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Neuropsychological Correlates of Early Symptoms of Autism

Geraldine Dawson, Andrew N. Meltzoff, Julie Osterling, and Julie Rinaldi

Both the medial temporal lobe and dorsolateral prefrontal cortex have been implicated in autism. In the present study, performance on two neuropsychological tasks—one tapping the medial temporal lobe and related limbic structures, and another tapping the dorsolateral prefrontal cortex—was examined in relation to performance on tasks assessing autistic symptoms in young children with autism, and developmentally matched groups of children with Down syndrome or typical development. Autistic symptoms included orienting to social stimuli, immediate and deferred motor imitation, shared attention, responses to emotional stimuli, and symbolic play. Compared with children with Down syndrome and typically developing children, children with autism performed significantly worse on both the medial temporal lobe and dorsolateral prefrontal tasks, and on tasks assessing symptoms domains. For children with autism, the severity of autistic symptoms was strongly and consistently correlated with performance on the medial temporal lobe task, but not the dorsolateral prefrontal task. The hypothesis that autism is related to dysfunction of the medial temporal lobe and related limbic structures, such as the orbital prefrontal cortex, is discussed.

INTRODUCTION

Advances in neurobiology, brain imaging, and neuropsychology have allowed new insights into the possible brain basis of autism (Bailey, Phillips, & Rutter, 1996). Several brain regions, ranging from the cerebellum and medial temporal lobe structures to the prefrontal cortex, have been suggested as possible core regions of abnormality in this disorder. Also, it is recognized that dysfunction in one brain region likely affects development and functioning of related brain regions (Dawson & Lewy, 1989). Indeed, autism most certainly involves dysfunction of brain circuits that support the functioning of a variety of brain regions.

Evidence for involvement in autism of the medial temporal lobe and related structures of the limbic system comes from a variety of sources, including behavioral/neuropsychological, animal lesion, and autopsy studies. A neuropsychological study conducted by Barth, Fein, and Waterhouse (1995) revealed that lower-functioning children with autism were impaired on a visual recognition memory task tapping medial temporal lobe functions. Furthermore, it is well established that individuals with autism have specific impairments in the processing of social and emotional stimuli, as evident on tasks such as face and emotion recognition, imitation of body movements, interpretation and use of gestures, and formation of a theory of mind (Baron-Cohen, Tager-Flusberg, & Cohen, 1993; Davies, Bishop, Manstead, & Tantam, 1994; Hobson, Ouston, & Lee, 1988a, 1988b; Mundy, Sigman, Ungerer, & Sherman, 1986; Smith & Bryson, 1994; Teunisse & DeGelder, 1994). This pattern of behavioral impairments suggests that autism is related to dysfunction of a brain system involved in social cognition. Animal and human lesion studies indicate that parts of the medial temporal lobe (amygdala, hippocampus, and entorhinal cortex) and the orbital frontal cortex are likely to comprise such a brain system, often referred to as the limbic system (Barbas, 1995; Brothers, 1990; Damasio, 1994; LeDoux, 1994).

A second line of evidence implicating the medial temporal lobe in autism is based on the results of early lesion studies of monkeys. Bachevalier (1994) has shown that monkeys with lesions of the hippocampus and amygdala made early in life exhibit persistent and severe cognitive and social impairments, as well as stereotyped and self-stimulatory behaviors. Monkeys with early damage only to the amygdaloid complex exhibit social disturbances similar to those found in animals with combined amygdalohippocampal lesions, although the disturbances are less severe. Finally, a third line of evidence supporting the role of the medial temporal lobe and related limbic regions in autism comes from autopsy studies (Bauman & Kemper, 1994) in which histoanatomic analysis revealed reduced neuronal cell size and increased cell-packing density in the hippocampus, amygdala, and adjacent limbic regions.

Other investigators have argued that autism is better characterized as a disorder of higher cortical func-

tions, and specifically of the dorsolateral prefrontal cortex (Minshew & Goldstein, 1993; Ozonoff, Pennington, & Rogers, 1991; Rogers & Pennington, 1991). According to this view, core behavioral impairments in autism are related to impairment in executive functions, such as working memory. Evidence supporting this view comes from neuropsychological studies. Specifically, studies of high-functioning verbal individuals with autism have found impairments on tasks tapping executive functions, and intact functioning on memory tasks known to be mediated by the medial temporal lobe (Minshew & Goldstein, 1993). Also, research has shown an association between executive function skill and specific autistic symptom domains, including motor imitation ability and the ability to understand the mental states of others (theory-of-mind) (McEvoy, Rogers, & Pennington, 1993; Ozonoff et al., 1991). Rogers and Pennington (1991) have proposed a developmental model of autism in which a primary impairment in motor imitation, which they hypothesize to be linked to executive functioning, disrupts social-emotional development, particularly domains such as social and emotional reciprocity.

In the present study, we examined autistic children's performance on two neuropsychological tasks—one known to be mediated by limbic structures, including the medial temporal lobe and orbital prefrontal cortex, and one known to be mediated by the dorsolateral prefrontal cortex—and their relation to degree of impairment in domains reflecting early emerging core symptoms of autism. Symptom domains included orienting to social stimuli, immediate and deferred motor imitation, responses to emotional stimuli, shared attention, and symbolic play. We predicted that early core symptoms of autism would be more closely correlated with performance on tasks tapping the limbic system than with those tapping the dorsolateral prefrontal cortex. This prediction was based on the hypothesis that early emerging symptoms of autism reflect core affective and social impairments that can be linked to dysfunction of the limbic system, particularly the amygdala and hippocampus and closely related brain regions, such as the orbital frontal region (see Dawson, 1996, for more elaborate discussion of this hypothesis). The animal and brain damage literatures suggest that the limbic system, particularly the amygdala, is critical for social perception, such as recognition of faces and facial expressions (Aggleton, 1992; Jacobson, 1986; Nelson & deHaan, 1996), the recognition of the affective significance of stimuli (LeDoux, 1987), and the perception of body movements and gaze direction (Brothers, Ring, & Kling, 1990), and for certain cognitive abilities that are likely to be important for social perception, such as cross-modal association (Murray & Mishkin, 1985) and recall of event sequences (McDonough, Mandlers, McKee, & Squire, 1994). Furthermore, we theorized that such early dysfunction of the limbic system has "downstream" consequences for the development of higher-order prefrontal functions, including those associated with the dorsolateral prefrontal cortex. Thus, although we predicted that performance on dorsolateral prefrontal tasks would be less closely linked to core autistic symptoms, we nevertheless expected that children with autism would exhibit impaired performance on both the limbic and dorsolateral prefrontal tasks, relative to matched control subjects. Importantly, we chose medial temporal lobe and dorsolateral prefrontal tasks that tap abilities in the same developmental range (toddler–preschool) and that require no verbal abilities, making them suitable for use with young children with autism.

METHOD

Participants

Three groups of children participated in the study: 20 children with autism (N = 13) or Pervasive Developmental Disorder—Not Otherwise Specified (PDD.NOS) (N = 7), 19 children with Down syndrome, and 20 children with typical development. Descriptive information for the three groups of children regarding chronological age, ethnicity, sex, and language and cognitive ability is shown in Table 1.

Diagnosis of autism or PDD.NOS was based on parent interview and a structured play session specifically designed to assess autistic symptoms listed in the *Diagnostic and Statistical Manual, Third Edition—Revised* (American Psychiatric Association, 1987). Diagnosis of each child was made independently by the first and third authors to insure reliability. In addition, each child was administered the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1986), and all children in the autism group scored above the clinical cutoff (30) on the CARS.

The three groups of children were matched in terms of their receptive language mental age as assessed by the Preschool Language Scale—3 (PLS; Zimmerman et al., 1991) and the communication subscale of the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984). In addition, children with autism were matched to children with Down

Table 1 Participant Characteristics

Group	*N*, Male:Female	Ethnicity	CA (Months)	Vineland[a] MA (Months)	Vineland Scale IQ	PLS[b] MA (Months)	PLS IQ	Nonverbal MA (Months)
Autism	20, 19:1	18 Caucasian 2 Biracial	64.6 (15.1)	30.4 (13.4)	62.0 (16.4)	28.1 (14.9)	58.9 (14.3)	51.0 (26.2)
Down	19, 16:3	17 Caucasian 1 African American 1 Native American	65.3 (16.5)	27.3 (10.2)	57.2 (8.2)	29.9 (12.3)	56.7 (9.4)	34.1 (11.8)
Typical	20, 19:1	17 Caucasian 3 Biracial	30.9 (14.4)	32.4 (14.6)	103.4 (4.4)	31.8 (14.8)	105.9 (12.6)	33.2 (13.4)
F			.00	.78	.70	.35	.31	5.89
p			*ns*[c]	*ns*	*ns*[c]	*ns*	*ns*[c]	.005

Note: Numbers represent means and standard deviations (in parentheses).
[a] Vineland Scale refers to Communication Subscale.
[b] Preschool Language Scale.
[c] Comparison is between autism and Down syndrome groups only.

syndrome in terms of chronological age and verbal IQ. Children with autism had significantly higher nonverbal ability as compared to the children with Down syndrome and typically developing children. Nonverbal ability was assessed by administration of a battery of developmentally graded visual-spatial tasks derived from the Bayley Scales of Infant Development, Second Edition, and the Stanford Binet IV. Nonverbal ability therefore was used as a covariate in analyses.

Neuropsychological Tasks

Delayed Non-Matching to Sample. Delayed Non-Matching to Sample (DNMS) assesses rule-learning ability (specifically, the ability to abstract the quality of novelty and associate it with reinforcement) and visual recognition memory. It has been linked to the amygdala and hippocampus, and closely related cortical structures, including the entorhinal cortex and orbital prefrontal cortex, in monkeys[1] (Bachevalier & Mishkin, 1986; Kowalska, Bachevalier, & Mishkin, 1991; Meunier, Bachevalier, & Mishkin, 1997; Zola-Morgan, Squire, & Amaral, 1989; Zola-Morgan & Squire, 1993) and in human amnesic patients (Squire, Zola-Morgan, & Chen, 1988). The child was shown a novel object (the sample). The child then reached for and displaced it to retrieve a reward (dry food snack, such as cheerios) underneath. The sample was then removed and a delay of 5 s was imposed. Following the delay, the child was shown the sample again paired with something new (the non-matching object) and rewarded for reaching to the non-matching object. New stimuli were used on each trial. Trials were administered until the child had reached criterion performance (defined as reaching for the novel object on five consecutive trials), or a maximum of 15 trials had been administered. The dependent variables were (1) the number of errors (i.e., chose familiar rather than novel item) made until the child reached criterion performance and (2) the number of trials required until reaching criterion performance. Note that in the present study, the DNMS was primarily a task of rule-learning, because only a short delay period was imposed. Animal studies have suggested that the rule-learning aspect of the DNMS may be specifically linked to the orbital prefrontal cortex (Meunier et al., 1997).

Delayed response. Delayed response requires both working memory and response inhibition. It has been linked to the dorsolateral prefrontal cortex based on both human infant studies and animal lesion studies (Diamond & Goldman-Rakic, 1986, 1989; Goldman, Rosvold, & Mishkin, 1970). Lesions to the medial temporal lobe and parietal cortex in the adult animal do not disrupt performance on this task (Diamond & Goldman-Rakic, 1989; Diamond, Zola-Morgan, & Squire, 1989). The child watched as the experimenter (1) hid a small toy in a container at the midline and then (2) moved that container to the right or left. A screen was lowered during the 5 s delay that followed, during which time an identical container was placed on the other side of the table. When the screen was raised the child was allowed to reach for the container. The side of hiding was reversed after the child searched correctly for the toy on two consecutive trials. Trials continued until the child had searched on

1. The central role of the amygdala and hippocampus in visual recognition memory has been disputed based on evidence that the adjacent rhinal and perirhinal cortices may be more directly responsible for this type of memory (see Zola-Morgan & Squire, 1993, for review).