation between frontal lobe and cerebellum sizes in children with autism, Brain 123 (2000) 836–844.
[16] R.A. Carper, P. Moses, Z.D. Tigue, E. Courchesne, Cerebral lobes in autism: early hyperplasia and abnormal age effects, NeuroImage 16 (2002) 1038–1051.
[17] M.F. Casanova, D.P. Buxhoeveden, A.E. Switala, E. Roy, Minicolumnar pathology in autism, Neurology 58 (2002) 428–432.
[18] M.F. Casanova, D.P. Buxhoeveden, A.E. Switala, E. Roy, Asperger's syndrome and cortical neuropathology, J. Child Neurol. 17 (2002) 142–145.
[19] B.J. Casey, C.T. Gordon, G.B. Mannheim, J.M. Rumsey, Dysfunctional attention in autistic savants, J. Clin. Exp. Neuropsychol. 15 (1993) 933–946.
[20] F. Castelli, C. Frith, F. Happé, U. Frith, Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes, Brain 125 (2002) 1839–1849.
[21] K.T. Ciesielski, E. Courchesne, R. Elmasian, Effects of focused selective attention tasks on event-related potentials in autistic and normal individuals, EEG Clin. Neurophysiol. 75 (1990) 207–220.
[22] V.P. Clark, S. Fannon, S. Lai, R. Benson, L. Bauer, Responses to rare visual target and distractor stimuli using event-related fMRI, J. Neurophysiol. 83 (2000) 3133–3139.
[23] J.D. Connolly, M.A. Goodale, J.F.X. Desouza, R.S. Menon, T. Vilis, A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing, J. Neurophysiol. 84 (2000) 1645–1655.
[24] M. Corbetta, Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems?, Proc. Natl. Acad. Sci. USA 95 (1998) 831–838.
[25] M. Corbetta, F.M. Miezin, G.L. Shulman, S.E. Petersen, A PET study of visuospatial attention, J. Neurosci. 13 (1993) 1202–1226.
[26] E. Courchesne, H. Chisum, J. Townsend, Neural activity-dependent brain changes in development: implications for psychopathology, Dev. Psychopathol. 6 (1994) 697–722.
[27] E. Courchesne, C. Karns, H.R. Davis, R. Ziccardi, R.A. Carper, Z.D. Tigue, H.J. Chisum, P. Moses, K. Pierce, C. Lord, A.J. Lincoln, S. Pizzo, L. Schreibman, R.H. Haas, N.A. Akshoomoff, R.Y. Courchesne, Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study, Neurology 57 (2001) 245–254.
[28] E. Courchesne, A.J. Lincoln, R. Yeung-Courchesne, R. Elmasian, C. Grillon, Pathophysiologic findings in nonretarded autism and receptive developmental language disorder, J. Autism Dev. Disord. 19 (1989) 1–17.
[29] E. Courchesne, J. Townsend, N.A. Akshoomoff, O. Saitoh, R. Yeung-Courchesne, A.J. Lincoln, R. Haas, L. Schreibman, L. Lau, Impairment in shifting attention in autistic and cerebellar patients, Behav. Neurosci. 108 (1994) 848–865.
[30] E. Courchesne, J. Townsend, N.A. Akshoomoff, R. Yeung-Courchesne, A.J. Lincoln, G. Press, J. Murakami, H. James, O. Saitoh, B. Egaas, R. Haas, L. Schreibman, A new finding: impairment in shifting attention in autistic and cerebellar patients, in: S.H. Broman, J. Grafman (Eds.), Atypical Cognitive Deficits in Developmental Disorders: Implications for Brain Function, Lawrence Erlbaum, Hillsdale, NJ, 1994, pp. 101–137.
[31] R.W. Cox, AFNI: software for analysis and visualization of functional magnetic resonance neuroimages, Comput. Biomed. Res. 29 (1996) 162–173.
[32] H.D. Critchley, E.M. Daly, E.T. Bullmore, S.C.R. Williams, T. Van Amelsvoort, D.M. Robertson, A. Rowe, M. Phillips, G. McAlonan, P. Howlin, D.G.M. Murphy, The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions, Brain 123 (2000) 2203–2212.
[33] C. Feinstein, A.L. Reiss, Autism: the point of view from fragile X studies, J. Autism Dev. Disord. 28 (1998) 393–405.
[34] K.J. Friston, A.P. Holmes, K.J. Worsley, J.P. Poline, C.D. Frith, R.S.J. Frackowiak, Statistical parametric maps in functional neuroimaging: a general linear approach, Hum. Brain Mapp. 2 (1995) 189–210.
[35] K.J. Friston, K.J. Worsley, R.S.J. Frackowiak, J.C. Mazziotta, A.C. Evans, Assessing the significance of focal activations using their spatial extent, Hum. Brain Mapp. 1 (1994) 210–220.
[36] U. Frith, Autism: Explaining the Enigma, Basil Blackwell, Oxford, 1989.

[37] U. Frith, Mind blindness and the brain in autism, Neuron 32 (2001) 969–979.
[38] U. Frith, F. Happé, Autism: beyond 'theory of mind', Cognition 50 (1994) 115–132.
[39] B. Gaymard, C.J. Ploner, S. Rivaud, A.I. Vermersch, C. Pierrot-Deseilligny, Cortical control of saccades, Exp. Brain Res. 123 (1998) 159–163.
[40] G. Goldstein, C.R. Johnson, N.J. Minshew, Attentional processes in autism, J. Autism Dev. Disord. 31 (2001) 433–439.
[41] C.M. Gomez-Gonzalez, V.P. Clark, S. Fan, S.J. Luck, S.A. Hillyard, Sources of attention-sensitive visual event-related potentials, Brain Topogr. 7 (1994) 41–51.
[42] W.T. Greenough, A.Y. Klintsova, S.A. Irwin, R. Galvez, K.E. Bates, I.J. Weiler, Synaptic regulation of protein synthesis and the fragile X protein, Proc. Natl. Acad. Sci. USA 98 (2001) 7101–7106.
[43] F. Happé, Autism: cognitive deficit or cognitive style?, Trends Cogn. Sci. 3 (1999) 216–222.
[44] N.S. Harris, E. Courchesne, J. Townsend, R.A. Carper, C. Lord, Neuroanatomic contributions to slowed orienting of attention in children with autism, Cogn. Brain Res. 8 (1999) 61–71.
[45] H.J. Heinze, G.R. Mangun, W. Burchert, H. Hinrichs, M. Scholz, T.F. Münte, A. Gös, M. Scherg, S. Johannes, H. Hundeshagen, M.S. Gazzaniga, S.A. Hillyard, Combined spatial and temporal imaging of brain activity during visual selective attention in humans, Nature 372 (1994) 543–546.
[46] S.A. Hillyard, H. Hinrichs, C. Tempelmann, S.T. Morgan, J.C. Hansen, H. Scheich, H.-J. Heinze, Combining steady-state visual evoked potentials and fMRI to localize brain activity during selective attention, Hum. Brain Mapp. 5 (1997) 287–292.
[47] A.P. Holmes, K.J. Friston, Generalisability, random effects and population inference, NeuroImage 7 (1998) S754.
[48] J.B. Hopfinger, M.H. Buonocore, G.R. Mangun, The neural mechanisms of top-down attentional control, Nat. Neurosci. 3 (2000) 284–291.
[49] C. Kemner, M.N. Verbaten, J.M. Cuperus, G. Camfferman, H. van Engeland, Visual and somatosensory event-related brain potentials in autistic children and three different control groups, EEG Clin. Neurophysiol. 92 (1994) 225–237.
[50] C. Kemner, M.N. Verbaten, J.M. Cuperus, G. Camfferman, H. van Engeland, Auditory event-related brain potentials in autistic children and three different control groups, Biol. Psychiatry 38 (1995) 150–165.
[51] A. Klin, F.R. Volkmar, S.S. Sparrow, Autistic social dysfunction: some limitations of the theory of mind hypothesis, J. Child Psychol. Psychiatry 33 (1992) 861–876.
[52] D.E.J. Linden, D. Prvulovic, E. Formisano, M. Völlinger, F.E. Zanella, R. Goebel, T. Dierks, The functional neuroanatomy of target detection: an fMRI study of visual and auditory oddball tasks, Cereb. Cortex 9 (1999) 815–823.
[53] C. Lord, M. Rutter, A. Le Couteur, Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders, J. Autism Dev. Disord. 24 (1994) 659–685.
[54] B. Luna, N.J. Minshew, K.E. Garver, N.A. Lazar, K.R. Thulborn, W.F. Eddy, J.A. Sweeney, Neocortical system abnormalities in autism: an fMRI study of spatial working memory, Neurology 59 (2002) 834–840.
[55] L.C. Maas, B.D. Frederick, P.F. Renshaw, Decoupled automated rotational and translational registration for functional MRI time series data: the DART registration algorithm, Magn. Reson. Med. 37 (1997) 131–139.
[56] G.R. Mangun, S.A. Hillyard, S.J. Luck, Electrocortical substrates of visual selective attention, Attention Perform. 14 (1993) 219–243.
[57] A. Martínez, L. Anllo-Vento, M.I. Sereno, L.R. Frank, R.B. Buxton, D.J. Dubowitz, E.C. Wong, H. Hinrichs, H.J. Heinze, S.A. Hillyard, Involvement of striate and extrastriate visual cortical areas in visual attention, Nat. Neurosci. 2 (1999) 364–369.
[58] G. McCarthy, M. Luby, J. Gore, P. Goldman-Rakic, Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI, J. Neurophysiol. 77 (1997) 1630–1634.
[59] N.J. Minshew, G. Goldstein, D.J. Siegel, Neuropsychologic functioning in autism: profile of a complex information processing disorder, J. Int. Neuropsychol. Soc. 3 (1997) 303–316.
[60] N.J. Minshew, B. Luna, J.A. Sweeney, Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism, Neurology 52 (1999) 917–922.
[61] A.F. Mirsky, B.J. Anthony, C.C. Duncan, M.B. Ahearn, S.G. Kellam, Analysis of the elements of attention: a neuropsychological approach, Neuropsychol. Rev. 2 (1991) 109–145.
[62] S.T. Morgan, J.C. Hansen, S.A. Hillyard, Selective attention to stimulus location modulates the steady-state visual evoked potential, Proc. Natl. Acad. Sci. USA 93 (1996) 4770–4774.
[63] R.-A. Müller, K. Pierce, J.B. Ambrose, G. Allen, E. Courchesne, Atypical patterns of cerebral motor activation in autism: a functional magnetic resonance study, Biol. Psychiatry 49 (2001) 665–676.
[64] T.P. Naidich, A.G. Valavanis, S. Kubik, Anatomic relationships along the low-middle convexity: part I—normal specimens and magnetic resonance imaging, Neurosurgery 36 (1995) 517–532.
[65] T.E. Nichols, A.P. Holmes, Nonparametric permutation tests for functional neuroimaging: a primer with examples, Hum. Brain Mapp. 15 (2002) 1–25.
[66] A.C. Nobre, G.N. Sebestyen, D.R. Gitelman, M.M. Mesulam, R.S. Frackowiak, C.D. Frith, Functional localization of the system for visuospatial attention using positron emission tomography, Brain 120 (1997) 515–533.
[67] B. Novick, D. Kurtzberg, H.G. Vaughn Jr., An electrophysiologic indication of defective information storage in childhood autism, Psychiatry Res. 1 (1979) 101–108.
[68] S. Ozonoff, B. Pennington, S.J. Rogers, Executive function deficits in high-functioning autistic individuals: relationship to theory of mind, J. Child Psychol. Psychiatry 32 (1991) 1081–1105.
[69] J.V. Pardo, P.T. Fox, M.E. Raichle, Localization of a human system for sustained attention by positron emission tomography, Nature 349 (1991) 61–64.
[70] K. Pierce, R.-A. Müller, J. Ambrose, G. Allen, E. Courchesne, Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI, Brain 124 (2001) 2059–2073.
[71] N.J. Rinehart, J.L. Bradshaw, S.A. Moss, A.V. Brereton, B.J. Tonge, A deficit in shifting attention present in high-functioning autism but not Asperger's disorder, Autism 5 (2001) 67–80.
[72] H.A. Ring, S. Baron-Cohen, S. Wheelwright, S.C.R. Williams, M.J. Brammer, C. Andrew, E.T. Bullmore, Cerebral correlates of preserved cognitive skills in autism, Brain 122 (1999) 1305–1315.
[73] S.J. Rogers, B.F. Pennington, A theoretical approach to the deficits in infantile autism, Dev. Psychopathol. 3 (1991) 137–162.
[74] J. Russell, R. Saltmarsh, E. Hill, What do executive factors contribute to the failure on false belief tasks by children with autism?, J. Child Psychol. Psychiatry 40 (1999) 859–868.
[75] R.T. Schultz, I. Gauthier, A. Klin, R.K. Fulbright, A.W. Anderson, F. Volkmar, P. Skudlarski, C. Lacadie, D.J. Cohen, J.C. Gore, Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome, Arch. Gen. Psychiatry 57 (2000) 331–340.
[76] B.F. Sparks, S.D. Friedman, D.W. Shaw, E.H. Aylward, D. Echelard, A.A. Artru, K.R. Maravilla, J.N. Giedd, J. Munson, G. Dawson, S.R. Dager, Brain structural abnormalities in young children with autism spectrum disorder, Neurology 59 (2002) 184–192.
[77] A.A. Stevens, P. Skudlarski, J.C. Gatenby, J.C. Gore, Event-related fMRI of auditory and visual oddball tasks, Magn. Reson. Imaging 18 (2000) 495–502.
[78] J. Talairach, P. Tournoux, Co-Planar Stereotactic Atlas of the Human Brain, Thieme, New York, 1988.
[79] J. Townsend, E. Courchesne, Parietal damage and narrow 'spotlight' spatial attention, J. Cogn. Neurosci. 6 (1994) 220–232.

[80] J. Townsend, E. Courchesne, B. Egaas, Slowed orienting of covert visual-spatial attention in autism: specific deficits associated with cerebellar and parietal abnormality, Dev. Psychopathol. 8 (1996) 563–584.
[81] J. Townsend, E. Courchesne, J. Covington, M. Westerfield, N.S. Harris, P. Lyden, T.P. Lowry, G.A. Press, Spatial attention deficits in patients with acquired or developmental cerebellar abnormality, J. Neurosci. 19 (1999) 5632–5643.
[82] J. Townsend, N. Singer-Harris, E. Courchesne, Visual attention abnormalities in autism: delayed orienting to location, J. Int. Neuropsychol. Soc. 2 (1996) 541–550.
[83] J. Townsend, M. Westerfield, E. Leaver, S. Makeig, T. Jung, K. Pierce, E. Courchesne, Event-related brain response abnormalities in autism: evidence for impaired cerebello-frontal spatial attention networks, Cogn. Brain Res. 11 (2001) 127–145.
[84] R. Vandenberghe, J. Duncan, K.M. Arnell, S.J. Bishop, N.J. Herrod, A.M. Owen, P.S. Minhas, P. Dupont, J.D. Pickard, G.A. Orban, Maintaining and shifting attention within left or right hemifield, Cereb. Cortex 10 (2000) 706–713.
[85] R. Vandenberghe, J. Duncan, P. Dupont, R. Ward, J. Poline, G. Bormans, J. Michiels, L. Mortelmans, G.A. Orban, Attention to one or two features in left or right visual field: a positron emission tomography study, J. Neurosci. 17 (1997) 3739–3750.
[86] R. Vandenberghe, P. Dupont, B. De Bruyn, G. Bormans, J. Michiels, L. Mortelmans, G.A. Orban, The influence of stimulus location on the brain activation pattern in detection and orientation discrimination. A PET study of visual attention, Brain 119 (1996) 1263–1276.
[87] M.N. Verbaten, J.W. Roelofs, H. van Engeland, J.K. Kenemans, J.L. Slangen, Abnormal visual event-related potentials of autistic children, J. Autism Dev. Disord. 21 (1991) 449–470.
[88] J.A. Wainwright-Sharp, S.E. Bryson, Visual orienting deficits in high-functioning people with autism, J. Autism Dev. Disord. 23 (1993) 1–13.
[89] J.A. Wainwright-Sharp, S.E. Bryson, Visual-spatial orienting in autism, J. Autism Dev. Disord. 26 (1996) 423–438.
[90] E. Wojciulik, N. Kanwisher, The generality of parietal involvement in visual attention, Neuron 23 (1999) 747–764.
[91] T. Yoshiura, J. Zhong, D.K. Shibata, W.E. Kwok, D.A. Shrier, Y. Numaguchi, Functional MRI study of auditory and visual oddball tasks, Neuroreport 10 (1999) 1683–1688.