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The amygdala and related structures in the pathophysiology of autism

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Abstract

Autism is a neurodevelopmental disorder that is defined behaviorally by severe deficiencies in reciprocal social interaction, verbal and nonverbal communication, and restricted interests. The amygdala is involved in the regulation of social behaviors and may be an important site of pathology for the social dysfunction seen in autism. This review focuses on lesion, postmortem, and neuroimaging studies that investigate the amygdala and related structures in this disorder. Other brain regions potentially involved in the neuropathology of autism are also briefly discussed. Although supportive evidence exists for amygdala dysfunction in autism, the currently available data are inconsistent and additional research is needed. © 2002 Elsevier Science Inc. All rights reserved.

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1. Introduction

Autism is a neurodevelopmental disorder that becomes manifest in the first 3 years of life. It is defined behaviorally by severe deficiencies in reciprocal social interaction, verbal and nonverbal communication, and a markedly restricted repertoire of activities and interests (APA, 1994). Associated phenomena can include mental retardation, emotional indifference, hyperactivity, aggression, self-injury, and repetitive behaviors such as body rocking or hand flapping. A related condition, Asperger's disorder, is characterized by significant social impairment and restricted behaviors, but lacks the severe deficits in communication and cognition.

Common to both autism and Asperger's disorder is severe social impairment. In the first description of autism, Kanner (1943) described these children as having "an innate inability to form the usual, biologically provided affective contact with people." While the cause of autism remains unknown, genetic, neurochemical, and neuroanatomical studies have begun to yield preliminary findings regarding the pathophysiology of the disorder. Although numerous brain areas have been implicated in the neuropathology of autism, the amygdala has been of particular interest due to its role in social and aggressive behaviors (Aggleton, 1992). This article will review lesion, postmortem, and neuroimaging studies that have examined the role of the amygdala in autism.

2. Human lesion studies

Localized disease of the brain can provide evidence for the function of damaged areas. Temporal lobe structures, including the amygdala and hippocampus, have been implicated in the pathophysiology of autism following studies of either damage to these areas in humans or experimental lesions in animals.

In several case reports, children with severe temporal lobe damage due to viral encephalitis (DeLong et al., 1981; Greer et al., 1989; Gillberg, 1986), tumors (Taylor et al., 1999; Hoon and Reiss, 1992), and other factors (Deonna et al., 1993; White and Rosenbloom, 1992; DeLong and Heinz, 1997) have developed autistic symptoms. Children with tuberous sclerosis have been reported to have a higher-than-expected incidence of autism (Gillberg et al., 1994). In these children, symptoms of autism are strongly related to the presence of tubers in the temporal lobes (Bolton and Griffiths, 1997). Additionally, amygdala damage has been associated with impairments in the processing of facial expressions in some cases (Adolphs et al., 1994, 1998; Young et al., 1995). Abnormalities in this function are also reported

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in subjects with autism or Asperger's disorder (Boucher and Lewis, 1992; Davies et al., 1994; Schultz et al., 2000).

3. Experimental lesions and other animal studies

Experimental lesion studies in nonhuman primates provide further evidence for medial temporal lobe involvement in autism. Some authors have noted similarities between autism and the Kluver–Bucy syndrome, a syndrome caused by bilateral lesions to the anterior temporal lobes in monkeys (Kluver and Bucy, 1939; Heltzler and Griffin, 1981). Monkeys with the Kluver–Bucy syndrome display features often seen in autistic subjects such as absence of social "chattering," lack of facial expression, and absence of emotional reactions. Other such similarities include repetitive abnormal movement patterns, increased aggression, and the tendency to examine objects by mouth or smell.

More specific research has focused on newborn monkeys who sustained bilateral removal of the amygdala, hippocampus, and adjacent cortical areas (Bachevalier, 1994, 1996). By 6 months of age, these monkeys were uninterested in and avoided social contacts. They also developed autistic-like characteristics, such as unexpressive faces, very little eye contact, locomotor stereotypies, and self-directed activity. These behaviors persisted into adulthood. However, monkeys receiving similar lesions as adults did not sustain such severe social deficits or display any other of the behavioral abnormalities (Malkova et al., 1997).

Further studies along these lines were undertaken to determine the effects of early amygdala versus hippocampal lesions (Bachevalier, 1994, 1996). Early amygdala damage caused a pattern of socioemotional disturbance almost identical to that described for complete medial temporal lobe lesions, but to a lesser extent. However, amygdala-lesioned animals did not show stereotypic behaviors or loss of facial expression. Early damage to the hippocampus alone caused some degree of socioemotional disturbance by 2 months of age, but by 6 months, these disturbances were not apparent. The author concluded that early damage to the amygdaloid complex appears to be more closely related to the emergence of autistic-like behavior than early damage to the hippocampal formation. The most severe autistic-like syndrome appeared only following combined damage to the amygdala, the hippocampus, and adjacent cortical areas.

Many animal studies have also supported the role of the amygdala in the regulation of social behaviors, particularly dyadic social interactions with a novel conspecific partner (Sanders and Shekhar, 1995; Sajdyk and Shekhar, 1997; Emery et al., 2001). Physiological activation of the basolateral nucleus of the amygdala (BLA) in rats, by either blocking tonic GABAergic inhibition or by enhancing glutamate or the stress-associated peptide corticotropin-releasing factor (CRF; or other CRF receptor agonists such as Urocortin, Ucn)-mediated excitation, causes reductions in social behaviors (Sajdyk and Shekhar, 2000; Sajdyk et al., 1999). On the other hand, lesioning of the amygdala (Emery et al., 2001) or blocking amygdala excitability with glutamate antagonists (Sajdyk and Shekhar, 1997) results in increased dyadic social interaction in conspecifics. More interestingly, overstimulation of the BLA by CRF elicits a profound and chronic disruption of social behaviors that are not restored by becoming familiar with the environment or partners (Shekhar and Sajdyk, unpublished results). In summary, both disease-associated alterations in the temporal lobes in humans and experimental manipulations of the amygdala in animals have produced syndromes with striking similarities to the social deficits in autism.

4. Postmortem studies

Approximately 30 postmortem cases of subjects exhibiting the behavioral syndrome of autism have been described. The largest group of cases consists of nine brains examined by Kemper and Bauman (1998). Compared to age- and sex-matched controls, microscopic amygdala abnormalities were described in all of these cases. Abnormalities consisted of small neuronal size and increased cell packing density predominantly in the cortical, medial, and central nuclei of the amygdala, whereas the basolateral complex showed an intermediate degree of involvement. The lateral nucleus of the amygdala appeared to be comparable to controls in eight of nine brains. The one exception to this pattern of pathology involved a 12-year-old boy whose entire amygdala was diffusely abnormal. Relatively small and densely packed neurons were also observed in hippocampal fields CA1–CA4, the subiculum, entorhinal cortex, mammillary bodies, medial septal nucleus, and anterior cingulate gyrus of all the autistic brains. Neurons in the diagonal band of Broca, deep cerebellar nuclei, and inferior olive were enlarged in all brains of subjects under 22 years of age, but small and pale or reduced in number in those of subjects 22 years of age or older. Purkinje cells of the cerebellum were reduced in number in all nine brains (Kemper and Bauman, 1998). In two of these cases, the neurons in hippocampal fields CA1 and CA4 showed reduced complexity and extent of their dendritic arbors (Raymond et al., 1996). Although one additional case report has found abnormal pathology in the temporal lobes, including the amygdala (Bailey et al., 1998), several other neuropathological studies have not found abnormalities of the amygdala or its related structures in subjects with autism (Williams et al., 1980; Coleman et al., 1985; Ritvo et al., 1984; Guerin et al., 1996; Rodier et al., 1996; Bailey et al., 1998).

Some of these discrepancies may be due to the different neuropathological techniques utilized and the degree of microscopic anatomy that was studied in the different investigations. Further research is needed into the microscopic

abnormalities of the amygdala in autism in order to replicate and extend the findings of Kemper and Bauman (1998).

5. Structural neuroimaging studies

Early neuroimaging studies using computerized axial tomography (CAT) scans did not find consistent evidence for major brain abnormalities in individuals with autism (Campbell et al., 1982; Creasey et al., 1986). The development of magnetic resonance imaging (MRI) and its better ability to quantify volumes of brain structures gave investigators a tool to measure the size of discrete brain structures.

Three investigations using MRI have found some differences in mesial temporal lobe structures in autism. The most recent of these studies focused on the amygdala by estimating volumes of the amygdala and related structures in 10 ''high-functioning'' autistic/Asperger's disorder subjects (ages 15–40 years) and 10 healthy controls matched for age, gender, and verbal IQ (Howard et al., 2000). Bilateral amygdala volume was significantly increased in the autistic subjects, whereas hippocampal and parahippocampal gyrus volumes were marginally reduced. No differences in overall temporal lobe volumes were found, but subjects with autistic spectrum disorders had significantly larger lateral ventricles and intracranial volumes. Neuropsychological testing revealed that the autistic subjects were impaired in their ability to identify facial expressions of fear, eye gaze direction, and facial recognition memory as has also been seen in some individuals with amygdala damage (Young et al., 1995).

Aylward et al. (1999) estimated volumes of the hippocampus, amygdala, and total brain in 14 nonmentally retarded autistic males (ages 11–37 years) and age-, race-, gender-, and IQ-matched controls. Amygdala volume was found to be significantly decreased in the autistic subjects, both with and without correction for total brain volume. Total brain volume and absolute hippocampal volume did not differ significantly between the groups. However, when corrected for total brain volume, hippocampal volume was significantly reduced in the autistic subjects.

Using MRI, Abell et al. (1999) performed whole brain voxel-based scans of 15 high-functioning young adults with autism (average age 28 years) and 15 normal controls matched for age, gender, handedness, and performance on tests of verbal and nonverbal ability. A number of differences were identified between the groups. In the autistic group, decreased gray matter volume was found in the right paracingulate sulcus, the left occipito-temporal cortex, and the left inferior frontal sulcus. Increased volume was observed in the left amygdala/periamygdaloid cortex, the right inferior temporal gyrus, and the left middle temporal gyrus. As well, there were bilateral increases in gray matter volume in the cerebellum of the autistic subjects.

Five other MRI studies have failed to find abnormalities in mesial temporal lobe structures in autistic subjects compared to controls. Haznedar et al. (2000) compared hippocampal and amygdala volumes of 10 subjects with autism and 7 subjects with Asperger's disorder (mean age 28 years) with age- and gender-matched healthy controls. Volumes of these structures did not differ between the two groups. However, significantly greater left amygdala volume was seen in the subjects with Asperger's disorder than in the autistic subjects. Significant differences were seen in the right anterior cingulate gyrus, specifically Brodmann's area 24, where subjects with autistic spectrum disorders had smaller volumes compared to healthy controls.

In 21 subjects (ages 6–32 years) studied by Courchesne et al. (1993), no autistic subjects had abnormalities in limbic structures compared to subjects from three separate control groups. In addition, no abnormalities were seen in the temporal lobe, basal ganglia, diencephalon, ventricles, or brainstem. In another study, a review of MRI of 53 autistic subjects and 32 age-matched controls found no abnormalities in the amygdala or limbic system in any of the autistic subjects (Nowell et al., 1990).

Two of these five negative studies have focused on hippocampal size in autistic individuals. Cross-sectional areas of the hippocampus, including the subiculum and the dentate gyrus, of 33 autistic subjects (ages 6–42 years) did not differ from 23 age-matched healthy controls (Saitoh et al., 1995). Also, no difference was found in the temporal horn of the lateral ventricles. However, analysis of the corpus callosum revealed that the midsaggital area or the most posterior subregion was significantly smaller in the autistic subjects. Other researchers have found similar reductions in the corpus callosum (Manes et al., 1999; Piven et al., 1997). Piven et al. (1998) found no difference in the estimated volume of the hippocampus between 35 autistic subjects (ages 12–29 years) and 36 healthy age- and IQ-matched controls in a study that controlled for total brain volume.

An interesting case study of a pair of monozygotic twin boys discordant for strictly defined autism compared their brain anatomy using quantitative MRI (Kates et al., 1998). The twin with autism had markedly smaller amygdalar, hippocampal, and caudate volumes and smaller cerebellar vermal lobules VI and VII compared to his twin brother.

Taken together, studies using MRI show inconsistent results regarding the size of the amygdala and related structures in autism. However, there is a wide range of patient populations and severity of psychopathology in these studies. Taking into account such differences, it is suggestive that at least in some subgroups of autistic children, amygdalar pathology may contribute to the deficits in function.

6. Functional neuroimaging studies

Positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI)

have greatly increased our ability to study the pathophysiology of autism.

One PET study focused on the amygdala and hippocampus. Ten subjects with autism and seven with Asperger's disorder (mean age 27.7 years) were compared with 17 age- and sex-matched healthy controls. ^{18}Fluorodeoxyglucose was administered while subjects performed a serial verbal learning test. No significant group metabolic differences were found in the amygdala or the hippocampus (Haznedar et al., 2000).

A recent technetium-99m (Tc-99m) ethyl cysteinate dimer (ECD) SPECT study of 23 children with autism (ages 2–13 years) and 26 age- and gender-matched mentally retarded controls found a decrease in regional cerebral blood flow (rCBF) in the bilateral insula, superior temporal gyri, and left prefrontal cortices in autistic subjects. As well, a positive correlation was found between rCBF in both the right hippocampus and amygdala and a behavioral rating subscale measuring "obsessive desire for sameness." Scores on a subscale measuring "impairment in communication and social interactions" correlated positively with rCBF in the left medial prefrontal cortex and the anterior cingulate gyrus (Ohnishi et al., 2000).

Otsuka et al. (1999) used proton MRS to detect brain metabolites in the right hippocampal–amygdala region and the left cerebellar hemisphere. Twenty-seven autistic subjects (ages 2–18 years) were compared with 10 normal children (ages 6–14 years). Metabolite peaks were calculated for *N*-acetyl aspartate (NAA), creatine, and choline. NAA levels were significantly lower in the autistic subjects in both areas, whereas the other metabolites did not differ between groups. The investigators hypothesized that lower levels of NAA in these regions may indicate neuronal hypofunction or immature neurons.

Two fMRI studies have demonstrated a deficiency in amygdala activation during specific tasks in autistic spectrum disorder subjects. Baron-Cohen et al. (1999) presented photographs of eyes to six individuals with high-functioning autism or Asperger's disorder (mean age 26.3 years) and 12 age- and IQ-matched normal controls. Participants were asked to discern the mental state of the photographed person while undergoing imaging. The control group demonstrated significantly greater activation in the left amygdala, right insula, and left inferior frontal gyrus during the task. The autistic group did not activate the left amygdala at all, but demonstrated significantly greater activity bilaterally in the superior temporal gyrus.

In a similar study, Critchley et al. (2000) investigated the brain activity of nine adult males (mean age 37 years) with Asperger's disorder or high-functioning autism and nine age-, gender-, and intelligence-matched controls. In two separate tasks, participants were asked to determine emotion or gender in a series of facial photographs while undergoing imaging. Overall, individuals with autistic spectrum disorders had significantly greater activity than controls in the left superior temporal gyrus and the left peristriate visual cortex, whereas controls had significantly more activity in the right fusiform cortex. While determining gender, subjects with autistic spectrum disorders showed less activity than controls in the left cerebellum and left amygdala–hippocampal region. However, when determining emotional facial expressions, the left middle temporal gyrus was activated in controls but not in autistic spectrum disorder subjects.

In summary, several recent studies using functional neuroimaging technologies have provided preliminary evidence of amygdala dysfunction in autism. Replication of these studies is needed to better determine the role of the amygdala and related areas in autism.

7. Additional brain regions implicated in the pathophysiology of autism

In addition to the amygdala and related structures, other brain regions have been implicated in the pathophysiology of autism. For example, neuropathological studies have identified abnormalities in the brainstem and cerebellum (Bailey et al., 1998; Kemper and Bauman, 1998). To date, at least 20 autopsy cases have reported reduced cerebellar Purkinje cell counts (Ritvo et al., 1984; Williams et al., 1980; Bailey et al., 1998; Kemper and Bauman, 1998; Fehlow et al., 1993).

Early structural neuroimaging studies using pneumoencephalography found abnormalities in the ventricles, in particular enlargement of the left temporal horn, in autistic children (Hauser et al., 1975). However, later studies using CAT scans found ventricular enlargement in a much smaller subset of subjects, if at all (Campbell et al., 1982; Caparulo et al., 1981, Damasio et al., 1980; Creasey et al., 1986). Subsequent CAT and MRI studies focused on the brainstem, midbrain, and cerebellum. Some investigators found reduced brainstem, midbrain, or pons size (Gaffney et al., 1988; Hashimoto et al., 1991, 1992), increased fourth ventricle size (Gaffney et al., 1987a), or cerebellar atrophy, specifically of vermal lobes VI and VII (Courchesne et al., 1988; Gaffney et al., 1987b; Murakami et al., 1989; Saitoh et al., 1995). Other studies, however, have found no differences in the size of the brainstem, midbrain, or pons (Hsu et al., 1991; Elia et al., 2000; Garber and Ritvo, 1992; Courchesne et al., 1993), fourth ventricle (Rumsey et al., 1988; Garber and Ritvo 1992; Garber et al., 1989; Holttum et al., 1992; Nowell et al., 1990) or cerebellum (Rumsey et al., 1988; Nowell et al., 1990; Elia et al., 2000; Garber and Ritvo, 1992; Holttum et al., 1992; Kleiman et al., 1992). Some MRI studies have found enlarged cortical brain size (Piven et al., 1995), specifically of the temporal, parietal, and occipital lobes (Piven et al., 1996), as well as other diffuse cortical abnormalities (Piven et al., 1990). Investigation of basal ganglia structures has yielded inconsistent results. Caudate size in adult autistics has been found to be normal (Creasey et al., 1986), decreased (Jacobson et al., 1988), or increased (Sears et al., 1999).

Results from functional neuroimaging studies have implicated various cortical lobes including the frontal (Zilbovicius et al., 1995), temporal (Gillberg et al., 1993; Zilbovicius et al., 2000), frontal and temporal (George et al., 1992; Hashimoto et al., 2000; Ohnishi et al., 2000), temporal and parietal (Mountz et al., 1995), temporal and occipital (Starkstein et al., 2000), and frontal and parietal (Horwitz et al., 1988). Other areas with noted abnormalities include the cingulate gyrus (Haznedar et al., 1997, 2000), thalamus (Horwitz et al., 1988; Starkstein et al., 2000; Buchsbaum et al., 1992; Ryu et al., 1999), dentato-thalamo-cortical pathway (Muller et al., 1998; Chugani et al., 1997), and basal ganglia (Buchsbaum et al., 1992; Horwitz et al., 1988; Starkstein et al., 2000). Hypoperfusion was observed in most of the above studies. In the cerebellum, some (Ryu et al., 1999; Muller et al., 1999; Chugani et al., 1999) but not all studies (Hashimoto et al., 2000; Heh et al., 1989) have reported evidence of reduced activation.

For a more detailed review of results from neuropathological and neuroimaging studies in autism, the reader is referred to recent summaries by Minshew et al. (1997), and Deb and Thompson (1998) and Rumsey and Ernst (2000), respectively.

8. Conclusion

Behaviors associated with damage to the amygdala and related temporal lobe structures in humans and nonhuman primates are strikingly similar to those seen in autism. Further evidence for the role of the amygdala in the pathophysiology of autism also comes from neuropathological and neuroimaging studies. However, not all of these studies have demonstrated consistent results and the extent to which amygdala dysfunction is involved in autism remains to be more fully elucidated. Although evidence of amygdala dysfunction in autism is presently inconclusive, it remains an area of much interest and active investigation. Abnormal social behavior is the core clinical element of impairment in autism and the amygdala has long been known for its involvement in social behavior in animals (Kling and Brothers, 1992). Recent animal studies have also implicated the amygdala as critical to dyadic social interactions (Sanders and Shekhar, 1995; Sajdyk and Shekhar, 1997; Emery et al., 2001). Secondary symptoms of increased aggression and emotional indifference could also be explained by amygdala dysfunction (Ramamurthi, 1988; Vaernet, 1972; Vaernet and Madsen, 1970). Furthermore, the amygdala is important in the processing of facial expressions (Thomas et al., 2001; Young et al., 1995; Adolphs et al., 1994), and many studies have shown abnormalities in this function in subjects with autism or Asperger's disorder (Boucher and Lewis, 1992; Schultz et al., 2000; Davies et al., 1994). Further research is needed to replicate these findings and determine the extent of involvement of the amygdala and related structures in autism.

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