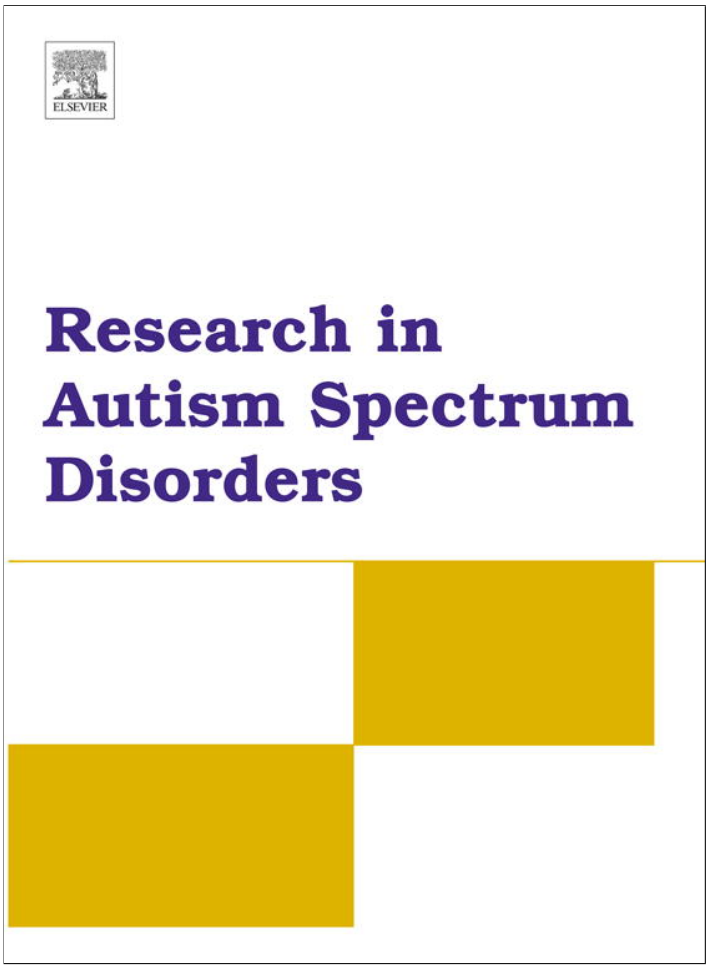

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Autistic traits, ADHD symptoms, neurological soft signs and regional cerebral blood flow in adults with autism spectrum disorders

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ABSTRACT

The resting regional cerebral blood flow (rCBF) patterns related to co-occurring symptoms such as inattention, hyperactivity, neurological soft signs and motor problems have not yet been disclosed in autism spectrum disorders (ASD).

In this study thirteen adults with ASD and ten matched neurotypical controls underwent PET. The scores of rating scales for autistic traits, attention deficit hyperactivity disorder (ADHD) and neurological soft signs were included in a factorial analysis and correlated with rCBF. Factors corresponding to "autistic/ADHD traits", "sensory-motor integration" and "Intelligence/Motor sequencing" were identified. In the ASD group, positive correlations with CBF were found for "autistic/ADHD traits" in caudate bilaterally and the inferior parietal lobule, for "sensory-motor integration" in parieto-occipital cortex and for "Intelligence/Motor sequencing" in the right temporal cortex. Notably, CBF in the left thalamus correlated negatively with all three factors. Autistic traits and ADHD symptoms were associated with shared neural substrates. The correlation between "autistic/ADHD traits" and rCBF in the caudate is possibly associated with the executive impairments and ritualistic/stereotyped behaviors apparent in ASD. Furthermore, sensory-motor deficits were correlated with rCBF in the occipital visual cortex, involved in atypical visual perception in ASD. Various behavioral and neurological symptoms are suggested to converge into the ASD phenotype.

1. Introduction

Co-occurrence of symptoms consistent with attention deficit hyperactivity disorder (ADHD) and sensory-motor problems is considered to play an important role in the phenotype of autism spectrum disorders (ASD) (Reiersen & Todd, 2008; Sturm, Fernell, & Gillberg, 2004). Individuals with ASD have qualitative impairments in reciprocal social interactions

Abbreviations: CBF, cerebral blood flow; rCBF, regional cerebral blood flow; rCMRgl, regional cerebral metabolic rate of glucose; NES, Neurological Evaluation Scale; NSS, neurological soft signs.

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and communication and have restricted repetitive and stereotyped patterns of behavior, interests and activities. ADHD is a broad diagnosis, characterized by inattention, hyperactivity and impulsivity. The diagnostic criteria for ADHD in the DSM-IV have not allowed for a patient with ASD to be given an ADHD diagnosis (American Psychiatric Association, 1994; Goldstein & Schwebach, 2004; Kooij et al., 2010). However, co-occurrence of ASD- and ADHD-related symptoms has been verified by population-based (Reiersen, Constantino, Volk, & Todd, 2007) and clinically based studies (Goldstein & Schwebach, 2004; Hofvander et al., 2009; Lee & Ousley, 2006; Mayes, Calhoun, Mayes, & Molitoris, 2012; Rydén & Bejerot, 2008). Investigations indicate that ADHD symptoms are present in about 20–80% of children with ASD (Sturm et al., 2004). Not only does the ADHD symptoms persist in adulthood (Hofvander et al., 2009), the severity of ASD seems to correlate with the co-occurrence of ADHD symptoms (Holtmann, Bolte, & Poustka, 2007). Moreover, a substantial proportion of clinically diagnosed children with ADHD meet the criteria for ASD (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010; Sturm et al., 2004). For reliable diagnosis of ASD it is appropriate to investigate different dimensions of the disorder, since no single test or neurophysiological examination is sufficiently accurate (Steer, Golding, & Bolton, 2010).

Impairment of motor control, including neurological soft signs (i.e. subtle impairments of sensory integration, motor coordination and difficulties in sequencing complex motor tasks) is common in both ASD (Mahone et al., 2006; Mayoral et al., 2010; Price, Shiffrar, & Kerns, 2012; Sahlander, Mattsson, & Bejerot, 2008; Tani et al., 2006) and ADHD (Chan et al., 2010; Gustafsson, Thernlund, Ryding, Rosen, & Cederblad, 2000; Pasini & D'agati, 2009). Motor dysfunction might precede the symptoms of linguistic and social problems in ASD (Teitelbaum et al., 2004) and a combination of motor problems with ADHD predicted more autistic traits than ADHD alone (Reiersen, Constantino, Grimmer, Martin, & Todd, 2008). Impaired integration of sensory input with motor commands has also been reported, supporting the hypothesis of a cerebellar and thalamic dysfunction in ASD (Gowen & Miall, 2005; Hardan et al., 2006).

Neurological Evaluation Scale (NES), which is an instrument for the systematic evaluation of neurological soft signs (Buchanan & Heinrichs, 1989), has been widely used in psychiatric populations with schizophrenia (Heinrichs & Buchanan, 1988; Peralta et al., 2010; Sewell et al., 2010), bipolar disorder (Negash et al., 2004) and obsessive compulsive disorder (Mergl & Hegerl, 2005; Poyurovsky et al., 2007). Patient groups scored higher in NES than healthy controls in all these studies. Furthermore, structural correlates of neurological soft signs were established by their relationship with gray matter reductions in a group of healthy controls (Dazzan et al., 2006) and in patients with psychosis (Bersani et al., 2007; Janssen et al., 2009).

A small number of neuroimaging studies, mainly performed in children and adolescents, have investigated neural correlates in ASD in direct comparisons with individuals with ADHD and neurotypical controls (NC). Correlations were reported between regional gray matter volume in the medial temporal lobe and inferior parietal cortex and symptoms of inattention, hyperactivity and autistic symptoms (Brieber et al., 2007; Yamasaki et al., 2010). In addition, increased white matter volume in the left primary motor and premotor cortex predicted poorer motor skills in children with autism as compared to groups of ADHD and healthy controls (Mostofsky, Burgess, & Gidley Larson, 2007). All these studies suggest that anatomical changes in ASD are likely to impair functional connections and to affect motor and neuropsychological performances.

Several positron emission tomography (PET) studies in ASD have shown localized metabolic changes in various cortical and subcortical regions (Chiron et al., 1995; Heh et al., 1989; Siegel et al., 1992). However, no common regional abnormalities have been found in regional cerebral blood flow (rCBF) or cerebral glucose metabolism studies (rCMRgl), possibly due to inhomogeneity in the individuals with ASD and the different methodologies implemented in various studies (Buchsbaum et al., 1992; Rumsey & Ernst, 2000; Zilbovicius et al., 1992). Further investigations to better describe the neurobiological correlates of ASD are therefore needed. In a previous study we compared adults with ASD to a group of NC and found increased rCBF, which is an index of regional brain activity, in the posterior part of the right hemisphere, confirming the involvement of cortical and subcortical structures in the phenotypic expression of the disorder (Pagani et al., 2012).

The aim of this study was to investigate the neural correlates of autistic traits, the symptoms of inattention, hyperactivity/impulsivity and neurological soft signs in the same individuals. We hypothesized that autistic traits, ADHD symptoms and neurological soft signs would share neural substrates and would correlate to rCBF in the temporo-parieto-occipital brain regions previously implicated in ASD.

2. Methods

2.1. Participants

Thirteen normal-intelligence adults with ASD, diagnosed in adolescence or in adulthood, and ten age-, sex- and IQ-matched neurotypical controls were included in the study. Exclusion criteria for all subjects were mental retardation, a history of brain damage, current or past medical or neurological disorders, epilepsy, alcohol abuse or dependence, past or present substance abuse and psychosis. In addition, NC were excluded if they had any past or current psychiatric or personality disorder, psychotropic medication or psychiatric disorders in first-degree family members. Demographic characteristics and descriptive statistics are presented in Table 1.

2.1.1. Neurotypical controls

Twelve NC were recruited from the Stockholm region. One subject was excluded since a first-degree family member had ASD and another subject dropped out of the study.

Table 1
Demographic and clinical characteristics of individuals with ASD compared with neurotypical controls.

Variables	ASD $n = 13$	Control $n = 10$	p-Value
Age, years	31.8 (8.6)	28.5 (7.5)	0.35
Male: female	7:6	5:5	0.85
Full scale IQ	104.2 (17.1)	115.7 (10.8)	0.08
Verbal IQ	105.3 (16.4)	114.6 (13.2)	0.176
Performance IQ	101.5 (17.6)	114.2 (9.9)	0.066
Handedness, right: left	12:1	9:1	0.85
Education			
<9 years, *n*	4	0	
9–12 years, *n*	4	3	
>12 years, *n*	5	5	
University degree, *n*	0	2	
Civil status, single:cohabit	12:1	6:4	0.04
Have children, yes:no	0:13	3:7	0.02
Independent living, yes:no	11:2	10:0	
In full time work/studies, yes:no	3:10	10:0	<0.0001
Nicotine use, yes:no	3:9[a]	2:8	0.96
Global assessment of functioning, total	54 (7.5)	86 (7.4)	<0.0001
Symptom-GAF	54.7 (6.8)	87.8 (7.2)	<0.0001
Function-GAF	56.3 (8.2)	90.7 (5.3)	<0.0001
Ritvo Autism Asperger Diagnostic Scale-Revised, total	109.7 (28.8)	19.6 (14.9)	<0.0001
Adult ADHD Self-Report Scale, total	32.2 (10.4)	19.6 (7.2)	0.003
Inattention	18.4 (6.4)	11.1 (5.4)	0.008
Hyperactivity/impulsivity	14.7 (6.2)	8.5 (3.4)	0.010
Wender Utah Rating Scale, total	57.9 (40.5)	11.5 (7.1)	0.001
Neurological Evaluation Scale, total	16 (6.7)	5 (3.0)	<0.001

Mean values are presented with the standard deviation in parentheses. IQ, intelligence quotient; GAF, global assessment of functioning; ASRS, Adult ADHD Self-Report Scale.
[a] Missing data in one subject.

2.1.2. Individuals with ASD

Recruitment of subjects with ASD was performed by a letter of request sent to 357 individuals registered at the community based unit for adults with ASD and to patients with ASD at the Neuropsychiatric unit, Northern Stockholm psychiatric clinic. Of the total fifty-five subjects with ASD that were willing to participate, 20 were interviewed, two were excluded on the basis of epilepsy and a history of alcohol and drug dependence and five were not available at the time of the PET scan, resulting in seven recruitments from the clinic and six from the community. This final selection was based on the desired distribution of sex. All but one, of Asian descent, were Caucasian.

Previous neuropsychiatric assessments, which included extensive interviews, rating scales, neuropsychological assessments and interviews with parents of the subjects, were requested for all ASD subjects. According to these, 11 subjects met the DSM-IV criteria for Asperger's disorder and two were diagnosed with high-functioning autism (American Psychiatric Association, 1994). The clinical diagnosis of ASD was confirmed in all subjects with the Autism Diagnostic Observation Schedule (ADOS) by one of the authors (SB) (Lord et al., 2000). Thereafter, two of the authors (SB and IM), board-certified psychiatrists specialized in diagnosing ASD in adults, agreed on the diagnosis and type of social style, according to Wing's definition (Wing, 1997). Nine subjects were defined as ''active-odd'' and four as ''schizoid and loners''. No ASD subject was classified as ''passive'' or ''rigid formal'' type. Eight subjects fulfilled diagnostic criteria for additional 1–5 psychiatric disorders (Agorophobia; Bulimia Nervosa; Major Depression; Dystymic disorder; Generalized Anxiety Disorder; Obsessive Compulsive Disorder; Panic Disorder; Social Phobia), and six subjects were currently treated with psychotropic medication.

2.2. Psychiatric and psychological assessments

The structured interview for Axis-I disorders Mini International Neuropsychiatric Interview (M.I.N.I., version 5.00) (Sheehan et al., 1998) and a semi-structured interview for past psychiatric disorders were administered to the ASD subjects whereas the Structured Clinical Interview for Diagnostic Statistical Manual of Mental Disorders 4th edition (DSM-IV), Axis I Disorders (SCID-I) and Structured Clinical Interview for DSM-IV-R Personality Disorders (SCID-II) were administered to the NC in order to rule out psychiatric disorders. General clinical impairment and function were assessed according the DSM-IV Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994). The Wechsler Adult Intelligence Scale-Revised (WAIS-III-R) provided intelligence quotient (IQ) estimates. Past and current medical disorders, family history of mental disorders, educational level, marital status and employment status were also covered in the semi-structured interview.

2.2.1. Neuropsychiatric assessments

Standardized, semi-structured assessment, the ADOS, module 4, was used to confirm the diagnosis of ASD. The ADOS includes four subscales: Communication, Social Interaction, Imagination/creativity and Stereotyped behaviors and restricted interest. Because the ADOS is assessed within one hour, it does not offer an opportunity to measure restricted and repetitive behaviors satisfactorily. Thus, ADOS algorithms include only the combined score from the two subscales "Communication" and "Social Interaction".

The Swedish version of the Ritvo Autism and Asperger Diagnostic Scale-Revised (RAADS-R) is an 80-item self-report diagnostic questionnaire based on DSM-IV-TR and ICD-10 criteria (Ritvo et al., 2011). The RAADS-R is self-administered and consists of four subscales (Social Interaction, Language, Circumscribed Interests and Sensory Motor Symptoms). However, the language sub-scale was excluded in this study since it showed low internal consistency in a Swedish validation study (Andersen et al., 2011). RAADS-R assesses deficits in perception and sensory-motor integration along with cognitive aspects of ASD. Each question is scored 0–3 and a score of 65 or greater is consistent with a clinical diagnosis of ASD. The self-rating scale, Adult ADHD Self-Report Scale (ASRS), was used to measure ADHD symptoms (Kessler et al., 2005). It consists of eighteen questions based on the DSM-IV criteria for ADHD (American Psychiatric Association, 1994) and includes two subscales: inattention and hyperactivity/impulsivity. A sum of scores between 17 and 23 for each subscale indicates that the subject is likely to have ADHD, while scores above 23 indicate a high likelihood of ADHD. Childhood ADHD symptoms were assessed using the Wender Utah Rating Scale (WURS) (Ward, Wender, & Reimherr, 1993), which is also self-assessed.

2.2.2. Neurological assessment

Neurological examination was carried out with the Neurological Evaluation Scale (NES), which is a 26-item clinically administered instrument for the systematic evaluation of neurological soft signs (Buchanan & Heinrichs, 1989). It covers four functional domains: Sensory Integration Signs (audio-visual integration, stereognosis, graphaesthesia, extinction and right-left confusion), Motor Coordination Signs (tandem walk, rapid alternating movements, finger-thumb opposition and finger-to-nose test), Motor Sequencing Signs (fist-ring, fist-edge-palm, rhythm tapping production movements and Ozeretski test) and other, e.g. "hard" neurological signs such as Romberg sign, tremor, mirror movements, synkinesis, convergence, gaze impersistence, primitive reflexes and short-term memory. Each item is rated from 0 to 2 (0 = no abnormality, 1 = mild but definitive impairment, 2 = marked impairment).

2.3. PET-scanning protocol

After the extended psychiatric assessment, all subjects underwent PET scans using [1-^{11}C]butanol to evaluate rCBF. Butanol, as a blood flow tracer labeled with either ^{11}C or ^{15}O, has been shown to have a high degree of reliability for human studies (Raichle et al., 1976; Saha, MacIntyre, & Go, 1994). It was produced using an in-house cyclotron and radiochemistry lab and was rapidly transported to the PET camera site.

The examinations were performed using a Siemens Biograph 64 Positron Emission Tomography/Computed Tomography (PET/CT) scanner, with a spatial resolution of 5 mm. The system combines a high-speed ultra 32-detector-row (672 detectors per row) CT unit and a PET scanner with 32448 LSO crystals in 52 rings and an axial field of view 21.6 cm.

The head was first scanned by CT, so corrections for attenuation and photon scatter could be made. Thereafter a bolus of [1-^{11}C]butanol (300 MBq) was injected simultaneously as the PET acquisition was started and data were acquired in the list mode for 5 min. The dynamic data were reconstructed to transverse images for rCBF evaluations. The interval between 40 and 100 s after injection was identified as the optimal window from which the raw data were extracted to reconstruct the images to be analyzed. During this interval the [1-^{11}C]butanol uptake reached a plateau before starting to decrease over time.

2.3.1. Image preprocessing

Data were analyzed with SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK) as implemented in Matlab 6.5.1. Raw data were subjected to affine and non-linear spatial normalization to a predefined PET template based on the MNI (Montreal Neurological Institute) reference brain by a bilinear interpolation method into a common anatomical space. The spatially normalized set of images were then smoothed with a 10 mm (FWHM) isotropic Gaussian filter to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio. Images were globally normalized using proportional scaling (0.5) to remove confounding effects to global CBF changes, with a gray matter masking threshold of 0.8.

2.4. Statistical analysis

Proportions of categorical variables at baseline were compared using the chi-square tests. Due to the small sample size, frequency data were computed through the Fisher exact test. Values of continuous measures were compared using either the *t*-test or, for non-normally distributed variables, the non-parametric Mann–Whitney *U*-test. The *p*-level was set to 0.05.

A principal component analysis, based on 13 original variables (scores of ADOS and GAF total, RAADS-, ASRS- and NES-subscales, verbal and performance IQ), was performed in all subjects to reduce their number into common factors (i.e. principle components). Each factor will then explain a different part of the total variance of the data set. In order to correct for the large variability in neuropsychiatric scales scores, data were normalized to a standard score (*z*-score) subtracting the

population mean from an individual raw score and then dividing the difference by the population standard deviation. The obtained *z*-scores for the 13 chosen variables were then submitted to OpenStat (Rummel, 1970) for statistical analysis.

Principal Component Analysis was performed and varimax orthogonal rotation was applied to the normalized 13 native neuropsychological measures to identify those scores expressing a similar part of total variance. Minimal root to rotate was set to 1.0 and the maximal number of iterations to 25. Factors with eigenvalues larger than 1 were initially extracted. Variables, with an absolute factor loading greater than 0.5, were regarded as representative of each factor. This value is purely arbitrary, but it is commonly used since it explains a moderate part of the variance of the factor. Kaiser–Meyer–Olkin measure of sampling adequacy (MSA) values higher than 0.7 were regarded as significant.

Positive and negative correlations between rCBF and each of three factors were carried out separately in subjects with ASD and NC. The "single-subjects covariates only" design model of SMP2 was implemented. All analyses were adjusted for age and gender. Due to the explorative nature of the study and to the number of subjects, statistical thresholds of $p = 0.05$ at voxel height, $p_{\text{uncorrected}} < 0.05$ at cluster level and $p_{\text{uncorrected}} < 0.001$ at voxel level were applied. Only those clusters containing more than 125 ($5 \times 5 \times 5$ voxels, i.e. 11 mm $\times$ 11 mm $\times$ 11 mm) contiguous voxels were accepted as significant, based on the calculation of the partial volume effect resulting from the spatial resolution of the PET camera (about double the intrinsic spatial resolution). The resulting statistical parametric maps, SPM{t}, were transformed into normal distribution (SPM{z}) units. Because the SPM template does not completely match the Talairach brain, it is necessary to correct its coordinates. This was achieved by the subroutine implemented by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging). Brodmann areas (BAs) were then identified at a range of 1 mm from the corrected Talairach coordinates of the SPM output isocentres, after importing them into Talairach client (http://www.talairach.org/index.html).

2.5. Ethical considerations

The study was approved by the Regional Ethical Review Board in Stockholm and the Radiation Safety Committee of the Karolinska University Hospital. Written informed consents were obtained from all subjects.

3. Results

Comparisons of demographic variables between the ASD and NC revealed no significant differences in age, IQ, smoking, handedness or sex distribution.

Principal component analysis of symptom scores identified three factors independent of age and educational level referred to as "Autistic/ADHD traits" (F1); "Sensory-motor integration" (F2) and "Intelligence/Motor sequencing" (F3). The pattern of loadings on each of three factors is presented in Table 2.

Each of three factors was correlated in both groups to significant increases (i.e. positive correlations) and decreases (i.e. negative correlations) in rCBF (Table 3 and Figs. 1 and 2).

In NC, positive correlations between the "Autistic/ADHD traits" factor and CBF were found in the occipital and temporal cortex and, in ASD, in the caudate bilaterally and in the right inferior parietal lobule, posterior cingulate and motor cortex. The ASD group showed also negative correlations in the right putamen and prefrontal cortex.

For the "Sensory-motor integration" factor opposite relationships in the occipital association cortex were found in ASD and NC with positive and negative correlations, respectively. The same was found for the putamen, in which NC correlated positively and ASD negatively with CBF.

Table 2
Factor loadings of the neuropsychiatric scale scores.

Variables	Component			h^2
	F1. Autistic/ADHD traits	F2. Sensory-motor integration	F3. Intelligence/Motor sequencing	
Hyperactivity/impulsivity subscale in ASRS	**0.841**	−0.254	0.334	0.88
Circumscribed interests subscale in RAADS-R	**0.826**	0.376	0.039	0.93
Inattention subscale in ASRS	**0.804**	0.036	0.065	0.65
ADOS communication and Social interaction	**0.798**	0.341	0.250	0.81
Sensory Motor Symptoms subscale in RAADS-R	**0.766**	0.318	0.514	0.95
Global assessment of function, total	**−0.757**	−0.469	−0.277	0.87
Social Interaction subscale in RAADS-R	**0.751**	0.452	0.272	0.84
"Hard" signs NES	**0.563**	0.385	0.413	0.63
Motor Co-ordination Signs subscale in NES	0.032	**0.935**	0.058	0.87
Sensory Integration Signs subscale in NES	0.316	**0.618**	0.186	0.51
Verbal IQ	−0.244	0.030	**−0.866**	0.80
Performance IQ	−0.237	−0.206	**−0.890**	0.89
Motor Sequencing Signs subscale in NES	0.298	0.519	**0.727**	0.88
Cumulative variance explained	38.6	19.7	22.9	

Highest factor loadings are in bold. h^2 is the communality, i.e. the proportion of variance of a single item that is explained by the factor solution. ADOS, Autism Diagnostic Observation Schedule; ASRS, Adult ADHD Self-Report Scale; NES, Neurological Evaluation Scale; RAADS-R, Ritvo Autism and Asperger Diagnostic Scale-Revised; IQ, Intelligence quotient.

Table 3
Regions with positive and negative correlations between the z-scores of the three factors and CBF.

Structures	Brodmann area	F1. Autistic/ADHD traits				F2. Sensory-motor integration				F3. Intelligence/Motor sequencing			
		ASD, $n = 13$		Control, $n = 10$		ASD, $n = 13$,		Control, $n = 10$		ASD, $n = 13$		Control, $n = 10$	
		Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg
Ventral lateral nucleus	Thalamus		R L				L				L		
Lentiform nucleus	Putamen		R				R L	L					
	Caudate	R L											
Sensory-motor cortex	3	R											
Precuneus	7					R							
Insula	13									R	L		
Cuneus	17			R L		L							
Cuneus	18			R		R L			R				
Fusiform gyrus	19					R L			R L			R	
Middle temporal gyrus	21							L		R			
Superior temporal gyrus	22				R			L		R			
Superior temporal gyrus	38			L									
Temporo-parietal junction	39/40	R		R									
Parahippocampal gyrus	Hippocampus		R										
Posterior cingulate	23	L											
Parahippocampal gyrus	35			L									
Parahippocampal gyrus	36			L									
Parahippocampal gyrus	37			L		R							
Uncus	20										R		
Inferior frontal gyrus	45									R			
Superior frontal gyrus	10, 11		R										
Anterior cingulate	32		R										
Inferior frontal gyrus	34						R L						
Inferior frontal gyrus	47						R						

ASD, individuals with ASD, R: right; L: left.

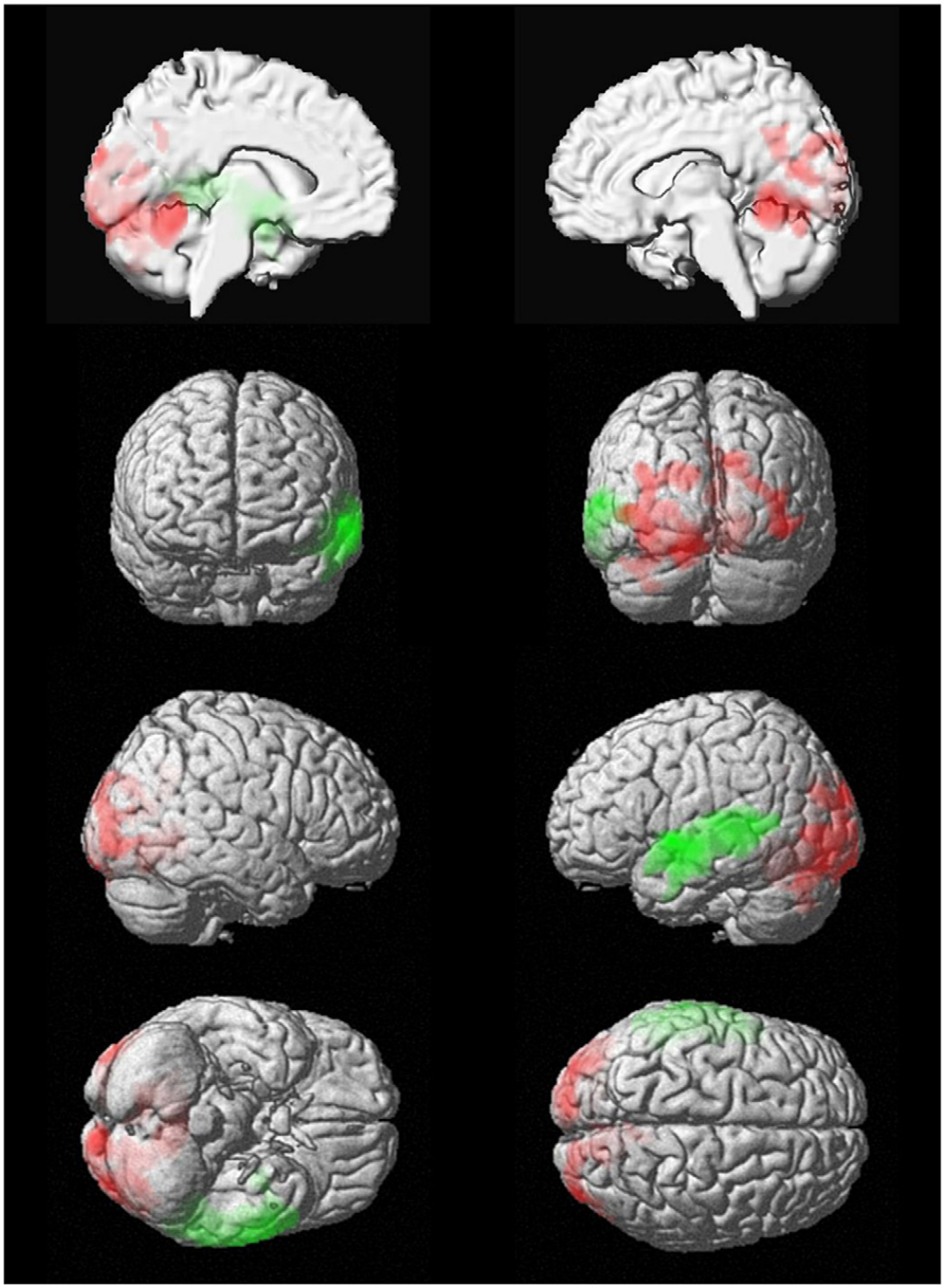

Fig. 1. Positive correlation between rCBF and "autistic/ADHD traits" in ASD (in red) and controls (in green). Regions showing a positive correlation between between rCBF and factor "autistic/ADHD traits" in ASD (in red) and NC (in green). The first row represents the medial aspect of left (on the left) and right (on the right) hemispheres; the second row represents the anterior (on the left) and posterior (on the right) aspect on the brain; the third row represents the lateral aspect of the right (on the left) and of the left (on the right) hemispheres; the fourth row represents the inferior (on the left) and the superior (on the right) aspects of the brain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The factor "Intelligence/Motor sequencing" was correlated with CBF only in the ASD group, positively in the right temporal cortex and negatively in the left insula and right uncus. The left thalamus correlated negatively with all three factors in the ASD group.

4. Discussion

In this study we could show that autistic traits and ADHD symptoms were grouped in the same factor ("Autistic/ADHD traits"). Thus, our data support the hypothesis that autistic traits and ADHD symptoms are correlated with resting rCBF in

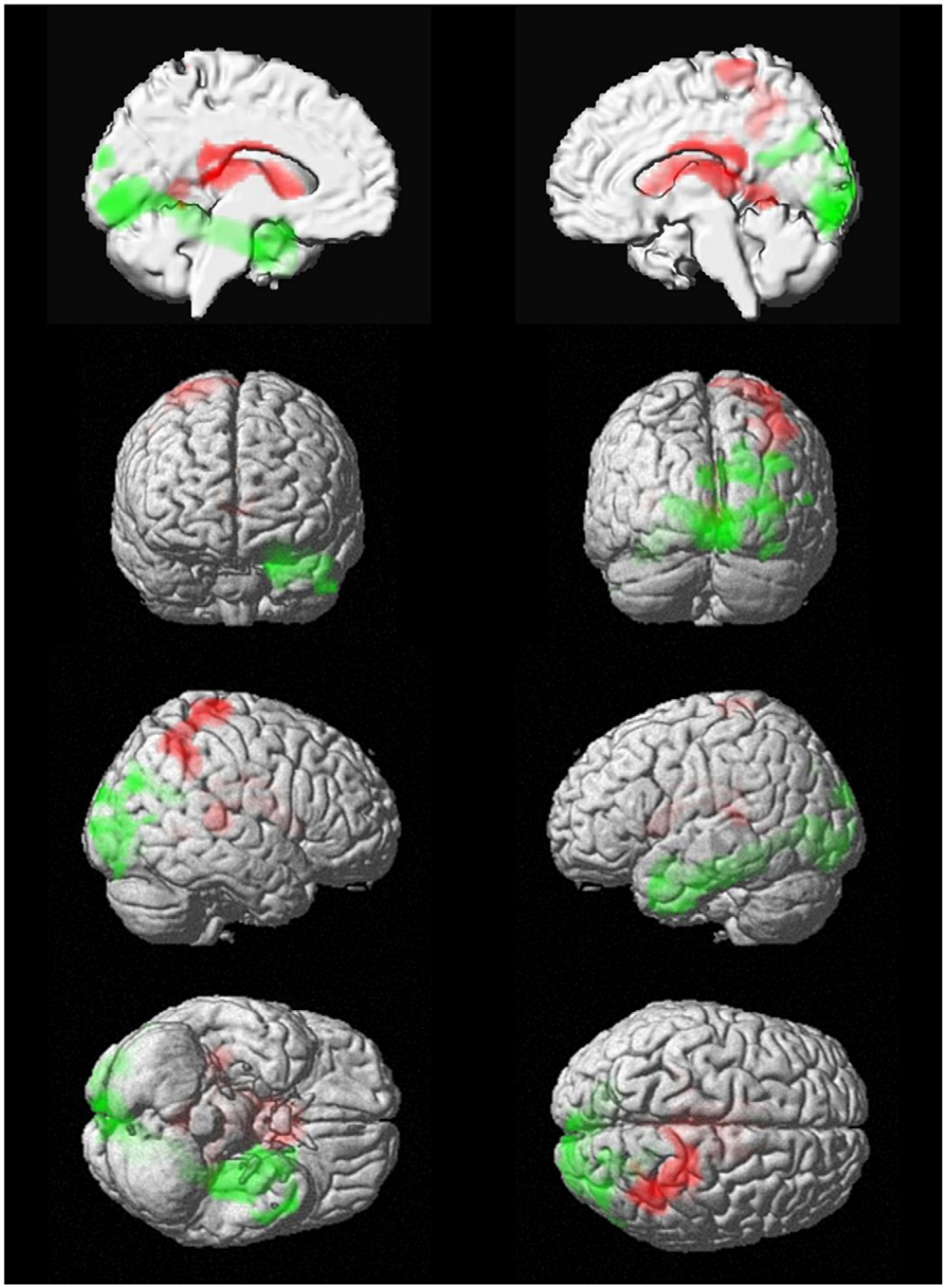

Fig. 2. Positive correlation between rCBF and "sensory-motor integration" in ASD (in red) and controls (in green). Regions showing a positive correlation between rCBF and factor "sensory-motor integration" in ASD (in red) and NC (in green). The first row represents the medial aspect of left (on the left) and right (on the right) hemispheres; the second row represents the anterior (on the left) and posterior (on the right) aspect on the brain; the third row represents the lateral aspect of the right (on the left) and of the left (on the right) hemispheres; the fourth row represents the inferior (on the left) and the superior (on the right) aspects of the brain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

superimposing brain regions. Neurological soft signs and intelligence/motor sequencing were correlated to rCBF independently from the ASD and ADHD dimensions.

4.1. "Autistic/ADHD traits" and rCBF

The positive relationship between CBF and the factor "Autistic/ADHD traits" in individuals with ASD reflects the neurobiological correlates of ASD- and ADHD symptoms in specific brain regions. These regions – the temporo-parietal junction, sensory-motor cortex, caudate and middle and superior temporal gyrus – have previously been reported to be

implicated in both ASD and ADHD (Ecker et al., 2012; Fassbender & Schweitzer, 2006; Lombardo, Chakrabarti, Bullmore, & Baron-Cohen, 2011).

The temporo-parietal junction (corresponding to BA 39/40) is implicated in complex behaviors, which require attention to biological motion (Allison, Puce, & McCarthy, 2000), spatial orientation of the eye gaze (Wicker et al., 2008) and integration of visual and auditory inputs with the purpose of providing meaningful social and emotional responses (Calvert, Campbell, & Brammer, 2000). It is also involved in moral judgment and in the ability to understand the intentions of other people and metaphors (Luria, 1970; Verhoeven, De Cock, Lagae, & Sunaert, 2010), further supporting the relevance of this area in ASD. Moreover, the tempo-parietal junction has been identified as a part of a right-lateralized ventral attention system related to distractibility (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006) and inattention to salient social cues, implicated in both ASD and ADHD. In addition, higher activations in this region were also found in a PET study in subjects with autism compared to healthy controls during a verbal memory task (Hazlett et al., 2004).

We also found positive correlations between the factor "Autistic/ADHD traits" and CBF in the postcentral gyrus (BA 3), i.e. a part of the primary somatosensory cortex. Possibly, positive correlations in this region may be related to abnormal perceptions of somatic sensations emerging during the PET scanning.

The caudate has also been implicated in ASD by being associated with executive deficits and ritualistic behaviors (Haznedar et al., 2006; Hollander et al., 2005). Associative cortices project in a segregated manner, mainly to the nucleus caudatus in the striatum. Since the caudate is the crucial part of several neural circuits, the positive correlation between the factor "Autistic/ADHD traits" and CBF in the caudate could be explained by the strong anatomical and functional connections of this structure with temporal and parietal lobes. Because the human brain is anatomically and functionally organized into complex networks, it allows both segregation and integration of information. It is likely that connectivity networks are impaired in ASD at the long-range level and incremented at the low-range level (Minshew & Keller, 2010). This latter anatomo-functional looping might under certain circumstances cause excessive information processing, resulting in a local increase in metabolism and blood flow. Therefore, the negative correlation between the factor "Autistic/ADHD traits" and the prefrontal cortex is likely due to the long-range disconnection between temporo-parietal junction/posterior cingulate cortex and the rostral part of the brain and may be partly explained by presence of ADHD-symptoms (Solomon et al., 2009).

4.2. "Sensory-motor integration" and rCBF

This study also provided evidence that neurological soft signs are part of the ASD phenotype since the factor "Sensory-motor integration" included the scores of NES sub-scales for assessment of motor coordination and sensory-integration. Positive correlations with CBF were found in the cuneus and fusiform gyrus in ASD, whereas a negative correlation was found in NC, as shown in Table 3.

Impaired eye-to-eye gaze and facial expressions are included in the diagnostic criteria for ASD (American Psychiatric Association, 1994) and face recognition deficit was suggested to be one of several factors that could lead to poor social skills (Barton et al., 2004). In a neurotypical population, activation in the fusiform gyrus was associated with face identification, face processing and object perception (Bly & Kosslyn, 1997) and the dorsolateral occipital cortex was selectively activated by face matching tasks (Haxby et al., 1991). We found in patients a positive correlation between CBF and the factor "Sensory-motor integration" in fusiform gyrus, in which increased gray matter volume has been reported in ASD (Waiter et al., 2004). This positive correlation could be explained by the abnormally intense and generalized pattern of information flow in autistic perception and by the increased local neuronal activity in the visual cortex (Belmonte & Yurgelun-Todd, 2003).

Individuals with ASD tend to use a visually oriented, asocial processing style (Koshino et al., 2008) and visual strategies to solve cognitive problems, regardless of whether they are visual or verbal (Sahyoun, Belliveau, Soulières, Schwartz, & Mody, 2010). Atypical visual perception and visuospatial abilities in individuals with ASD may be linked to savant capacities and exceptional attention to details and possibly also to social interaction deficits (Dakin & Frith, 2005; Sutherland & Crewther, 2010; Völlm et al., 2006). Thus, the positive correlations shown in this study between the factor "Sensory-motor integration" and CBF in cuneus and fusiform gyrus in individuals with ASD, may reflect difficulties in the cross-modal integration of visual, auditive, proprioceptive and tactile information, typical for the disorder. Also, our findings confirm an involvement of the temporo-occipital regions, implicated in decoding intentions and emotions of other people.

4.3. "Intelligence/Motor sequencing" and rCBF

Positive correlation was found in the ASD group between the factor representing "Intelligence/Motor sequencing" and CBF in the right insula and middle and superior temporal gyrus. Insula (BA 13) is also involved in visuo-spatial (Damarla et al., 2010) and multisensory processing (Downar, Crawley, Mikulis, & Davis, 2001). Moreover, the insula was proposed to play a key role in switching attention between external stimuli and internal reflections (Sridharan, Levitin, & Menon, 2008) and in mediating attention to novel sensory stimuli. In addition, the insula is involved in temporal processing, phonological processing and visual–auditory integration (Bamiou, Musiek, & Luxon, 2003), functions that are affected in ASD. The positive correlation in this region between CBF and the factor "Intelligence/Motor sequencing" could possibly reflect compensatory mechanisms for the deficits in integrative functions (Ornitz, 1974). Also the insula, along with the superior temporal gyrus, contribute to neural networks for empathizing, consciousness and identity (Craig, 2002; Damasio et al., 2000; Singer et al., 2006). Interestingly, increased rCBF was found in the right insular cortex in individuals with gender identity disorder (GID)

(Nawata et al., 2010), a condition that is clearly overrepresented in ASD (de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010). In addition, the increases of gray matter volumes in the temporo-parietal junction and in the insular cortex in individuals with GID was recently suggested to be related to the involvement of these regions in sensory-motor processing (Savic & Arver, 2011), which opens new directions for research on a "comorbidity" between ASD and GID.

The superior temporal gyrus (corresponding to BA 21, 22) is considered to be the neuroanatomical substrate for language, speech, mentalizing (Frith & Frith, 2003), empathy (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Völlm et al., 2006) and sensory integration (Dazzan et al., 2006). Thus, this region is considered to be the neural basis for social- and communication deficits in ASD and ADHD combined with substantial perceptual, motor and attention deficits (Gepner & Feron, 2009; Gillberg & Rasmussen, 1982; Herrington et al., 2007; Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011; Leekam, Nieto, Libby, Wing, & Gould, 2007). In the present study the factor "Intelligence/Motor sequencing" was positively correlated with CBF in the superior temporal gyrus in the ASD group, but not in the controls.

4.4. Thalamus involvement

Notably, the left thalamus showed negative correlations with all three factors.

This is in agreement with the previously reported lower metabolic activity in the anterior thalamus bilaterally (Haznedar et al., 2006) and abnormal neurotransmission in individuals with ASD (Bernardi et al., 2011). Also, thalamus abnormalities have shown to be associated with an abundance of neurological soft signs in earlier studies (Dazzan et al., 2006; Thomann et al., 2009). Since the thalamus mediates both sensory perception and motor planning and serves as an active filter for the information flow to the cerebral cortex, it is suggested to be implicated in the inappropriate multisensory integration processing in ASD as well as in ADHD (Hardan et al., 2008; Zhu et al., 2008). In addition, the thalamus regulates cortical arousal through thalamo-cortical connections and can therefore elicit a hyperarousal condition, which is well known in ASD.

Taken together, a neurobiological-based model for ASD is supported by our findings and is consistent with previous reports about the co-occurrence of inattention, hyperactivity and motor control deficits in ASD. This is also in line with studies that showed phenotypic overlap between ASD and ADHD (Reiersen et al., 2008) and shared genetic variance (Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010). Moreover, our findings are in agreement with a previously reported underlying factor of a major effect contributing to both autistic traits and ADHD symptoms (Constantino et al., 2004). Therefore, co-occurring ADHD symptoms are suggested to be a representation of a broader ASD phenotype and not a separate co-morbid disorder, which is of relevance for diagnosis and treatment. Thus, the use of factor analysis of different signs and symptoms is suggested to be a valuable approach for exploring underlying ethiological and pathophysiological causes (Dworzynski, Happe, Bolton, & Ronald, 2009; Steer et al., 2010) and biological correlates in ASD (Sacco et al., 2010).

4.5. Measures of autistic traits

RAADS-R, a rating scale to assist in the assessment of the ASD diagnosis, was used in the present study to measure autistic traits. A wide selection of impairments in cognitive functions, the existence of repetitive and stereotyped behaviors and sensory-motor deficits are assessed by this instrument. Our results suggest that ASD is a clinical syndrome with various symptomatic dimensions composing the autism spectrum phenotype. Doubtlessly, the autism phenotype is a consequence of an atypical brain development (Kaplan, Crawford, Cantell, Kooistra, & Dewey, 2006; Kaplan, Dewey, Crawford, & Wilson, 2001), which affects brain connectivity and synchronicity (Gepner & Feron, 2009). Similar findings have been reported in ADHD (Fair et al., 2010). These anatomic and functional similarities may be associated to intertwined impairments in language, motor coordination, activity, mood, and sleep, as shown in children diagnosed with a neuropsychiatric disorder (Gillberg, 2010). In our adult ASD sample, co-occurrence of symptoms of ADHD and deficits in motor and sensory-integration, along with a number of other psychiatric and psychological problems are suggested to represent the clinical manifestation of this atypical brain development. Certain areas, engaged in ASD, are similarly affected in other psychiatric disorders (Kleinhans et al., 2010; Menzies et al., 2008; Ravindran et al., 2009; Seminowicz et al., 2004). In adults with ASD, coexisting sensory-motor abnormalities, assessed rather than self-reported, may represent a specific clinical subtype, separable from ASD alone, and supported by neuroimaging findings in this study. Inattention and hyperactivity seem to be integrated in the ASD diagnosis and share neural substrates.

4.6. Limitations

The analyses were performed accepting significances of $p < 0.05$ uncorrected at peak level. Due to the small sample size, not unusual in neuroimaging studies, this liberal choice was adopted to avoid type II errors attributable to over-conservative thresholds (Oishi et al., 2005). Effectively, given the exploratory nature of this analysis and considering the relatively low sensitivity of PET without repeated measures, higher thresholds could lead to false-negative results in PET studies. Another limitation was the lack of blinded assessors.

5. Conclusions

Although ASD and ADHD can be described as distinct categories, autistic traits and ADHD-symptoms were associated with common neural substrates, while sensory-motor deficits were grouped in another independent factor. These different

symptom dimensions may reflect underlying brain dysfunctions in atypical organized neuronal networks. Our findings contribute to the hypothesis that in ASD resting neural activity in local neuronal circuits is associated with metabolic and blood flow alterations.

Conflict of interest statement

The authors declare that they have no competing interests.

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References

Allison, T., Puce, A., & McCarthy, G. (2000). Social perception from visual cues: Role of the STS region. *Trends in Cognitive Sciences, 4*, 267–278.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV* (4th ed.). Washington, DC: American Psychiatric Association.

Andersen, L. M., Näswall, K., Manouilenko, I., Nylander, L., Edgar, J., Ritvo, R. A., et al. (2011). The Swedish version of the Ritvo autism and asperger diagnostic scale: Revised (RAADS-R). A validation study of a rating scale for adults. *Journal of Autism and Developmental Disorders, 41*, 1635–1645.

Bamiou, D. E., Musiek, F. E., & Luxon, L. M. (2003). The insula (Island of Reil) and its role in auditory processing. Literature review. *Brain Research. Brain Research Reviews, 42*, 143–154.

Barton, J. J., Cherkasova, M. V., Hefter, R., Cox, T. A., O'Connor, M., & Manoach, D. S. (2004). Are patients with social developmental disorders prosopagnosic? Perceptual heterogeneity in the Asperger and socio-emotional processing disorders. *Brain, 127*, 1706–1716.

Belmonte, M. K., & Yurgelun-Todd, D. A. (2003). Functional anatomy of impaired selective attention and compensatory processing in autism. *Brain Research. Cognitive Brain Research, 17*, 651–664.

Bernardi, S., Anagnostou, E., Shen, J., Kolevzon, A., Buxbaum, J. D., Hollander, E., et al. (2011). In vivo (1)H-magnetic resonance spectroscopy study of the attentional networks in autism. *Brain Research, 1380*, 198–205.

Bersani, G., Paolemili, M., Quartini, A., Clemente, R., Gherardelli, S., Iannitelli, A., et al. (2007). Neurological soft signs and cerebral measurements investigated by means of MRI in schizophrenic patients. *Neuroscience Letters, 413*, 82–87.

Bly, B. M., & Kosslyn, S. M. (1997). Functional anatomy of object recognition in humans: Evidence from positron emission tomography and functional magnetic resonance imaging. *Current Opinion in Neurology, 10*, 5–9.

Brieber, S., Neufang, S., Bruning, N., Kamp-Becker, I., Remschmidt, H., Herpertz-Dahlmann, B., et al. (2007). Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry, 48*, 1251–1258.

Buchanan, R. W., & Heinrichs, D. W. (1989). The Neurological Evaluation Scale (NES): A structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Research, 27*, 335–350.

Buchsbaum, M., Siegel, B. J., Wu, J., Hazlett, E., Sicotte, N., Haier, R., et al. (1992). Brief report: Attention performance in autism and regional brain metabolic rate assessed by positron emission tomography. *Journal of Autism and Developmental Disorders, 22*, 115–125.

Calvert, G. A., Campbell, R., & Brammer, M. J. (2000). Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. *Current Biology, 10*, 649–657.

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences of the United States of America, 100*, 5497–5502.

Chan, R. C., McAlonan, G. M., Yang, B., Lin, L., Shum, D., & Manschreck, T. C. (2010). Prevalence of neurological soft signs and their neuropsychological correlates in typically developing Chinese children and Chinese children with ADHD. *Developmental Neuropsychology, 35*, 698–711.

Chiron, C., Leboyer, M., Leon, F., Jambaqué, I., Nuttin, C., & Syrota, A. (1995). SPECT of the brain in childhood autism: Evidence for a lack of normal hemispheric asymmetry. *Developmental Medicine and Child Neurology, 37*, 849–860.

Constantino, J. N., Gruber, C. P., Davis, S., Hayes, S., Passanante, N., & Przybeck, T. (2004). The factor structure of autistic traits. *Journal of Child Psychology and Psychiatry, 45*, 719–726.

Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature reviews. Neuroscience, 3*, 655–666.

Dakin, S., & Frith, U. (2005). Vagaries of visual perception in autism. *Neuron, 48*, 497–507.

Damarla, S. R., Keller, T. A., Kana, R. K., Cherkassky, V. L., Williams, D. L., Minshew, N. J., et al. (2010). Cortical underconnectivity coupled with preserved visuospatial cognition in autism: Evidence from an fMRI study of an embedded figures task. *Autism Research, 3*, 273–279.

Damasio, A. R., Grabowski, T. J., Bechara, A., Damasio, H., Ponto, L. L., Parvizi, J., et al. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience, 3*, 1049–1056.

Dazzan, P., Morgan, K. D., Chitnis, X., Suckling, J., Morgan, C., Fearon, P., et al. (2006). The structural brain correlates of neurological soft signs in healthy individuals. *Cerebral Cortex, 16*, 1225–1231.

de Vries, A. L., Noens, I. L., Cohen-Kettenis, P. T., van Berckelaer-Onnes, I. A., & Doreleijers, T. A. (2010). Autism spectrum disorders in gender dysphoric children and adolescents. *Journal of Autism and Developmental Disorders, 40*, 930–936.

Downar, J., Crawley, A. P., Mikulis, D. J., & Davis, K. D. (2001). The effect of task relevance on the cortical response to changes in visual and auditory stimuli: An event-related fMRI study. *Neuroimage, 14*, 1256–1267.

Dworzynski, K., Happe, F., Bolton, P., & Ronald, A. (2009). Relationship between symptom domains in autism spectrum disorders: A population based twin study. *Journal of Autism and Developmental Disorders, 39*, 1197–1210.

Ecker, C., Suckling, J., Deoni, S. C., Lombardo, M. V., Bullmore, E. T., Baron-Cohen, S., et al. (2012). Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: A multicenter magnetic resonance imaging study. *Archives of General Psychiatry, 69*, 195–209.

Fair, D. A., Posner, J., Nagel, B. J., Bathula, D., Dias, T. G., Mills, K. L., et al. (2010). Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 68*, 1084–1091.

Fassbender, C., & Schweitzer, J. B. (2006). Is there evidence for neural compensation in attention deficit hyperactivity disorder?. A review of the functional neuroimaging literature. *Clinical Psychology Review, 26*, 445–465.

Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences of the United States of America, 103*, 10046–10051.

Frith, U., & Frith, C. D. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 358*, 459–473.
Gepner, B., & Feron, F. (2009). Autism: A world changing too fast for a mis-wired brain? *Neuroscience and Biobehavioral Reviews, 33*, 1227–1242.
Gillberg, C. (2010). The ESSENCE in child psychiatry: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. *Research in Developmental Disabilities, 31*, 1543–1551.
Gillberg, C., & Rasmussen, P. (1982). Perceptual, motor and attentional deficits in six-year-old children. Screening procedure in pre-school. *Acta Paediatrica Scandinavica, 71*, 121–129.
Goldstein, S., & Schwebach, A. J. (2004). The comorbidity of pervasive developmental disorder and attention deficit hyperactivity disorder: Results of a retrospective chart review. *Journal of Autism and Developmental Disorders, 34*, 329–339.
Gowen, E., & Miall, R. C. (2005). Behavioural aspects of cerebellar function in adults with Asperger syndrome. *Cerebellum, 4*, 279–289.
Gustafsson, P., Thernlund, G., Ryding, E., Rosen, I., & Cederblad, M. (2000). Associations between cerebral blood-flow measured by single photon emission computed tomography (SPECT), electro-encephalogram (EEG), behaviour symptoms, cognition and neurological soft signs in children with attention-deficit hyperactivity disorder (ADHD). *Acta Paediatrica, 89*, 830–835.
Hardan, A., Girgis, R., Adams, J., Gilbert, A., Keshavan, M., & Minshew, N. (2006). Abnormal brain size effect on the thalamus in autism. *Psychiatry Research, 147*, 145–151.
Hardan, A. Y., Minshew, N. J., Melhem, N. M., Srihari, S., Jo, B., Bansal, R., et al. (2008). An MRI and proton spectroscopy study of the thalamus in children with autism. *Psychiatry Research, 163*, 97–105.
Haxby, J. V., Grady, C. L., Horwitz, B., Ungerleider, L. G., Mishkin, M., Carson, R. E., et al. (1991). Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proceedings of the National Academy of Sciences of the United States of America, 88*, 1621–1625.
Hazlett, E. A., Buchsbaum, M. S., Hsieh, P., Haznedar, M. M., Platholi, J., LiCalzi, E. M., et al. (2004). Regional glucose metabolism within cortical Brodmann areas in healthy individuals and autistic patients. *Neuropsychobiology, 49*, 115–125.
Haznedar, M. M., Buchsbaum, M. S., Hazlett, E. A., LiCalzi, E. M., Cartwright, C., & Hollander, E. (2006). Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. *The American Journal of Psychiatry, 163*, 1252–1263.
Heh, C., Smith, R., Wu, J., Hazlett, E., Russell, A., Asarnow, R., et al. (1989). Positron emission tomography of the cerebellum in autism. *The American Journal of Psychiatry, 146*, 242–245.
Heinrichs, D. W., & Buchanan, R. W. (1988). Significance and meaning of neurological signs in schizophrenia. *The American Journal of Psychiatry, 145*, 11–18.
Herrington, J. D., Baron-Cohen, S., Wheelwright, S. J., Singh, K. D., Bullmore, E. I., Brammer, M., et al. (2007). The role of MT+/V5 during biological motion perception in Asperger Syndrome: An fMRI study. *Research in Autism Spectrum Disorders, 1*, 14–27.
Hofvander, B., Delorme, R., Chaste, P., Nydén, A., Wentz, E., Ståhlberg, O., et al. (2009). Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BioMed Central Psychiatry, 9*, 35.
Hollander, E., Anagnostou, E., Chaplin, W., Esposito, K., Haznedar, M., Licalzi, E., et al. (2005). Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. *Biological Psychiatry, 58*, 226–232.
Holtmann, M., Bolte, S., & Poustka, F. (2007). Attention deficit hyperactivity disorder symptoms in pervasive developmental disorders: Association with autistic behavior domains and coexisting psychopathology. *Psychopathology, 40*, 172–177.
Janssen, J., Diaz-Caneja, A., Reig, S., Bombín, I., Mayoral, M., Parellada, M., et al. (2009). Brain morphology and neurological soft signs in adolescents with first-episode psychosis. *The British Journal of Psychiatry, 195*, 227–233.
Kaplan, B., Crawford, S., Cantell, M., Kooistra, L., & Dewey, D. (2006). Comorbidity, co-occurrence, continuum: What's in a name? *Child: Care, Health and Development, 32*, 723–731.
Kaplan, B. J., Dewey, D. M., Crawford, S. G., & Wilson, B. N. (2001). The term comorbidity is of questionable value in reference to developmental disorders: Data and theory. *Journal of Learning Disabilities, 34*, 555–565.
Kessler, R. C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E., et al. (2005). The World Health Organization Adult ADHD Self-Report Scale (ASRS): A short screening scale for use in the general population. *Psychological Medicine, 35*, 245–256.
Kleinhans, N. M., Richards, T., Weaver, K., Johnson, L. C., Greenson, J., Dawson, G., et al. (2010). Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders. *Neuropsychologia, 48*, 3665–3670.
Kooij, S. J., Bejerot, S., Blackwell, A., Caci, H., Casas-Brugue, M., Carpentier, P. J., et al. (2010). European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. *BioMed Central Psychiatry, 10*, 67.
Koshino, H., Kana, R. K., Keller, T. A., Cherkassky, V. L., Minshew, N. J., & Just, M. A. (2008). fMRI investigation of working memory for faces in autism: Visual coding and underconnectivity with frontal areas. *Cerebral Cortex, 18*, 289–300.
Kwakye, L. D., Foss-Feig, J. H., Cascio, C. J., Stone, W. L., & Wallace, M. T. (2011). Altered auditory and multisensory temporal processing in autism spectrum disorders. *Frontiers in Integrative Neuroscience, 4*, 129.
Lee, D. O., & Ousley, O. Y. (2006). Attention-deficit hyperactivity disorder symptoms in a clinic sample of children and adolescents with pervasive developmental disorders. *Journal of Child and Adolescent Psychopharmacology, 16*, 737–746.
Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. *Journal of Autism and Developmental Disorders, 37*, 894–910.
Lichtenstein, P., Carlström, E., Råstam, M., Gillberg, C., & Anckarsäter, H. (2010). The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *The American Journal of Psychiatry, 167*, 1357–1363.
Lombardo, M. V., Chakrabarti, B., Bullmore, E. T., & Baron-Cohen, S. (2011). Specialization of right temporo-parietal junction for mentalizing and its relation to social impairments in autism. *Neuroimage, 56*, 1832–1838.
Lord, C., Risi, S., Lambrecht, L., Cook, E. J., Leventhal, B., DiLavore, P., et al. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders, 30*, 205–223.
Luria, A. (1970). *Traumatic aphasia: Its syndromes, psychology and treatment*. Mouton: The Hague.
Mahone, E. M., Powell, S. K., Loftis, C. W., Goldberg, M. C., Denckla, M. B., & Mostofsky, S. H. (2006). Motor persistence and inhibition in autism and ADHD. *Journal of the International Neuropsychological Society, 12*, 622–631.
Mayes, S. D., Calhoun, S. L., Mayes, R. D., & Molitoris, S. (2012). Autism and ADHD: Overlapping and discriminating symptoms. *Research in Autism Spectrum Disorders, 6*, 277–285.
Mayoral, M., Merchán-Naranjo, J., Rapado, M., Leiva, M., Moreno, C., Giráldez, M., et al. (2010). Neurological soft signs in juvenile patients with Asperger syndrome, early-onset psychosis, and healthy controls. *Early Intervention in Psychiatry, 4*, 283–290.
Menzies, L., Chamberlain, S. R., Laird, A. R., Thelen, S. M., Sahakian, B. J., & Bullmore, E. T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited. *Neuroscience and Biobehavioral Reviews, 32*, 525–549.
Mergl, R., & Hegerl, U. (2005). Neurological soft signs in patients with obsessive-compulsive disorder. *Fortschritte der Neurologie-Psychiatrie, 73*, 504–516.
Minshew, N. J., & Keller, T. A. (2010). The nature of brain dysfunction in autism: Functional brain imaging studies. *Current Opinion in Neurology, 23*, 124–130.
Mostofsky, S. H., Burgess, M. P., & Gidley Larson, J. C. (2007). Increased motor cortex white matter volume predicts motor impairment in autism. *Brain, 130*, 2117–2122.
Nawata, H., Ogomori, K., Tanaka, M., Nishimura, R., Urashima, H., Yano, R., et al. (2010). Regional cerebral blood flow changes in female to male gender identity disorder. *Psychiatry and Clinical Neurosciences, 64*, 157–161.
Negash, A., Kebede, D., Alem, A., Melaku, Z., Deyessa, N., Shibire, T., et al. (2004). Neurological soft signs in bipolar I disorder patients. *Journal of Affective Disorders, 80*, 221–230.
Oishi, N., Udaka, F., Kameyama, M., Sawamoto, N., Hashikawa, K., & Fukuyama, H. (2005). Regional cerebral blood flow in Parkinson disease with nonpsychotic visual hallucinations. *Neurology, 65*, 1708–1715.
Ornitz, E. M. (1974). The modulation of sensory input and motor output in autistic children. *Journal of Autism and Childhood Schizophrenia, 4*, 197–215.

Pagani, M., Manouilenko, I., Stone-Elander, S., Odh, R., Salmaso, D., Hatherly, R., et al. (2012). Brief Report: Alterations in cerebral blood flow as assessed by PET/CT in adults with autism spectrum disorder with normal IQ. *Journal of Autism and Developmental Disorders, 42*, 313–318.
Pasini, A., & D'agati, E. (2009). Pathophysiology of NSS in ADHD. *The World Journal of Biological Psychiatry, 10*, 495–502.
Peralta, V., de Jalón, E. G., Campos, M. S., Basterra, V., Sanchez-Torres, A., & Cuesta, M. J. (2010). Risk factors, pre-morbid functioning and episode correlates of neurological soft signs in drug-naive patients with schizophrenia-spectrum disorders. *Psychological Medicine, 41*, 1–11.
Poyurovsky, M., Faragian, S., Pashinian, A., Levi, A., Viosburd, A., Stryjer, R., et al. (2007). Neurological soft signs in schizophrenia patients with obsessive-compulsive disorder. *The Journal of Neuropsychiatry and Clinical Neurosciences, 19*, 145–150.
Price, K. J., Shiffrar, M., & Kerns, K. A. (2012). Movement perception and movement production in Asperger's syndrome. *Research in Autism Spectrum Disorders, 6*, 391–398.
Raichle, M., Eichling, J., Straatmann, M., Welch, M., Larson, K., & Ter-Pogossian, M. (1976). Blood–brain barrier permeability of 11C-labeled alcohols and 15O-labeled water. *The American Journal of Physiology, 230*, 543–552.
Ravindran, A. V., Smith, A., Cameron, C., Bhatla, R., Cameron, I., Georgescu, T. M., et al. (2009). Toward a functional neuroanatomy of dysthymia: A functional magnetic resonance imaging study. *Journal of Affective Disorders, 119*, 9–15.
Reiersen, A. M., Constantino, J. N., Grimmer, M., Martin, N. G., & Todd, R. D. (2008). Evidence for shared genetic influences on self-reported ADHD and autistic symptoms in young adult Australian twins. *Twin Research and Human Genetics, 11*, 579–585.
Reiersen, A. M., Constantino, J. N., Volk, H. E., & Todd, R. D. (2007). Autistic traits in a population-based ADHD twin sample. *Journal of Child Psychology and Psychiatry, 48*, 464–472.
Reiersen, A. M., & Todd, R. D. (2008). Co-occurrence of ADHD and autism spectrum disorders: Phenomenology and treatment. *Expert Review of Neurotherapeutics, 8*, 657–669.
Ritvo, R. A., Ritvo, E. R., Guthrie, D., Ritvo, M. J., Hufnagel, D. H., McMahon, W., et al. (2011). The Ritvo Autism Asperger Diagnostic Scale-Revised (RAADS-R): A scale to assist the diagnosis of Autism Spectrum Disorder in adults: An international validation study. *Journal of Autism and Developmental Disorders, 41*, 1076–1089.
Rommelse, N. N., Franke, B., Geurts, H. M., Hartman, C. A., & Buitelaar, J. K. (2010). Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. *European Child and Adolescent Psychiatry, 19*, 281–295.
Rummel, R. J. (1970). *Applied factor analysis*. Evanston, IL: Northwestern University Press.
Rumsey, J., & Ernst, M. (2000). Functional neuroimaging of autistic disorders. *Mental Retardation and Developmental Disabilities Research Reviews, 6*, 171–179.
Rydén, E., & Bejerot, S. (2008). Autism spectrum disorders in an adult psychiatric population. A naturalistic cross-sectional controlled study. *Clinical Neuropsychiatry, 5*, 13–21.
Sacco, R., Curatolo, P., Manzi, B., Militerni, R., Bravaccio, C., Frolli, A., et al. (2010). Principal pathogenetic components and biological endophenotypes in autism spectrum disorders. *Autism Research, 3*, 237–252.
Saha, G. B., MacIntyre, W. J., & Go, R. T. (1994). Radiopharmaceuticals for brain imaging. *Seminars in Nuclear Medicine, 24*, 324–349.
Sahlander, C., Mattsson, M., & Bejerot, S. (2008). Motor function in adults with Asperger's disorder: A comparative study. *Physiotherapy Theory and Practice, 24*, 73–81.
Sahyoun, C. P., Belliveau, J. W., Soulières, I., Schwartz, S., & Mody, M. (2010). Neuroimaging of the functional and structural networks underlying visuospatial vs. linguistic reasoning in high-functioning autism. *Neuropsychologia, 48*, 86–95.
Savic, I., & Arver, S. (2011). Sex dimorphism of the brain in male-to-female transsexuals. *Cerebral Cortex, 21*, 2525–2533.
Seminowicz, D. A., Mayberg, H. S., McIntosh, A. R., Goldapple, K., Kennedy, S., Segal, Z., et al. (2004). Limbic-frontal circuitry in major depression: A path modeling metanalysis. *Neuroimage, 22*, 409–418.
Sewell, R., Perry, E. J., Karper, L., Bell, M., Lysaker, P., Goulet, J., et al. (2010). Clinical significance of neurological soft signs in schizophrenia: Factor analysis of the Neurological Evaluation Scale. *Schizophrenia Research, 124*, 1–12.
Sheehan, D., Lecrubier, Y., Sheehan, K., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry, 59*(Suppl 20), 22–33.
Siegel, B. J., Asarnow, R., Tanguay, P., Call, J., Abel, L., Ho, A., et al. (1992). Regional cerebral glucose metabolism and attention in adults with a history of childhood autism. *The Journal of Neuropsychiatry and Clinical Neurosciences, 4*, 406–414.
Singer, T., Seymour, B., O'Doherty, J. P., Stephan, K. E., Dolan, R. J., & Frith, C. D. (2006). Empathic neural responses are modulated by the perceived fairness of others. *Nature, 439*, 466–469.
Solomon, M., Ozonoff, S. J., Ursu, S., Ravizza, S., Cummings, N., Ly, S., et al. (2009). The neural substrates of cognitive control deficits in autism spectrum disorders. *Neuropsychologia, 47*, 2515–2526.
Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America, 105*, 12569–12574.
Steer, C. D., Golding, J., & Bolton, P. F. (2010). Traits contributing to the autistic spectrum. *PLoS One, 5*, e12633.
Sturm, H., Fernell, E., & Gillberg, C. (2004). Autism spectrum disorders in children with normal intellectual levels: Associated impairments and subgroups. *Developmental Medicine and Child Neurology, 46*, 444–447.
Sutherland, A., & Crewther, D. P. (2010). Magnocellular visual evoked potential delay with high autism spectrum quotient yields a neural mechanism for altered perception. *Brain, 133*, 2089–2097.
Tani, P., Lindberg, N., Appelberg, B., Nieminen-von Wendt, T., von Wendt, L., & Porkka-Heiskanen, T. (2006). Clinical neurological abnormalities in young adults with Asperger syndrome. *Psychiatry and Clinical Neuroscience, 60*, 253–255.
Teitelbaum, O., Benton, T., Shah, P. K., Prince, A., Kelly, J. L., & Teitelbaum, P. (2004). Eshkol-Wachman movement notation in diagnosis: The early detection of Asperger's syndrome. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 11909–11914.
Thomann, P. A., Wüstenberg, T., Santos, V. D., Bachmann, S., Essig, M., & Schröder, J. (2009). Neurological soft signs and brain morphology in first-episode schizophrenia. *Psychological Medicine, 39*, 371–379.
Verhoeven, J. S., De Cock, P., Lagae, L., & Sunaert, S. (2010). Neuroimaging of autism. *Neuroradiology, 52*, 3–14.
Völlm, B. A., Taylor, A. N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., et al. (2006). Neuronal correlates of theory of mind and empathy: A functional magnetic resonance imaging study in a nonverbal task. *Neuroimage, 29*, 90–98.
Waiter, G. D., Williams, J. H., Murray, A. D., Gilchrist, A., Perrett, D. I., & Whiten, A. (2004). A voxel-based investigation of brain structure in male adolescents with autistic spectrum disorder. *Neuroimage, 22*, 619–625.
Ward, M., Wender, P., & Reimherr, F. (1993). The Wender Utah Rating Scale: An aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. *The American Journal of Psychiatry, 150*, 885–890.
Wicker, B., Fonlupt, P., Hubert, B., Tardif, C., Gepner, B., & Deruelle, C. (2008). Abnormal cerebral effective connectivity during explicit emotional processing in adults with autism spectrum disorder. *Social Cognitive and Affective Neuroscience, 3*, 135–143.
Wing, L. (1997). The autistic spectrum. *Lancet, 350*, 1761–1766.
Yamasaki, S., Yamasue, H., Abe, O., Suga, M., Yamada, H., Inoue, H., et al. (2010). Reduced gray matter volume of pars opercularis is associated with impaired social communication in high-functioning autism spectrum disorders. *Biological Psychiatry, 68*, 1141–1147.
Zhu, C. Z., Zang, Y. F., Cao, Q. J., Yan, C. G., He, Y., Jiang, T. Z., et al. (2008). Fisher discriminative analysis of resting-state brain function for attention-deficit/hyperactivity disorder. *Neuroimage, 40*, 110–120.
Zilbovicius, M., Garreau, B., Tzourio, N., Mazoyer, B., Bruck, B., Martinot, J., et al. (1992). Regional cerebral blood flow in childhood autism: A SPECT study. *The American Journal of Psychiatry, 149*, 924–930.