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Frontal hypoactivation during a working memory task in children with 22q11 deletion syndrome

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Abstract

Impairments in executive function, such as working memory, are almost universal in children with chromosome 22q11.2 deletion syndrome. Delineating the neural underpinnings of these functions would enhance understanding of these impairments. In this study, children and adolescents with 22q11 deletion syndrome were compared with healthy control participants in an fMRI study of working memory. When the 2-back condition was contrasted with the 1-back and 0-back conditions, the participants with 22q11 deletion syndrome showed lower activation in several brain areas involved in working memory—notably dorsolateral prefrontal cortex, anterior cingulate, and precuneus. This hypoactivation may be due to reduced gray matter volumes or white matter connectivity in frontal and parietal regions, differences that have previously been documented in children with 22q11 deletion syndrome. Understanding differences in brain function will provide a

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AUTHOR CONTRIBUTIONS

Waverly Harrell wrote the first draft of the paper, analyzed behavioral and demographic data, conducted cognitive testing, accompanied patients to MRI scans, and ran the task. Ling Zou analyzed imaging and behavioral data. Zoe Englander analyzed imaging data, created the figures, and wrote the imaging analysis portion of the methods section. Stephen Hooper supervised cognitive testing. Matcheri Keshavan provided guidance on study design based on his experience conducting fMRIs with patients with mental illness. Allen Song supervised analyses of imaging data. Vandana Shashi designed the study and edited and contributed to the paper.

DECLARATION OF CONFLICTING INTERESTS

None of the authors report conflicting interests.

ETHICAL APPROVAL

The study was approved by the Duke Medicine Institutional Review Board for Clinical Investigations. Informed consent was obtained from the parents of participants, who were minor children, and assent was obtained from participants 12 years of age and older.

foundation for future interventions to address the wide range of neurodevelopmental deficits observed in 22q11 deletion syndrome.

Keywords

velocardiofacial; DiGeorge; 22q; fMRI

INTRODUCTION

Chromosome 22q11.2 deletion syndrome, also called velocardiofacial syndrome or DiGeorge syndrome, is caused by a microdeletion on the long arm of chromosome 22 at band 11.2.[1] Phenotypic presentation is variable, including congenital heart disease, velopharyngeal abnormalities, immunodeficiency, and cognitive impairment.[2] Anxiety, depressive disorders, and attention deficit hyperactivity disorder (ADHD) are prevalent in childhood,[3] and by adulthood, up to 30% of patients with 22q11 deletion syndrome develop psychosis.[4] Additionally, children with 22q11 deletion syndrome have brain structural abnormalities, including reduced gray matter and white matter volumes and abnormal white matter connectivity, which have been associated with the neuropsychological impairments.[5]

The neurocognitive phenotype of 22q11 deletion syndrome includes impaired verbal working memory.[6] Working memory, the mental system permitting a person to retain and manipulate a limited amount of information for a limited time,[7] is necessary for reading comprehension[8] and predicts general fluid intelligence.[9] The importance of working memory in cognition makes understanding its neural underpinnings imperative to delineating the pathogenesis of cognitive impairments in 22q11 deletion syndrome.

Adults performing working memory tasks during functional magnetic resonance imaging (fMRI) typically show blood oxygenation level dependent signal in both hemispheres in prefrontal areas (dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, frontal operculum, frontal pole, rostral prefrontal cortex); premotor cortex and supplementary motor area; dorsal cingulate; parietal areas (precuneus, inferior parietal lobule, and posterior parietal cortex); thalamus;[10] and inferior temporal lobe.[11] Similar areas are activated in children,[12] but extent of activation changes as a function of development from childhood to early adulthood.[13]

One other fMRI study examined non-spatial working memory in 22q11 deletion syndrome by comparing a 2-back task with a 0-back control task and found that when matched for performance, children with 22q11 deletion syndrome had less frontal activation than either their unaffected siblings or healthy controls.[14] The paper proposed that the frontal neural network related to working memory may be disrupted in 22q11 deletion syndrome. Another earlier study examined fMRI activation during spatial working memory tasks in children with 22q11 deletion syndrome[15] by contrasting two n-back tasks with a 0-back baseline task. These researchers found reduced activation of the precuneus, which was expected given the role of the parietal lobe in spatial working memory, but unexpectedly found no group differences in dorsolateral prefrontal cortex.

The current study is intended to further explore neural activation associated with working memory in children with 22q11 deletion syndrome and healthy participants, incorporating a hierarchical tiered working memory task for the first time (0-, 1-, and 2-back conditions). The 0-back condition, which does not require updating information in memory, was used to control for attention and the motor components of the task in an attempt to isolate brain regions involved in working memory. We hypothesized that participants with 22q11 deletion syndrome would show incremental reductions in frontal activation as task complexity increased.

METHODS

Participants

Participants were recruited at Duke University Medical Center from an ongoing research study on neurodevelopment in 22q11 deletion syndrome and through personal contacts. Children ages 10 to 17 years with 22q11 deletion syndrome, confirmed by fluorescence in situ hybridization/microarray or DNA polymerase chain reaction studies, were matched with typically developing children by gender and by age within 9 months. Informed consent approved by Duke Institutional Review Board was obtained from parents and written assent from minor children. Children with any psychotic disorder were excluded to minimize cognitive alterations due to psychosis. Children with IQ < 60 were excluded because they might have difficulty with the task, and control participants with IQ >120 were excluded to minimize cognitive differences between the groups. Psychotropic medications were noted but not used as bases for exclusion.

Neurobehavioral Assessment

To estimate each participant's current level of cognitive functioning, participants were evaluated with the Similarities, Vocabulary, Block Design, and Matrix Reasoning subtests of the Wechsler Intelligence Scale for Children, 4th edition or, for those older than 16 years, the Wechsler Adult Intelligence Scale, 4th edition.[16,17] The Digit Span subtest was also administered as a measure of working memory. Reaction time (a measure of the speed of processing), percent correct and omission rates (reflective of working memory) were recorded from the N-back task.

N-back task

All stimuli were presented in the same spatial position in a constant manner. In the 1-back condition, participants were asked to press a button when the same letter appeared twice in a row. In the 2-back condition they were asked to respond when a letter appeared twice with one letter intervening. In the control 0-back task, participants responded when an X appeared. Each stimulus was presented for 1250 ms, followed by a 1250-ms pause. Data were collected from three runs, resulting in a total of 48 trials of the 1- and 2-back conditions and 72 trials of the 0-back condition. Participants practiced the tasks outside the scanner, and a mock scanner was employed to improve compliance with the fMRI procedure. Three contrasts were considered: 1-back vs. 0-back, 2-back vs. 0-back, and 2-back vs. 1-back. Image acquisition.

Magnetic resonance imaging scans were performed on a 3.0T GE high definition scanner (Waukesha, WI). High-resolution T1 structural images were acquired using a 3D fast spoiled gradient echo pulse sequence (166 contiguous axial slices; repetition time = 7.49 ms; echo time = 2.98 ms; inversion time = 450 ms; field-of-view = 25.6 cm^2; flip angle = 12°, voxel size = 1×1×2 mm). Functional images were acquired using an echo planar spiral pulse sequence (repetition time = 1.5 s; echo time = 30 ms; field-of-view = 25.6 cm^2; flip angle = 80°; voxel size = 4 mm^3; 30 contiguous axial slices).

Analysis of fMRI and behavioral data

Analysis of fMRI data was performed using FSL (FMRIB's Software Library, Oxford, UK). Data processing was carried out using fMRI Expert Analysis Tool Version 5.98. Two scans with excessive motion, defined as a deviation > 3 mm from the center of mass, were excluded from the group analysis and are not presented in this manuscript. Pre-statistics processing included motion correction,[18] slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal using Brain Extraction Tool,[19] spatial smoothing with a 5-mm Gaussian kernel full width and half maximum, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0s). Time-series statistical analysis was carried out using FMRIB's Improved Linear Model with local autocorrelation correction.[20] Individual participants' data were coregistered to the Montreal Neurologic Institute Template using FMRIB's Linear Image Registration Tool.[18] Group analysis was performed using FMRIB's Local Analysis of Mixed Effects.[21,22] Statistical activation maps were thresholded using clusters determined by Z > 2.3, corresponding to a familywise error rate-corrected cluster significance threshold of p = 0.05.[23] Behavioral data were analyzed using IBM SPSS Statistics 21.

RESULTS

Demographic Data

Participants consisted of 11 children with 22q11 deletion syndrome and 8 healthy controls. The participants with 22q11 deletion syndrome had a mean age of 14.5 (±1.7) years while mean age for the control participants was 14.0 years (±1.8; $p = 0.57$). In the group of participants with 22q11 deletion syndrome, 64% were female, while in the control group 63% were female ($p = 1.0$). Half of the healthy controls were Caucasian and half were African-American, while of the 22q11 deletion syndrome participants 73% were Caucasian and 27% were African-American or biracial ($p = 0.38$). Mean socioeconomic status, rated using Hollingshead's two-factor index of parental education and employment, was 33.4 (±13.8) for the participants with 22q11 deletion syndrome and 39.8 (±17.1) for control participants ($p = 0.38$). Participants with psychiatric diagnoses were being treated with appropriate medications; two participants with 22q11 deletion syndrome and one control were taking ADHD medications at assessment, and two participants with 22q11 deletion syndrome were taking anxiolytics with no group differences (Fisher's exact test for any medication = 0.603).

Psychological assessment results

The control participants had higher Wechsler Intelligence Scale scores. Mean estimated Full-Scale IQ was 103 in the control group and 80 in the group of patients with 22q11 deletion syndrome ($p = 0.005$). Scaled scores on the Digit Span subtest, a measure of working memory, were similar in both groups (mean score 11 for healthy controls [sd = 4.2], 8.8 for patients with 22q11 deletion syndrome [sd = 4.0], $p = 0.241$), although the effect size was medium (Cohen's d = 0.73), suggesting the presence of significant differences in working memory between the groups.

Behavioral results

No significant differences were found between the healthy controls and patients with 22q11 deletion syndrome in terms of average reaction time, percent correct responses, or percent missing responses in any of the three conditions (see Table 1). Consequently, behavioral data were not used as covariates. Accuracy deteriorated and reaction time increased as memory load increased in each group. Medium effect sizes were found for mean percent correct and percent missing in the 1- and 2-back conditions, healthy controls having more items correct and fewer missing than participants with 22q11 deletion syndrome.

fMRI Results

Participants with 22q11 deletion syndrome were compared with healthy controls in three contrasts: 2-back vs. 0-back, 1-back vs. 0-back, and 2-back vs. 1-back. In both 2-back contrasts, the healthy participants showed significantly more activation than participants with 22q11 deletion syndrome in right dorsolateral prefrontal cortex (portions of the superior and middle frontal gyri), right frontal pole, and anterior cingulate and paracingulate —areas typically activated by n-back tasks (see Figure 1). In the 2- vs. 1-back contrast, the healthy participants showed significantly more activation in bilateral precuneus, intracalcarine cortex, and in the right hemisphere in superior and middle frontal gyri, frontal pole, anterior cingulate, and paracingulate (see Figure 2). The 1-back vs. 0-back contrast revealed no differences between groups. In none of the three contrasts did the participants with 22q show higher activation than the controls.

DISCUSSION

Children and adolescents with 22q11 deletion syndrome and healthy control participants took part in a fMRI study to investigate brain activation during a working memory task. Task performance was similar in both groups, as was functional activation for the 1-back minus 0-back contrast, suggesting that both groups were equally able to respond to this level of task difficulty. Contrasting the 2-back condition with either the 1-back or 0-back revealed greater activation by healthy participants than patients with 22q11 deletion syndrome in several brain regions involved in working memory. The 2-back vs. 1-back contrast can be taken to represent manipulation of information in memory, while the 2-back vs. 0-back contrast represents maintenance and manipulation.[24] Our results suggest that participants with 22q11 deletion syndrome experienced hypoactivation despite comparable performance at a task requiring shutting out irrelevant information, maintenance and manipulation of information

in working memory. This hypoactivation may reflect less effective recruitment of neurons during the working memory task.

These results are consistent with the findings of earlier fMRI working memory studies in children with 22q11 deletion syndrome[14,15] and with a study of individuals (not 22q11 deletion syndrome patients) with prodromal signs of psychosis.[25] Kates et al. examined only a 2-back vs. 0-back condition, while Fusar-Poli et al. analyzed the 2-back plus 1-back vs. 0-back activation, but both found that during the n-back task the patients showed lower activation in frontal and parietal regions than healthy controls. Using a spatial working memory task, Azuma and colleagues found lower activation in a parietal region in patients with 22q11 deletion syndrome compared with healthy controls, but similar recruitment of dorsolateral prefrontal cortex by both groups. Kates et al. (2007) found that patients with 22q11 deletion syndrome and community controls recruited operculum but not dorsolateral prefrontal cortex or cingulate in the 2-back vs. 0-back condition, suggesting reliance on phonological rehearsal as a working memory strategy. In contrast, both of our groups recruited dorsolateral prefrontal cortex and cingulate during the 2-back task, although as in the Kates study, our patients with 22q11 deletion syndrome did not recruit the anterior cingulate to the extent that healthy controls did.

We found reduced activation in frontal regions and cingulate in the 2-back vs. 0-back and 2-back vs. 1-back contrasts, as well as the precuneus in the 2-back vs. 1-back contrast. These are all regions typically activated by n-back tasks. In particular, dorsolateral prefrontal cortex activation is associated with manipulating and monitoring information held in working memory,[26] and the anterior cingulate is thought to act in discriminating salient stimuli,[27] while the precuneus is associated with manipulation and storage of verbal and spatial information.[28] Hypoactivation of these areas suggests frontal and parietal dysfunction in patients with 22q11 deletion syndrome, possibly due to differences in gray matter volumes, vasculature, white matter structure, or connectivity.

A previous study including many of the same patients with 22q11 deletion syndrome who participated in the current study found reductions in prefrontal, anterior cingulate and cerebellar gray matter.[29] Reduced white matter has also been reported in 22q11 deletion syndrome,[30] as well as reduced white matter connectivity between areas involved in information maintenance, visual perception, and executive function.[31] These abnormalities may result in reduced activation of these areas when working memory is utilized in children with 22q11 deletion syndrome. Our sample size was too small to perform correlations between the brain volumes and the blood oxygenation level dependent activation within the 22q11 deletion syndrome group, but this would be a topic for examination in a future study.

It is intriguing to note that brain plasticity-based non-pharmacological cognitive interventions can be associated with improvements in brain volume,[32] raising the possibility that specific interventions in children with 22q11 deletion syndrome may mitigate the neural abnormalities, thus leading to improvements in the targeted domains as well as overall cognition. We have already demonstrated that such a cognitive intervention is feasible and results in improvements in multiple cognitive domains.[33] Assessing neural activity patterns

before and after such an intervention would provide much needed data on the neural substrates that underlie improvements in neurocognitive function.

The strengths of our paper include replication of earlier research; use of a tiered n-back task, which allowed us to study incremental changes in blood flow with increasing task complexity; and the implementation of stringent motion correction. A limitation of the current study is the small sample size. It is possible that a larger sample size might have revealed a significant difference between groups in task accuracy, which could help explain group differences in fMRI activation patterns. In the 1- and 2-back conditions, the control participants performed slightly better than the patients with 22q11 deletion syndrome, as demonstrated by medium effect sizes for percent correct and missing responses. An analysis using performance on the behavioral tasks as a covariate resulted in similar results to those reported here.

In conclusion, reduced neuronal activity compared with healthy controls in areas associated with working memory suggests that the working memory impairments documented in patients with 22q11 deletion syndrome may stem from hypoactivation of prefrontal and parietal areas. Observations of fMRI changes in the absence of significant performance differences suggest that these neurobiological measures might be sensitive to emerging preclinical cognitive impairments and may therefore eventually be of value in early detection efforts. Better understanding neural substrates of working memory in children with 22q11 deletion syndrome would improve our ability to design and evaluate cognitive remediation programs for this population.

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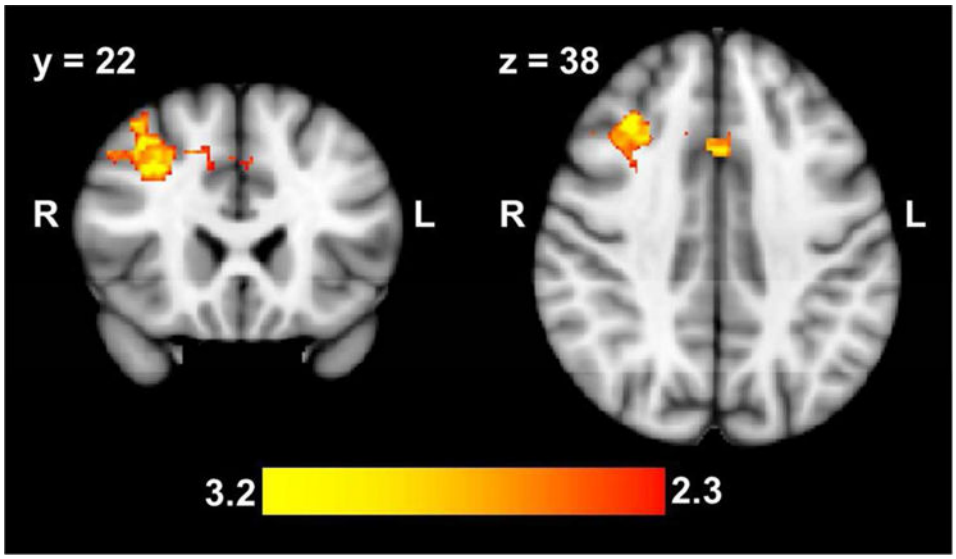

Figure 1.

2back > 0back, control group > 22q11 deletion syndrome group. Clusters were identified in the middle frontal gyrus (832 voxels, maximum z-stat 4.08 at x=30, y=26, z=42) and frontal pole (738 voxels, maximum z-stat at x=26, y=60, z=12).

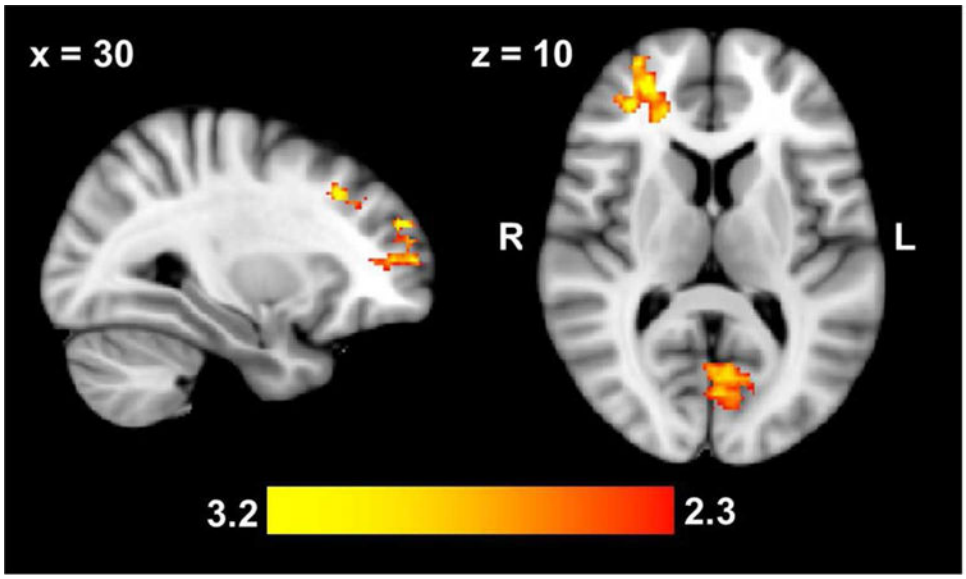

Figure 2.

2back > 1back, control group > 22q11 deletion syndrome group. Clusters were identified in the middle frontal gyrus (488 voxels, maximum z-stat 3.47 at x=30, y=26, z=38), frontal pole (450 voxels, maximum z-stat 3.87 at x=26, y=48, z=10), and precuneus (1278 voxels, maximum z-stat 3.92 at x=−10, y=−50, z=48).

TABLE 1

Details of the performance on the N-back conditions in the 22q11DS group relative to the control group. T-tests did not demonstrate any significant group differences but medium effect sizes for differences in percent correct and errors of omission were seen.

N-Back Condition	Mean percent correct			Mean errors of Omission (%)			Mean reaction time in milliseconds		
	22q11DS	Controls	*d*	22q11DS	Controls	*d*	22q11DS	Controls	*d*
2-back	63	75	**0.58**	34	22	**0.64**	870	983	0.23
1-back	82	87	**0.57**	10	5	**0.52**	813	801	0.07
0-back	96	95	0.08	4	5	0.12	524	517	0.08

d= Cohen's d effect size. Medium effect sizes are in bold