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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