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Dorso-Lateral Prefrontal Cortex MRI Measurements and Cognitive Performance in Autism

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Abstract

This study examined the relationships between volumetric measurements of frontal lobe structures and performance on executive function tasks in individuals with autism. MRI scans were obtained from 38 individuals with autism and 40 matched controls between the ages of 8 and 45 years. Executive function was assessed using neuropsychological measures including the Wisconsin Card Sorting Test and Tower of Hanoi. Differences in performance on the neuropsychological tests were found between the two groups. However, no differences in dorsolateral prefrontal cortex volumes were observed between groups. No correlations between volumetric measurements and performance on the neuropsychological tests were found. Findings from this study suggest that executive function deficits observed in autism are related to functional but not anatomical abnormalities of the frontal lobe. The absence of correlations suggests that executive dysfunction

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is not the result of focal brain alterations but, rather, is the result of a distributed neural network dysfunction.

Keywords

autism; frontal lobe; dorsolateral prefrontal cortex; magnetic resonance imaging; executive function

Introduction

Autistic disorder is a pervasive developmental disorder characterized by social impairments, communication deficits, and idiosyncratic or stereotypic behaviors with evidence of wide-spread cognitive deficits.[1] Neuropsychological studies have provided evidence of disruption in executive functioning in individuals with autism.[2-5] Executive functioning includes cognitive processes such as working memory, planning, inhibition of responses, and cognitive flexibility.[6,7] Previous studies have shown that individuals with autism have deficits in some or all of these domains leading to characteristic behavioral impairments,[8-13] but it remains unclear whether or not all aspects of these cognitive functions are affected.

The most common neuropsychological tests used to assess executive functioning have been the Tower of Hanoi [14] and the Wisconsin Card Sorting Test.[15,16] The Tower of Hanoi task challenges problem solving and concept formation and has been shown to activate prefrontal and parietal areas in healthy individuals.[17] Several investigations have reported that individuals with autism show impaired performance on this task over time.[18-21] Using a simplified version of the Tower of Hanoi, the Tower of London, Hughes et al.[22] and Barnard et al.[23] found that participants with autism performed significantly worse on this test compared to controls, indicating deficits in forward planning. These observations are consistent with several other studies that have used the Tower of London and Tower of Hanoi to examine executive functioning deficits in autism.[24,25] Similarly, other investigations have found individuals with autism to have less efficient or impaired abilities to plan and organize tasks or activities.[3,20,26-30] The Wisconsin Card Sorting Test is another executive function test, but unlike the Tower tasks, it assesses cognitive flexibility, or shifts in planning, and measures difficulties with conceptualization, perseveration, and inefficient learning.[16] Studies have shown that individuals with autism demonstrate some rigidity and difficulties developing problem-solving strategies.[20-24,29,31-34] Investigations have also found that individuals with autism without intellectual disabilities have a higher percentage of perseverative responses on the Wisconsin Card Sorting Test compared to matched controls with learning disabilities[3] and typically developing controls,[35,36] indicating a deficit in cognitive flexibility regardless of IQ.[6,24] Although the relationship between performance on the Wisconsin Card Sorting Test and IQ is unclear in the typical population,[16,37-44] performance on this test has been found to be related to both age and education level.[16,37,45,46] High-functioning individuals with autism, however, perform poorly on the Wisconsin Card Sorting Test with increased perseverative errors despite controlling for age, education level, and IQ.[47] Furthermore, performance on the Wisconsin Card Sorting Test, as reflected by the number of perseverative errors, appears to be related to the severity of clinical features,[35] which indicates difficulties in flexibly applying categorical concepts. Overall, the executive functioning deficits that have consistently been reported in autism provide evidence of frontal lobe in this disorder.[48]

Furthermore, there is substantial evidence regarding the role of the prefrontal cortex and its connections to executive functioning.[49] After two decades of volumetric MRI studies, the consensus appears to be that there is a general increase in cortical gray matter volume with a

rostral caudal gradient that is manifest by about 9 months of postnatal age and persists until about 4-6 years of age.[50] Neuroimaging studies of the frontal lobe in autism have reported several abnormalities implicating this structure in the pathophysiology of this disorder. A review of various anatomical studies by Brambilla et al.[51] indicates conflicting results among multiple studies of the frontal lobe with some investigations,[52-59] but not all,[60-63] reporting increase in volume. Varying results across these studies are most likely due to methodological differences, particularly related to the differing age of subjects studied, suggesting the presence of developmental effect. In contrast, functional imaging studies have been more consistent in their findings, perhaps because they are confined to older, more cooperative subjects. These investigations have frequently implicated underconnectivity of cerebral cortical structures, particularly the frontal cortex, and underlying cognitive impairments observed in autism.[64-72] In fact, a recent study reported abnormal activation in the frontal lobe in individuals with autism while performing Tower of Hanoi executive functioning tasks.[66] These studies have suggested that there is a lower level of functional coordination among brain areas in autism[48,73] and warrant further investigations of the size of the frontal lobe and its subdivisions, including the dorsolateral prefrontal cortex and orbitofrontal cortex, using large sample sizes.

The purpose of this study was to examine performance on executive function tasks, the size of the dorsolateral prefrontal cortex, and the relationship between these measures in a group with autism and age-, gender-, and IQ-matched healthy controls. We hypothesized that structural abnormalities would be observed in the patient group and differences in executive function abilities would be found between the two groups. We also predicted the existence of a relationship between structural alterations and performance on the neuropsychological tests.

Methods

Participants

Subjects were 38 individuals with high-functioning autism and 40 age-, gender-, and IQ-matched controls between the ages of 8 and 45 years. The sample was restricted to individuals with autism without mental retardation (e.g., Full-Scale, Performance, and Verbal IQ scores ≥ 80) (hereafter referred to as having High Functioning Autism) to ensure cooperation for scanning and cognitive testing, matching to normal controls, and low likelihood of associated disorders. All participants in both groups were prescreened for history of metal, claustrophobia, or weight ≥ 114 kg. All participants in both groups were administered the age-appropriate version of the Wechsler Adult Intelligence Scale-Revised or Wechsler Intelligence Scale for Children-Revised to measure Full-Scale, Performance, and Verbal IQ. All autism participants and most controls were recruited through the Subject Core of the University of Pittsburgh Collaborative Program of Excellence in Autism (University of Pittsburgh- Carnegie Mellon University CPEA) funded by the National Institutes of Health. The methodology of the study, including MRI for minors, was approved by the institutional review boards at the University of Pittsburgh and Carnegie Mellon University. Procedures were fully explained to all subjects and, when appropriate, to their parent or legal guardian. Written informed consent was obtained from subjects and/or their guardians.

Subjects with autism represented all consecutive community referrals to a research clinic who met the criteria for participation in the study. The diagnosis of autism was established through expert clinical evaluation in accordance with published clinical descriptions of high-functioning individuals with autism[74] and two structured research diagnostic instruments, the Autism Diagnostic Interview-Revised [75] and the Autism Diagnostic Observation Schedule.[76] The individuals with High Functioning Autism, recruited from autism

conferences and parent support groups, were medically healthy and had no identifiable genetic, metabolic, or infectious etiology for their disorder. Their personal and family health histories were evaluated in the initial screening interview and in the medical review portion of the Autism Diagnostic Interview [75]. All participants with autism met all criteria on the Autism Diagnostic Observation Schedule[76] for autism, e.g., for Communication (cutoff, 3; range, 3–7), Reciprocal Social Interaction (cutoff, 6; range, 7–13) and Total (cutoff, 10; range, 10–18) algorithm scores. Additionally, these participants met autism criteria on the Autism Diagnostic Interview-Revised[75] including age of onset. The diagnosis of autism was confirmed by expert opinion (N.J.M.). Additionally, subjects meeting the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule criteria for autism but without delayed or abnormal language development were considered to have Asperger's disorder and were excluded from this study.

Controls were recruited from the community through advertisements in areas socio-economically comparable to those of the families of origin of the subjects with autistic disorder and were chosen to individually match the autism participants. All subjects were medically healthy and had a Wechsler Full-Scale and Verbal IQ of 80 or higher. Candidates were prescreened with questionnaires regarding current/past personal and family history of medical/neurological/psychiatric disorders. Inclusion criteria were good physical health, no regular CNS medications, good school/job record, and good peer relationships based on parent- or self-report and staff observations during eligibility testing.

Potential control and autistic subjects were excluded if found to have evidence of an associated infectious, genetic, or metabolic disorder (e.g., fragile-X syndrome or tuberous sclerosis), birth asphyxia, head injury, or a seizure disorder. Exclusions were based on neurologic history and examination, physical examination, and chromosomal analysis or, metabolic testing if indicated. Potential control subjects were also screened to exclude those with a family history of autism in first-, second-, or third-degree relatives; developmental cognitive disorder; learning disability; schizophrenia or obsessive-compulsive disorder, or other neurologic or psychiatric disorders thought to have a genetic component, including first-degree family history of developmental cognitive disorders or mood/anxiety disorders (other than a single episode of situational depression in one first-degree relative). The socioeconomic status of the family of origin was assessed using the Hollingshead method.[77]

Procedures

Neuropsychological Battery

All participants were given a battery of neuropsychological tests, including the Tower of Hanoi [14] and Wisconsin Card Sorting Test.[15] Performances on these tests were correlated with frontal structural measurement.

Tower of Hanoi

The Tower of Hanoi assesses the ability to plan and decide which steps are necessary to complete a desired goal. The participant is presented with five rings of different sizes on one of three pegs that appear on a computer screen. The participant's goal is to move all five rings from the first peg to the third empty peg by moving one ring at a time and by not placing a larger ring on top of a smaller ring in the fewest moves possible.[14]

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test assesses the capacity for identifying inherent rules and flexibly changing from one rule to another in response to environmental cues. The participant is presented with a deck of cards and four stimulus cards. The participant then

has to decide how to sort and match each card in the deck to one of the four stimulus cards either by color, number, or shape while the criterion continually changes.[15,16]

Magnetic Resonance Imaging

Neuroimaging scans were obtained using a General Electric (Milwaukee) 1.5-T Tesla Signa scanner. The imaging protocol consisted of two T1-weighted (TR=500, TE=20) series: a sagittal series of 3mm slice thickness parallel to the midline structure, and an axial series of 5 mm slice thickness. An additional 1.5 mm SPGR (spoiled gradient recalled echo in steady state) coronal series (TR = 35; TE = 5, NEX = 1, flip angle = 45°) was collected, which was used for all the measurements reported in this study.[78] All images were transferred from the acquisition facility to the image analysis laboratory via File Transfer Protocol and archived on CD-ROM disks. Magnetic resonance imaging (MRI) data were identified by scan number in order to retain blindness.

Tracing Guidelines

Dorsal lateral prefrontal cortex. The tracing of the dorsolateral prefrontal cortex was done using Brain Research Analysis of Images, Networks, and Systems 2 (BRAINS2, University of Iowa, Iowa City, IA, USA) software package.[79] Measurements were done on coronal slices while observing the outline of the tracings on axial and sagittal sections. The boundaries were determined initially on the coronal slice and confirmed by its correspondence to the anatomical landmark on axial and sagittal sections. The tracing started posteriorly at the posterior end of the genu of the corpus callosum one slice anterior to the point where septum pellucidum disappears. The inferior limit was the Sylvian fissure posteriorly and horizontal ramus of the lateral fissure anteriorly, in order to exclude Broadman areas 47, 45 and 44. The superior delimitation was superior frontal sulcus from the posterior most extent of the tracing to the anterior tip of the genu of the corpus callosum; from the anterior end of the genu, the superior boundary was the interhemispheric fissure that included the superior frontal gyrus until the anterior end of the tracing. This was done in order to exclude Brodmann area 8 as much as possible. Anteriorly, the tracing ended at the tip of the horizontal ramus of the lateral fissure so that most of area 10 could be excluded. Medially, the tracings were divided into the part of the dorsolateral prefrontal cortex that lies along the extent of the genu of the corpus callosum where the inferior tracings were extended to the tip of the lateral fissure/ horizontal ramus, while the superior tracing extended to the very depths of the superior frontal sulcus and the medial most points were connected. Anterior to the tip of the genu, while the guideline for the inferior tracing remained the same, the superior tracing extended up to the cingulate sulcus along the interhemispheric sulcus and the medial-most points were connected. Wherever paracingulate sulcus was detected, the supero-medial tracing extended up to the paracingulate sulcus only.

Total Brain Volume. Measurements were made on a Gateway 2000 graphics workstation (N. Sioux City, SD) using locally developed custom graphics software.[79] A semi-automated thresholding procedure was used for segmenting brain from cerebrospinal fluid and extra-cerebral tissue, as described elsewhere.[80] Measurements were performed blind to diagnosis. Intra-rater reliability for obtaining brain volumes with this procedure yielded an intraclass correlation coefficient of 0.99 on 10 brains. Since two different programs were used to conduct the morphometric studies, total brain volume measurements were obtained from 10 scans using both software and revealed high reliability between the two programs (0.95) and acceptable intraclass correlation coefficient (R=0.85).

Data Analysis

A two-tailed statistical significance level was set at $p<0.05$ for all analyses. All volumetric measurements and frontal lobe test performances from participants with autism were compared with controls using Student's t-test. An analysis of covariance was used to compare the two groups on structure volumes while controlling for total brain volume. Regression analyses were conducted to examine the relationships between the two groups and performance on the Tower of Hanoi and Wisconsin Card Sorting Test.

Results

The demographic characteristics of the total sample were previously published.[81] Neuropsychological tests and good quality MRI scans were available on subgroups of the original sample. The subgroups demographic variables remained unchanged with no differences between the autism group and controls on any of the characteristics (age, gender, socioeconomic status, and Full Scale IQ). Summary of the demographic of the different subgroups are included in Table 1 and 2. On the Wisconsin Card Sorting Test, individuals with autism committed significantly more total errors and preservative errors when compared to controls (Table 1). Participants with autism had difficulties on this test and several were not able to complete the Wisconsin Card Sorting Test because of perseveration. On the Tower of Hanoi, individuals with autism performed significantly more slowly than the healthy control group and required significantly more moves to achieve a solution (Table 1). However, no volumetric differences were found in dorsolateral prefrontal cortex structures between the two groups before and after controlling for total brain volume (Table 2). No relationships between performance on the neuropsychological tests and dorsolateral prefrontal cortex volume were observed.

Discussion

In the present investigation, the autism group was found to have evidence of executive functioning deficits based on their performance on neuropsychological tests commonly used to characterize executive functioning by assessing rule learning, flexibility, and concept formation. Participants with autism were generally able to identify rules inherent in a task, but had difficulties with cognitive flexibility and with forming concepts. Interestingly, no volumetric alterations in the dorsolateral prefrontal cortex were observed between the autism and control groups, and no associations were found between the frontal lobe volume and performance on the neuropsychological measures in either group.

Findings from the cognitive testing in the present study are consistent with previous investigations reporting deficits in executive functioning in children and adults with autism and implicating these abnormalities in characteristic behaviors in autism.[3-5,8-10] These results are concordant with findings from an article reviewing the literature by Pennington and Ozonoff,[7] which found that in 13 out of 14 studies deficits in at least one measure of executive functioning were observed in subjects with autism, and in 25 out of 32 executive functioning tasks, individuals with autism displayed deficits when compared to controls. However, it is important to note that these deficits have also been reported in several other neuropsychiatric disorders including schizophrenia and attention deficit hyperactivity disorder (ADHD),[30,82,83] suggesting that executive functioning deficits are not specific to autism. Interestingly, emerging evidence examining attention abnormalities in several neuropsychiatric disorders suggest that executive functioning abnormalities differ among these disorders with lack of deficits in sustained attention in autism.[84] Therefore, further investigations examining the nature of these deficits and the underlying neural networks are

warranted to determine whether or not executive functioning deficits, as observed in different disorders, share the same neurobiological underpinnings.

Despite the deficits in executive functioning, no volumetric alterations were found in the present investigations of the dorsolateral prefrontal cortex, a brain region within the frontal lobe well-known to be related to mental planning and cognitive flexibility. Additionally, no relationships were observed between volumetric measurements and performance on cognitive tasks. The absence of volumetric alterations observed here is consistent with one previous study describing an increase in the parietal, occipital and temporal but not the frontal lobes in autism.[86] However, our findings are not concordant with several other investigations reporting structural abnormalities in the frontal lobe in individuals with autism.[86-89] Increased total frontal lobe volume was found in a study of young children with autism which was related to the enlargement of grey and white matter in the dorsolateral and medial frontal cortices.[86,88] Consistent with this finding, increased grey matter volume was observed in a sample of 21 medication-naive children with autism between 7 and 15 years of age when compared to 21 gender-, age-, and IQ-matched controls.[87] In contrast, a decrease in frontal lobe parenchyma was observed in a recent study examining this structure in 9 individuals with autism between 29 and 47 years of age compared to matched controls.[89] The discrepancies are most likely related to differences in the morphometric methodology used and to differences in the samples' characteristics included in each study.

This study is limited by the relatively small number though carefully diagnosed subjects with autism who span a narrow IQ range but wide age range. While it is possible that a much larger number of subjects might reveal differences between the groups on volumetric measures or correlations between frontal volume and executive function, the existing structural MRI literature in autism provides substantial evidence that gross changes in brain size are a function of age, and are most prominent in the first few years of life in autism.[50] There is also substantial accumulated evidence to document rather wide-spread abnormalities in the functional connectivity of frontal cortex predominantly in subjects over the age of 10 years. Collectively, these studies strongly suggest that the neural basis of the cognitive dysfunction in this developmental disorder will not be found in gross structural changes as it is in acquired brain injury. More detailed investigation of local and distant functional and structural connectivity of cortex as a function of both age and gene status will likely provide the greatest insight into the neurobiologic basis of cognitive dysfunction in autism.[90-92]

Conclusions

Findings from this study suggest that the executive functioning deficits observed in this sample of children and adults with autism are probably not associated with gross anatomical abnormalities of the frontal lobe. However, they are consistent with the numerous fMRI studies demonstrating reduced functional connectivity of frontal cortex with other cortical and subcortical regions during a variety of tasks. Conclusions from this investigation are limited by the small sample size and should be considered with caution in light of its methodological limitations such as the broad age range of the sample, the exclusion of lower functioning individuals, the dorsolateral prefrontal cortex measurement methodology, and the lack of adjustment of the p values due to the multiple comparisons. Therefore, additional research is needed to examine the frontal lobe in autism while using multimodal imaging techniques (structural MRI, diffusion tensor imaging, functional MRI, and magnetic resonance spectroscopy) that include the capacity to assess different aspects of connectivity and molecular pathophysiology in autism. These strategies will lead to a better understanding of the relationships between executive functioning deficits and brain structure

and function, including the neural network connections that underlie these cognitive abnormalities critical to adaptive function.

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Table 1

Performance on Wisconsin cart sorting test and tower of Hanoi task in autism and controls:

WCST[1]	Autism N=24 Mean	SD	Controls N=38 Mean	SD	t	df	p
TOTERR	30.04	18.733	19.18	15.691	2.461	60	.017
PERSERR	15.38	9.969	8.74	6.717	3.136	60	.003
NPERSERR	14.67	10.520	10.45	10.093	1.577	60	.120
TOH[2]	**N = 37 Mean**	**SD**	**N = 38 Mean**	**SD**	**t**	**df**	**p**
T1 Move	48.76	26.665	36.74	22.495	2.14	73	.036
T1 Time	240.3	266.487	137.56	100.002	2.247	73	.028
T2 Move	41.27	28.276	27.21	12.218	2.84	73	.006
T2 Time	197.73	186.184	105.97	45.251	2.987	73	.004
T3 Move	37.32	21.951	23.62	11.35	3.446	73	.001
T3 Time	163.89	152.224	90.36	33.44	2.944	73	.004
T4 Move	35.89	20.386	25.33	13.923	2.649	73	.010
T4 Time	141.00	105.923	89.24	48.69	2.731	73	.008
Total Move	163.38	61.337	112.9	44.515	4.122	73	.045

WCST: Wisconsin card sorting test; 1. Sample characteristics, FSIQ: autism=104 ± 15, controls =104 ± 10; age: autism=17.9 ± 10 years, controls =18.6 ± 9 years; gender: autism= 2 females, controls =2 females; socioeconomic status: autism=3.7 ± 1.4, controls =3.5 ± 1.2; TOH: tower of Hanoi; 2. Sample characteristics, FSIQ: autism=104 ± 15, controls =104 ± 10; age: autism=19.1 ± 9 years, controls =18.8 ± 9 years; gender: autism= 2 females, controls =2 females; socioeconomic status: autism=3.8 ± 1.5, controls =3.5 ± 1.2; TOTERR: total numbers of errors; PERSERR: perseverative errors; NPERSERR: non perseverative errors.

Table 2

Volumetric Measurements for Grey and White Matter DLPFC and Frontal Lobe

	Autism		Control				TBV as covariate	
DLPFC[1]	**n = 33 Mean**	**SD**	**n = 37 Mean**	**SD**	**t**	**P**	**F**	**P**
TBV	1315.4	124.5	1349.8	136.5	1.155	.726	.124	.252
DLPC Grey	27.85	8.08	26.22	8.45	.873	.388	.343	.560
DLPFC White	13.58	4.55	12.89	4.32	.688	.999	.078	.781
Total DLPFC	41.44	12.22	39.11	12.56	.828	.441	.245	.622

DLPFC: Dorsolateral prefrontal cortex; 1: Sample characteristics, FSIQ: autism=103 ± 14, controls =104 ± 10; age: autism=19.8 ± 9 years, controls =18.3 ± 8 years; gender: autism= 2 females, controls =2 females; socioeconomic status: autism=3.8 ± 1.6, controls =3.6 ± 1.2; TBV: total brain volume.

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