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The 'amygdala theory of autism' revisited: Linking structure to behavior

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Abstract

The 'amygdala theory of autism' suggests a crucial role for the amygdala in the neurobiological basis of autism spectrum disorders. However, to date evidence is lacking of a direct relationship between amygdala measures and behavioral manifestations of autism in affected individuals. In 17 adult individuals with Asperger syndrome (AS) and 17 well-matched controls we therefore assessed associations between MRI-derived amygdala volume and behavioral variables of emotion recognition and social cognition, as well as with core AS symptomatology. Results revealed that individuals with AS exhibited impairments in emotion recognition and social cognition compared to controls and also showed atypical relationships between amygdala volumes and overall head size. We found positive associations between emotional and social understanding and amygdala volume in the control group, but not in the AS group. In the AS group however, amygdala size was negatively related to diagnostic parameters, with smaller amygdala volumes involving higher levels of restricted-repetitive behavior domains. Our data seem to indicate that in AS the amygdala is not crucially involved in social and emotional understanding. It may, however, be a mediator for narrow interest patterns and the imposition of routines and rituals. Our data, in conjunction with current literature, seem to argue for a modification of the 'amygdala theory of autism'.

Keywords: Asperger syndrome; MRI; Social cognition; Theory of mind

1. Introduction

Asperger syndrome (AS) is a neurodevelopmental disorder on the autism spectrum, which involves impairments in reciprocal social interactions and restricted-repetitive patterns of behavior in the absence of intellectual dysfunction (American Psychiatric Association, 1994). Although the etiology of AS and autism remains to be established, it is well accepted that these conditions strongly impact the central nervous system (Brambilla et al., 2003). Of the several structures that have been suggested to play a part in the neurobiological basis of autistic symptomatology, evidence for involvement of the amygdala is particularly compelling (Pelphrey, Adolphs, & Morris, 2004). This has led to the postulation of the 'amygdala theory of autism' (Baron-Cohen et al., 2000). Most of the support for the 'amygdala theory of autism' comes from studies in non-autistic populations implicating the amygdala in social and emotional behaviors, while little evidence has emerged from studies involving affected individuals.

A crucial role of the amygdala in social behavior and cognition, as well as emotional functioning has been established by studies of non-human primates (Brothers, Ring, & Kling, 1990; Emery et al., 2001; Thompson & Towfighi, 1976), humans with selective amygdala lesions (Adolphs et al., 1999; Adolphs, Baron-Cohen, & Tranel, 2002; Heberlein & Adolphs 2004), and PET and fMRI activation studies of neurotypical individuals (Baas, Aleman, & Kahn, 2004; Kawashima et al., 1999; Phan et al., 2005; Singer, Kiebel, Winston, Dolan, & Frith, 2004; Winston, Strange, O'Doherty, & Dolan, 2002). It is these findings, along with the impairments of autistic individuals to process emotional and social information (Frith, 2004; Kleinman, Marciano, & Ault, 2001; Macdonald et al., 1989), that has led researchers to postulate an involvement of the amygdala in autism.

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Other, albeit also indirect support for the 'amygdala theory of autism' comes from both neuropathological and structural brain imaging studies that reported abnormalities in the amygdala of affected individuals (for review see, Brambilla et al., 2003; Palmen, van Engeland, Hof, & Schmitz, 2004). However, most neuropathological findings were not specific (e.g., also applied to the hippocampus) (Kemper & Bauman, 1993) and volumetric in vivo studies have been largely inconsistent, reporting no change (Haznedar et al., 2000), increases (Howard et al., 2000), or decreases (Aylward et al., 1999) in amygdala volume. More importantly, studies assessing the amygdala in vivo have failed to report concomitant autism related behavioral and cognitive impairments. Data on such associations would be especially helpful and provide information on whether amygdala structural findings are relevant to autism; that is whether they are a true pathophysiological mediator, or whether they only represent an epiphenomenon. The single structural brain imaging study in individuals with autism that measured both amygdala volumes and behavioral parameters that are considered suggestive of amygdala damage (impaired emotion recognition), did not report associations between the two (Howard et al., 2000).

More direct evidence for the 'amygdala theory of autism' can be derived from a few functional imaging studies involving autistic individuals. Compared to control subjects, autistic individuals showed less amygdala activation when inferring mental states from eyes (Baron-Cohen et al., 1999), viewing faces of emotional expressions (Critchley et al., 2000), or in response to changing task demands in an emotion recognition task (Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004). However, it should be noted that the first two studies do not report relationships between task accuracy and amygdala activation, and the latter study found no such association.

Interestingly, to date no studies have tried to link the amygdala to core diagnostic features of autism spectrum disorders as defined by the diagnostic criteria in DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1992). Although problems in social cognition and emotion recognition could be interpreted as indicative of impairments in social interaction, which in turn represents diagnostic cluster A in the DSM-IV and ICD-10, they are currently not an integral part of the diagnostic criteria. Hence, it can be argued that for the 'amygdala theory of autism' to be validated, a link between core diagnostic criteria of autism spectrum disorders and the amygdala needs to be established.

In sum, although the last decade has generated a host of evidence supportive of the 'amygdala theory of autism', relatively little of this evidence comes from studies directly relating the structure to behavior relevant to autism. To date, relationships between amygdala structure and behavioral variables of emotion recognition and social cognition have not been assessed in affected individuals. In addition, the relationship between amygdala structure and the core symptoms of autism and AS is poorly understood. Thus, in the current study we sought to assess relationships between amygdala volume and emotional and social cognition, as well as amygdala volume and diagnostic parameters of AS.

2. Materials and methods

2.1. Participants

Seventeen adults with Asperger syndrome (14 men and 3 women, mean age = 41.4) participated in the study. Individuals with AS were recruited through local support groups or were referred by specialized clinicians. Every subject underwent a videotaped semi-structured diagnostic interview and diagnoses of AS were made according to DSM-IV AS criteria (American Psychiatric Association, 1994). Diagnostic discrepancies were resolved by consensus of one psychiatrist and two psychologists. In addition, diagnoses were confirmed with the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) in 13 subjects with available parental informants.

A group of 17 healthy (neurotypical) control subjects (15 men and 2 women, mean age = 40.2), chosen to match the Asperger group as closely as possible with respect to age, education, and IQ, also participated in the study. Individuals in the control group were volunteers participating in ongoing studies of normal aging at the NYU Center for Brain Health.

All study participants underwent medical (including electrocardiogram, blood pressure, and routine blood tests), neurological, neuropsychological, psychiatric, and neuroradiologic (MRI) examinations. Any present or prior evidence of significant neurological or medical disease lead to exclusion from the study. Thirty of the subjects in this study were part of a larger study on social cognition in AS (Dziobek et al., in press). All participants gave informed written consent and the research protocol was approved by the IRB of the New York University School of Medicine.

2.2. Measures

2.2.1. Diagnostic measures

2.2.1.1. Autism Diagnostic Interview-Revised (ADI-R). Autistic symptomatology of the study participants was assessed using the ADI-R (Lord et al., 1994). The ADI-R is a valid and reliable semi-structured interview administered to the parents of the autistic individual. The instrument contains an algorithm for the diagnosis of autism according to DSM-IV criteria (American Psychiatric Association, 1994) as a result of probes regarding social, communication, and restricted-repetitive behavior domains corresponding to the different diagnostic criteria. For each of the three domains, a separate score is derived by summing up the items pertaining to it, where each item describing abnormal behavior is coded as either 0 (absent), 1 (present but not sufficiently severe or frequent to meet criteria for 2), 2 (definitely present), or 3 (a more severe manifestation of 2).

2.2.1.2. Asperger Syndrome Diagnostic Interview (ASDI). Although we selected AS subjects based on DSM-IV criteria, we also administered the Asperger Syndrome Diagnostic Interview (ASDI) (Gillberg, Gillberg, Rastam, & Wentz, 2001). The main reason for inclusion of this instrument was its directedness to individuals with Asperger Syndrome and its scalar nature, which allowed us to enter the different symptom domains into correlation analyses.

The ASDI has proven valid and reliable in establishing a diagnosis of AS. It was developed because of a need for diagnostic instruments specifically targeting higher functioning individuals on the autism spectrum, in particular those with AS. The ASDI was designed to cover diagnostic criteria for AS as described by Gillberg and Gillberg in 1989. Specifically, the interview is comprised of 20 different items, which cover the following six criteria: (1) social interaction, (2) narrow interest patterns, (3) imposition of routines and rituals, (4) speech and language peculiarities, (5) non-verbal communication, and (6) motor clumsiness. For each item, the interviewer assigns a score of 1 (does not apply), 2 (applies sometimes or somewhat), or 3 (definitely applies). Separate scores for each one of the six diagnostic criteria can be derived by summing up the items operationalising it. In addition, we created a global severity index by totaling these scores in a weighted fashion, taking into account the different numbers of items pertaining to each separate criteria.

2.2.2. Neuropsychological measures

2.2.2.1. Intellectual functioning. To assess intellectual functioning, the Shipley Institute of Living Scale (Prado & Taub, 1966) was utilized, comprised of a

vocabulary and an abstract thinking test. Based on the sum of the raw scores of the tests, WAIS-R full scale IQ was estimated using published procedures (Zachary, Paulson, & Gorsuch, 1985).

2.2.2.2. Basic emotion recognition. Participants were given a series of 28 pictures of facial expressions of happiness, sadness, anger, fear, surprise, and disgust, intermixed with neutral expressions (Ekman & Friesen, 1971). With each face, a wordlist of these basic emotional states was displayed in random order and the subjects were required to choose the one word that they considered to best describe what the person in the photo was feeling. Four different individuals' photographs were utilized, with every individual displaying each emotional state once. The criterion measure was ascertained by totaling the number of items correctly identified (maximum score = 28).

2.2.2.3. Movie for the Assessment of Social Cognition (MASC). The MASC is a computerized test of social cognition (theory of mind) (Dziobek et al., in press). It involves watching a 15 minute film about four characters getting together for a dinner party and it requires subjects to make inferences about the featured characters' mental states. The film is stopped at 46 points during the plot and questions referring to the characters' feelings, thoughts, and intentions are asked (e.g. "What is Betty feeling?", "What is Cliff thinking"). Subjects' correct responses are scored as one point and added to an overall score. In addition, the MASC allows separate quantification of the extent to which emotional mental states (EMS) (e.g. "Betty is angry") and non-emotional mental states (non-EMS) (e.g. "Cliff is thinking about leaving") are inferred correctly.

2.2.3. Magnetic resonance imaging

2.2.3.1. Volumetric measurements. For the brain measurements, a thin slice 3D coronal T1-weighted spoiled gradient recalled (SPGR) sequence was used. The SPGR sequence parameters were: TR 35 ms; TE 2 ms; flip angle 60° and 1 signal average; 124 slices; 1.6 mm slice thickness with no gap, acquisition matrix 256 × 128; FOV 200 mm × 200 mm; acquisition time 9 min. The SPRG study provided data to create reformatted (coronal, axial, sagittal, and oblique) images and adequate T1-weighted contrast for the accurate determination of the regional volumes. Using our locally developed Multimodal Image Data Analysis System (MIDAS) software, regions of interest were drawn on coronal images (pathological angle) created as reformats from the coronal SPRG images. We outlined the amygdala using our published method (Convit et al., 1999) briefly outlined below. Although we had no a priori hypothesis regarding whether the amygdala would be increased or decreased in size, all brain measurements were made blind to group membership. We also obtained measures of intracranial vault volume and global brain atrophy. The volume of structures was calculated by multiplying the cross-sectional area by the slice thickness and summing across slices.

Amygdala: The anterior hippocampus merges with the amygdala and this boundary is difficult to discriminate on coronal orientation. In addition, the tail of the caudate is often contiguous with the major amygdaloid body, and surrounding anterior temporal lobe cortex is often difficult to distinguish from the anterior pole of the amygdala. Our image analysis software MIDAS allows the simultaneous display of the sagittal and axial views, which greatly simplifies distinguishing the amygdala from surrounding structures. The anterior pole of the amygdala is found approximately 7 mm posterior to the fronto-temporal junction and about 5 mm behind the anterior limit of the entorhinal cortex (Amaral & Insausti, 1990). The medial border of the amygdala is the angular bundle, which separates it from the entorhinal cortex. The superio-medial border of the amygdala is demarcated where the semilunar gyrus, which contains the cortical nucleus of the amygdala, comes in contact with the overlying CSF. The posterior boundary is the hippocampal-amygdala transitional area. Using our method, we obtain high levels of agreement between two independent raters (ICC = 0.93, $n = 57$) (Convit et al., 1999).

Cerebral vault size: To obtain a measure of head size and overall (global) atrophy, we obtained an intracranial vault volume. We used every fifth sagittal image to trace the outline of the supratentorial compartment by following the margins of the dura and tentorium. A thresholding procedure was applied to estimate the cerebral spinal fluid (CSF) portion of this intracranial vault volume, which was then used as a measure of global atrophy (Convit et al., 2001).

The intracranial vault volume is also used to account for the variability in overall brain size, which may in turn impact on the size of the brain structures of interest. Several methods have been used to adjust for individual differences in head size, including the computation of ratios or the use of regression to obtain residualized volumes. A recent review (Van Petten, 2004) shows that the use of ratios can lead to spurious correlations. Thus, we residualized all brain volumes to intracranial vault volume by means of regression analyses and then used the residualized volumes in the subsequent statistical analyses. Similarly, the measure of global atrophy, the CSF volume within the intracranial vault was residualized to intracranial vault volume. For ease of reference and to make our results comparable with other published studies, we have included Table 2, which contains the raw values for the brain volumes.

2.3. Statistical analysis

Group differences in demographic variables, neuropsychological measures, and brain volumes were assessed with independent samples *t*-tests. Associations between amygdala volumes and neuropsychological functions, as well as AS related symptom domains were analyzed with Pearson correlation analysis. All analyses were two-tailed and the alpha level was set at $p < .05$. All statistical procedures were performed using the Statistical Package for the Social Sciences version 12.0 (SPSS, Chicago, IL).

3. Results

3.1. Between group differences

3.1.1. Background variables

As expected because of group matching, comparisons between groups for age, gender, education, and IQ were non-significant. Descriptive statistics of the two groups are shown in Table 1.

3.1.2. Measures of emotion recognition and social cognition

Individuals with AS scored significantly lower than the control group in the emotion recognition task. In addition, the difference in correct mental state inferences for the MASC was highly significant, indicating greater difficulties in the group with AS. The same difficulties were reflected in lower scores on the MASC's subcomponents 'emotional mental states' (EMS) and 'non-emotional mental states' (non-EMS). Because the

Table 1
Demographic variables and scores on the emotion recognition test (Faces) and the MASC (overall, emotional mental states (EMS), non-emotional mental states (non-EMS)) for Asperger ($n = 17$) and control subjects ($n = 17$)

	Asperger	Control	*p*
Gender (male/female)	14/3	15/2	.63
Age	41.4 ± 9.9	40.2 ± 13.0	.77
Education	16.6 ± 1.7	16.5 ± 1.3	.82
Shipley IQ	113 ± 6	115 ± 5	.30
Faces (max score = 28)	21.6 ± 2.9	25.4 ± 1.9	.001
MASC (overall score)[a]	55 ± 11	76 ± 6	.001
MASC (EMS)[a]	59 ± 19	86 ± 11	.001
MASC (non-EMS)[a]	49 ± 14	74 ± 13	.001

p values reflect level of significance from independent samples *t*-test and χ^2 as appropriate. Values are given in mean ± S.D.

[a] Values reflect % of raw scores.

Table 2
Amygdala volumes, cerebral vault size, and global atrophy (cm^3) for Asperger ($n = 17$) and control subjects ($n = 17$)

	Asperger	Control	p
Left amygdala	0.98 ± 0.14	1.03 ± 0.23	.51
Right amygdala	0.98 ± 0.17	1.04 ± 0.24	.44
Average amygdala ((left + right)/2)	0.98 ± 0.14	1.04 ± 0.22	.43
Cerebral vault size	1306.6 ± 99.1	1313.4 ± 132.9	.87
Global atrophy (CSF volume)	97.0 ± 37.9	94.6 ± 42.2	.83

Raw – not residualized – volumes are given for comparability. p values reflect level of significance from independent samples t-tests using residualized brain volumes (except for cerebral vault size). Values are given in mean ± S.D.

different MASC subcomponents are composed of different numbers of items (overall = 46, EMS = 14, non-EMS = 10), raw sum scores were converted to percentage scores for better comparability (these results are shown in Table 1).

3.1.3. Magnetic resonance imaging

The AS and control group did not differ in overall brain size (intracranial vault volume). There were also no significant differences between the groups for the residualized volumes of the left or right amygdala, nor for the average of left and right amygdala. In addition, overall atrophy (residualized CSF volume) did not differ between the groups. All raw volumes are presented in Table 2.

We had no hypotheses referring to laterality of amygdala volumes. Consequently, to reduce variability in the data and minimize the number of comparisons, we used the average volume of left and right amygdala for all subsequent analyses.

3.2. Correlation analyses

3.2.1. Amygdala volumes and intracranial volume

We ran intragroup correlations between amygdala volume (average of left and right) and intracranial vault volume. In the control group, as expected, we found a strong statistical trend for a positive association ($r = .47$, $p = .056$), whereas in the AS group, we observed a non-significant negative association ($r = -.14$, $p = .58$) (Fig. 1).

3.2.2. Amygdala volumes and social cognition

For each group individually, we calculated correlations between amygdala volume and performance on the emotion recognition test and the MASC scores. We used the average (residualized to intracranial vault volume) amygdala volume for all subsequent correlational analyses. Almost identical results were obtained when the raw amygdala volumes were used instead of the residualized volumes (data not shown).

In the control group, there was a highly significant correlation between amygdala volume and the emotion recognition test and a trend for the overall performance on the MASC. In addition, there was a significant correlation between amygdala volume and the emotional mental state items of the MASC.

There were no significant associations between emotion recognition or MASC scores and amygdala volumes in the group of individuals with AS. All relationships are shown in Table 3.

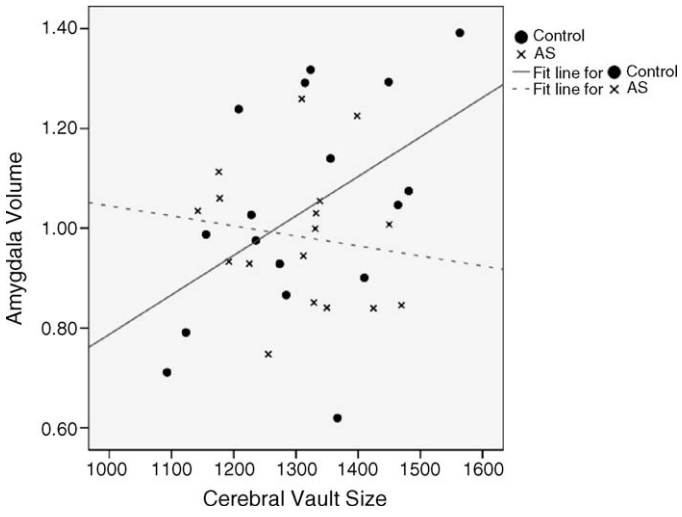

Fig. 1. Correlations between raw amygdala volumes (average of left and right in cm^3) and cerebral vault size (in cm^3) for controls ($n = 17$) and individuals with AS ($n = 17$).

3.2.3. Amygdala volumes and AS symptomatology

To assess relationships between Asperger symptomatology and amygdala volume, the ASDI overall severity index for the AS participants as well as their scores for the six different diagnostic criteria were entered into a correlation analysis. There was a significant negative association between the overall ASDI index and amygdala volume, indicating that individuals with more symptomatology had smaller amygdala volumes. These associations seemed to be largely driven by a significant correlation between ASDI criteria 2 (narrow interest patterns) and amygdala volume (Fig. 2).

We also assessed the degree of association between amygdala volumes and ADI-R scores. However, given that only 12 AS subjects had complete data for the three different symptom clusters (one of the 13 subjects with available ADI-R was missing raw data), analyses were performed on an exploratory basis only. Although none of the observed relationships reached statistical significance, R^2 were noticeably similar to the associations between ASDI and amygdala volume (see Table 4).

Table 3
Correlations between amygdala volumes (residualized for intracranial vault) and social cognition measures (emotion recognition test (Faces) and MASC scores (overall score, emotional mental states (EMS), non-emotional mental states (non-EMS))) for Asperger ($n = 17$) and control subjects ($n = 17$)

	Asperger amygdala volume	Control amygdala volume
Faces	.25	.60**
MASC (overall score)	.17	.45+
MASC (EMS)	.07	.50*
MASC (non-EMS)	−.07	.35

* $p < .05$.
** $p < .01$.
\+ $p < .10$.

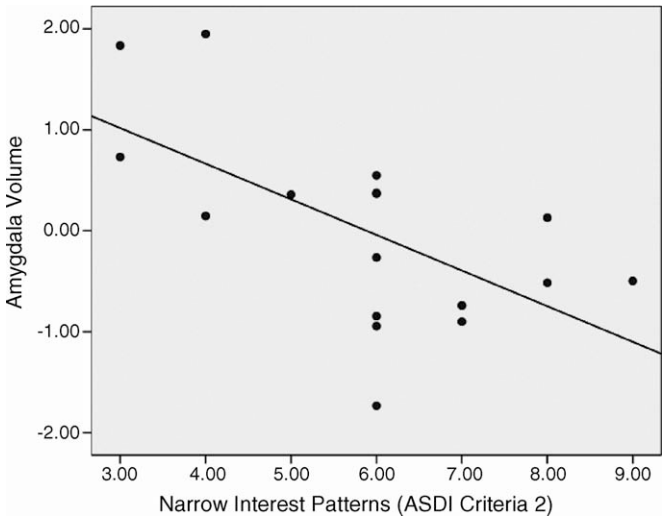

Fig. 2. Correlation between amygdala volumes (average of left and right residualized to cerebral vault size) and narrow interest patterns in individuals with AS ($n = 17$).

Table 4
Correlations between amygdala volumes (residualized for intracranial vault) and Asperger syndrome symptomatology (ASDI: Asperger Syndrome Diagnostic Interview, ADI-R: Autism Diagnostic Interview-Revised) for individuals with AS ($n = 17$)

	Amygdala volume
ASDI	
Overall score	−.55*
Social interaction	−.24
Narrow interest patterns	−.62**
Imposition of routines and rituals	−.41
Speech and language peculiarities	.15
Non-verbal communication	−.13
Motor clumsiness	−.24
ADI-R[a]	
Reciprocal social interaction	−.41
Communication	−.43
Restricted-repetitive behavior	−.49

[a] For $n = 12$ with available ADI-R data.
* $p < .05$.
** $p < .01$.

4. Discussion

The main goal of the current study was to determine relationships between amygdala volume and emotional and social cognition, as well as amygdala volume and diagnostic parameters in individuals with Asperger syndrome. To this end, we administered a test of basic emotion recognition and the Movie for the Assessment of Social Cognition (MASC). Furthermore, we assessed amygdala volumes by means of manual anatomical tracings.

4.1. Group differences in emotion recognition, social cognition, and amygdala volume

Individuals with AS scored significantly lower than controls on the basic emotion recognition test and the MASC, which is consistent with previous findings of impaired social cognition and emotion processing in individuals on the autism spectrum (e.g. Frith, 2004; Kleinman et al., 2001; Klin, 2000). In the current study we did not specifically control for possible confounding factors such as gaze fixation, which has been reported abnormal in autism (Dalton et al., 2005). However, the MASC as well as other social cognition tests that were part of the test battery entail control conditions that require subjects to make non-social inferences based on the same stimulus material used for the social inferences. In these control conditions the AS group scored as well as the control group (Dziobek et al., in press). If gaze fixation differences between the groups were sufficient to affect their social task performance, they should have also affected the control tasks.

Volumetric analyses did not yield differences in amygdala size between the groups, which is in keeping with studies in high functioning adults with autism spectrum disorder (Haznedar et al., 2000) and in adolescents with autism (Schumann et al., 2004). However, results of studies assessing amygdala volumes in individuals on the autism spectrum have been markedly inconsistent, as there is also evidence for increased (Abell et al., 1999; Howard et al., 2000) and decreased (Aylward et al., 1999; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Rojas et al., 2004) amygdala volume.

While the exact reasons for these inconsistencies remain to be established, the different methodologies used to assess amygdala volumes and heterogeneity of subject populations are likely contributing factors. For example, in the studies mentioned, raw amygdala volumes for control subjects vary from 1.01 to 2.60 cm^3. In the current study, we report on mean amygdala volumes of 1.04 cm^3, which is well in line with postmortem studies reporting amygdala volumes between 0.63–1.62 cm^3 (Brierley, Shaw, & David, 2002; Convit et al., 1999). The method we used to measure amygdala volume has proven valid and reliable (Convit et al., 1999) and was found in a recent systematic review of more than 40 MRI volumetric studies of the amygdala to be one of the better methods (Brierley et al., 2002).

Also adding to the discrepancies between studies is the heterogeneity of the subjects studied. Some study groups were composed of definite autism cases (Pierce et al., 2001), while others consisted of mixed groups with autism and AS cases (Abell et al., 1999; Haznedar et al., 2000). In our study, we were careful to only include individuals with AS that had no reported delay in language acquisition to reduce potential accompanying brain variability.

Another issue that complicates the interpretation of in vivo volume studies of the amygdala in autism spectrum conditions is that they are gross measures that likely fail to detect more subtle amygdala differences such as in microstructural properties. For example, postmortem studies of individuals with autism have reported an increased cell packing density and smaller neuronal size in limbic regions including the amygdala (Kemper & Bauman, 1993). This questions the validity of studies in autism spectrum disorders that solely rely on brain volumetric data. Future studies should also include measures such as magnetic resonance spectroscopy (MRS) or measures of tissue properties (such as T1 relaxation time), which may allow inferences about

neuronal density. MRS has been applied successfully before in individuals on the autism spectrum (Murphy et al., 2002).

Interestingly, when correlating amygdala volume with overall brain size for the groups separately, we found an almost significant positive trend ($p = .056$) for the control group, whereas we observed a small negative association in the AS group. From work in our laboratory as well as from work of other groups we know that in healthy individuals there is usually a close association between amygdala volume and overall brain size (Brierley et al., 2002; Convit et al., 1999; Watson et al., 1997). Consequently, the dissociation between amygdala volumes and brain size in the individuals with AS may be indicative of structural abnormalities in the amygdala. As such, our observation is in line with findings from a study by Sparks and collaborators (2002), who reported that amygdala enlargement was disproportionate to increased cerebral volume in children with autism spectrum disorder.

4.2. Associations between amygdala volume and emotion recognition and social cognition

To ascertain relationships between amygdala volume and emotion recognition and social cognition, we ran correlation analyses for the AS and control groups separately. In the control group, both performance on the emotion recognition test and the MASC was positively related to amygdala volume. To the best of our knowledge, this is the first report on an association between emotion recognition/social cognition and amygdala volume in healthy individuals.

Although emotional and social functioning have long been thought to depend on amygdala integrity (e.g. Adolphs et al., 2002; Anderson & Phelps, 2001; Kawashima et al., 1999), the structure is only one component, among many, in a distributed neural system (Adolphs, 2003). Recent studies by Amaral and colleagues (e.g. Amaral et al., 2003; Bauman, Lavenex, Mason, Capitanio, & Amaral, 2004) support this view. In these studies rhesus monkeys received toxic lesions of the amygdala that spared fibers passing through and around the amygdala. As a result, the monkeys demonstrated more subtle changes in social behavior than previously reported with cruder lesion techniques (Bachevalier, 1994). Thus, other brain areas connected with and via the amygdala may be as important as the function of the amygdala itself.

It is interesting to note that the associations between amygdala volume and the MASC were stronger when the mental states that had to be inferred were emotional (EMS) than when they were non-emotional thoughts or intentions (non-EMS). This may indicate the relative selectivity of the amygdala to process emotional stimuli within social contexts. A recent report seems to support this notion by showing that amygdala activation was greater for social-emotional than for social-neutral pictures (Norris, Chen, Zhu, Small, & Cacioppo, 2004).

In contrast to the neurotypical group, in the AS group we did not observe significant associations between any of the variables of emotional or social reasoning and amygdala volume. This might indicate that in AS the amygdala is less involved in social and emotional information processing than in neurotypical individuals.

4.3. Associations between amygdala volume and diagnostic variables

In order to test for associations between amygdala measurements and symptomatology directly linked to a diagnosis of AS, we performed correlation analyses between amygdala volumes and severity sub-scores of the ASDI (Gillberg et al., 2001) and ADI-R (Lord et al., 1994). There were significant negative associations between amygdala size and overall symptom severity on the ASDI, indicating that among individual with AS, those who were more severely affected had smaller amygdala volumes. Correlation analyses of the individual diagnostic clusters revealed no significant associations between amygdala volume and diagnostic criteria targeting social behavior or non-verbal communication, both of which are at the core of symptom cluster A in the DSM-IV. This is in line with the lack of an association between amygdala volumes and emotional and social reasoning described above, and seems to indicate once more that in individuals with AS the amygdala is not crucially involved in social behavior.

The association between the severity index of the ASDI and amygdala size was mainly driven by the ASDI criteria 'narrow interest patterns'. In addition, the association between amygdala size and the criteria 'imposition of routines and rituals' was high, although only significant for the left amygdala volume ($r = -.62$, $p < .01$), as revealed by subsequent laterality analyses. Together, these two diagnostic criteria closely match symptom cluster B of a diagnosis of AS as defined in the DSM-IV and operationalized by the ADI-R in the category 'restricted-repetitive behavior' (RRB). Although none of the correlational analyses between the amygdala and the ADI-R categories reached significance (likely because of the small N), the strength and pattern of the associations (R^2) was similar to the ones for the ASDI subscores, with associations being higher for restricted-repetitive behaviors than for social symptomatology.

This first finding of relationships between RRB and the amygdala in autism spectrum conditions is somewhat surprising and merits further discussion. RRB has been studied mostly in Tourette syndrome and obsessive-compulsive behavior and has traditionally been associated with basal ganglia dysfunction (e.g. Mink, 2001; Rosenberg et al., 1997). Consequently, the only two studies relating RRB to brain structures in autism spectrum disorders have only assessed basal ganglia (McAlonan et al., 2002; Sears et al., 1999). However, there is increasing literature from other fields in support of a link between RRB and the amygdala. For example, in neurotypical subjects, activation of the amygdala has been shown in response to obsessive-compulsive-related stimuli (Mataix-Cols et al., 2003). Moreover, patients with obsessive-compulsive disorder were reported to have smaller amygdala volumes (Szeszko et al., 1999) and amygdala activation was attenuated among these patients in response to emotional stimuli (Cannistraro et al., 2004). Furthermore, non-human primates with medial temporal lobe lesions including the amygdala and periamygdaloid cortex

exhibit more stereotypies than control animals (Bachevalier, 1994).

The extensive projections from the basal and accessory basal nuclei of the amygdala to the ventral striatum also provide further theoretical rationale for an amygdala involvement in RRB. For example, studies in monkeys with lesions to the temporal lobe encompassing the amygdala showed delayed maturation of the dorsolateral prefrontal cortex, which was associated with a dysregulation of striatal dopaminergic neurotransmission (Heinz et al., 1999) and increased volume of the caudate nucleus (Bachevalier & Loveland, 2006). This link between caudate nucleus and RRB was supported by the above mentioned study by Sears and colleagues (1999), where increased volume of the caudate correlated significantly with stereotyped repetitive behaviors in autistic individuals. Moreover, the connections between amygdala and striatum were hypothesized to mediate the beneficial effects of extinction-based behavioral therapies for obsessive-compulsive disorder (Rauch & Jenike, 1993).

4.4. The 'amygdala theory of autism' revisited

In the current report, we have shown between-group differences in emotion recognition and social cognition tests generally thought to be reflective of amygdala functioning (Phan et al., 2005; Winston et al., 2002). Although we did not observe group differences in amygdala volumes, the AS group showed differing associations between amygdala size and overall brain volume, which might be indicative of amygdala structural abnormalities in AS. Both results replicate previous reports in autism spectrum conditions.

More importantly, we reported on associations between emotional and social reasoning and amygdala volume in neurotypical, but not in AS individuals, which points more directly to a role of the amygdala in the neurobiology of autism spectrum disorders. Interestingly though, the results inform about behavior that the amygdala may not (or not sufficiently) subserve in AS. This leaves open the question as to which behaviors the amygdala does subserve in AS. Thus, our finding of negative associations between AS symptom severity (especially RRB) and amygdala volume represents some more direct evidence for an, albeit modified, 'amygdala theory of autism'. It suggests also that among individuals with AS the amygdala seems to serve a function, namely of inhibiting restrictive-repetitive behaviors. One possible implication from these findings, although speculative, may be that in AS only circumscribed parts of the amygdala are dysfunctional, specifically the ones involved in emotional and social behaviors.

The reported positive amygdala-social/emotional behavior associations in the neurotypical individuals and the negative amygdala-RRB associations in the AS individuals seem to indicate that in both diagnostic groups, large amygdala volumes are associated with better or "healthier" functionality. However, given reports on possible differences in amygdala tissue properties (Kemper & Bauman, 1993), this does not exclude the possibility of quite different underlying mechanisms for the groups.

That being said, we do not suggest that the neuropathology of autism spectrum disorders is restricted to the amygdala nor that social cognition and behavior rely solely on amygdala functioning. Many other brain regions have been associated with social behavior such as the orbitofrontal cortex, temporopolar region, anterior cingulate, and the cerebellum, all of which have also been implicated in some autistic symptomatology. Interestingly, these brain areas are directly or indirectly connected to the amygdala and it seems likely that not only early dysfunction of the amygdala but also of its interconnections with other brain areas are key mediators of the social problems seen in autism spectrum disorders (Bachevalier & Loveland, 2006). In support of this view are animal studies involving neonatal medial temporal lobe lesions that have widespread effects on developing structures distant from the site of the lesion, such as the prefrontal cortex (Bertolino et al., 1997). To allow assessment of the specific role of the amygdala in autistic symptomatology, future studies should also include measurements of other candidate brain regions and should be longitudinal in nature to allow for a brain developmental perspective. Furthermore, it would be advantageous to combine structural and functional analyses within one MRI evaluation. Although volumetric measurements are likely reflective of the functionality of a brain structure, they are relatively crude measures that would profit from additional information about the structure's functioning and its connectivity with other brain regions.

5. Conclusion

The data presented in this paper lends further support to a role of the amygdala in autism spectrum disorders. We corroborated findings of impaired emotion recognition and social cognition as well as differing associations between amygdala volume and overall head size in AS. In addition, we extended the current literature by reporting for the first time associations between amygdala size and emotional/social reasoning in neurotypical individuals and between amygdala size and symptom severity in AS individuals. Specifically, our data seem to indicate that in AS the amygdala is not a key mediator for emotional or social information, but that it may be implicated in the restricted-repetitive behaviors that are an integral part of the diagnosis of AS. Given the likely involvement of many other brain areas in autistic symptomatology as well as in social cognition and behavior, the 'amygdala theory of autism' is in need of modification. It seems evident that only a neurodevelopmental network theory that considers all these brain areas as well as their interconnections will be able to explain the neuronal underpinnings of autism spectrum disorders.

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