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BRIEF COMMUNICATION

The Test of Everyday Attention Reveals Significant Sustained Volitional Attention and Working Memory Deficits in Friedreich Ataxia

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Abstract

Sustained volitional attention and working memory capacity was examined for the first time in people with Friedreich ataxia (FRDA). We administered subtests of the Test of Everyday Attention to 16 individuals with molecularly confirmed FRDA and gender-, age-, and IQ-matched controls. Clinically significant impairment in working memory and sustained volitional attention was evident. Working memory deficits correlated significantly with GAA repeat number on the shorter allele of the *FXN* gene, and separately, with disease severity, as measured by the Friedreich Ataxia Rating Scale score. Sustained volitional attention was not correlated with disease parameters, suggesting that this impairment may not be related to the disease process in a simple way. The deficits observed may be the result of disruption to corticocerebellar pathways, or directly related to the cortical and/or cerebellar pathology evident in people with FRDA. (*JINS*, 2011, *17*, 196–200)

Keywords: Friedreich ataxia, Attention, Working memory, Memory, Short-term, Cognition, Volition

INTRODUCTION

Friedreich ataxia (FRDA), an autosomal recessive disease characterized by progressive and unremitting ataxia, involves brain, spinal cord, peripheral nervous system, and cardiac pathology (Pandolfo, 2008), with abnormal auditory pathway functioning (Rance et al., 2008). The condition typically results from a homozygous unstable GAA triplet repeat expansion within intron 1 of the *FXN* gene, resulting in decreased production of frataxin; a longer GAA repeat on the shorter *FXN* allele is associated with less frataxin and more serious disease (Delatycki, Williamson, & Forrest, 2000).

There is atrophy of the dentate nucleus of the cerebellum, the main source of cerebellar output (Pandolfo, 2008), with cerebral atrophy also evident in some individuals with FRDA (Junck et al., 1994). Any demonstrated cerebral pathology in FRDA could be directly caused by the FRDA gene, or could be an indirect consequence of chronic partial cerebral deafferentation, perhaps during development, from the already genetically compromised cerebellum. Separately, any apparently cortical functional deficits could be the result of absence of adequate cerebellar input or priming. Evidence, however, suggesting individuals with cerebellar atrophy may be impaired on tasks assessing prefrontal cortex function (Schmahmann & Sherman, 1998), alongside evidence demonstrating a role of the cerebellum in cognitive functions (Baillieux et al., 2009), highlights the potential for people with FRDA to be impaired in executive functioning.

There are inconsistencies in the attention function literature regarding deficits associated with FRDA. With the Stroop Test, while White, Lalonde, and Botez-Marquard (2000) noted significantly poorer performance, Wollmann, Barroso, Monton, and Nieto (2002) found no impairment. Both studies, however, support impaired information processing speed in people with FRDA. Mantovan et al. (2006) further examined the cognitive

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profile of 12 adults with molecularly confirmed FRDA; Trail-Making, Stroop, and Tower of London Tests revealed impaired cognitive information processing. Contrasting to research reporting a positive correlation between repeat number on the shorter *FXN* allele and disease severity (Delatycki et al., 2000), Mantovan et al. (2006) found no significant relationship between GAA repeat number and information processing speed, attention, or planning. There was, however, a significant negative relationship between disease duration and Stroop Test and Tower of London Test performance.

Given inconsistent findings in previous research, and a lack of research directly examining sustained volitional attention and working memory, we sought to investigate these abilities in individuals with FRDA. We employed five subtests from the Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), which primarily test sustained volitional attention and/or working memory capacity, and determined whether clinical features correlated with task performance. We hypothesized that individuals with FRDA would perform worse (i.e., lower scores) on the TEA subtests and that performance would correlate with clinical and genetic disease parameters.

METHODS

Participants

Seventeen adults (11 males) homozygous for a GAA expansion in intron 1 of the *FXN* gene participated. The average age of disease onset was 18.69 years ($SD = 6.33$); average disease duration was 16.73 years ($SD = 8.60$); mean number of GAA repeats on the shorter *FXN* allele was 564 ($SD = 175$); and average Friedeich Ataxia Rating Scale score (FARS; Subramony et al., 2005), a measure of disease severity scored out of 167, was 79.90 ($SD = 18.06$). Seventeen normal controls, with no neurological disease, participated, matched on age (FRDA $Md = 32$; Control $Md = 30$, $U = 130$, $z = -.022$, $p > .05$), gender, and IQ (NART- National Adult Reading Test; Nelson & O'Connell, 1978; FRDA $Md = 112.3$; Control $Md = 115.55$, $U = 87.5$, $z = -1.75$, $p > .05$) to individuals with FRDA. They were all recruited from the normal population. Critical to the experimental design, participants with a known auditory neuropathy or hearing impairment, as identified by the technique described by Rance et al. (2008), were excluded. Furthermore, all participants accurately heard pure tones at octave frequencies across the audiometric range at 15 dBHL (assessed using a Beltone Model 119 Audiometer). Study approval was obtained from the Southern Health and Monash University Human Research Ethics Committees (Ref no. 04052C). All participants gave their informed, written consent in accordance with the Declaration of Helsinki.

MATERIALS AND PROCEDURE

The Test of Everyday Attention

The TEA subtests (Robertson et al., 1994) assess important clinical aspects of attention and, on face validity, examine working memory function. The Elevator Counting (EC), Elevator Counting with Distraction (ECD), Visual Elevator (VE), Elevator Counting with Reversal (ECR), and Lottery subtests were administered. The scenarios of these subtests are based largely on everyday situations, making it an ecologically valid instrument (Robertson et al., 1994).

Elevator Counting (EC): Sustained volitional attention

Participants imagine they are in an elevator, with each level indicated by a 500 Hz tone. Participants count the tones and report at what floor they have finished.

Elevator Counting with Distraction (ECD): Working memory and sustained volitional attention

Participants count the number of repetitions of a 500 Hz tone, while ignoring a higher pitched (571.4 Hz) distractor.

Visual Elevator (VE): Working memory (sustained volitional attention contribution)

Participants count up and down (aloud) as they follow a series of pictures indicating the direction of elevator travel, and report at which floor the lift has finished. The number of correct responses is recorded.

Elevator Counting with Reversal (ECR): Working memory (sustained volitional attention contribution)

The auditory equivalent of the VE subtest where tones of different pitches indicate whether the elevator is going up (571.4 Hz tone) or down (421.6 Hz tone); a 500 Hz tone represents floors being passed.

The Lottery subtest: Sustained volitional attention

Participants listen to ticket numbers beginning with two letters, and ending with three letters (e.g., WX154). Tickets ending in 55 are targets, requiring the participant to write down the letters preceding these numbers.

The EC, ECD, ECR, and the Lottery subtests use auditory stimuli and do not rely on timed motor responses. A frequency analysis of the tones ensured suitability for people with FRDA, and successful completion of a training task enabled participants to progress to the experimental phase. A TEAC Portable Compact Disc System (PCD806) administered the auditory stimuli. To standardize presentation, a Digital Sound Level Meter (Dick Smith Electronics Q1362) measured signal level at the participant's head (volume range 65–70 dB SPL; every participant confirmed this was comfortable). The VE subtest does not involve the rapid presentation of visual stimuli, thus performance is not confounded by visual problems common in people with FRDA.

The FARS (Subramony et al., 2005) was administered to participants with FRDA. This disease severity measure assesses ataxia, activities of daily living, and includes a neurological subscale, measuring upper and lower limb

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Table 1. Median values of TEA subtest accuracy scores for the FRDA and control groups, and Mann-Whitney *U*, *z* scores, and effect sizes of group differences

	Median				
	FRDA ($n = 16$)	Control ($n = 17$)	Mann-Whitney *U*	*z* score	Effect size
EC	7	7	127.5	−1.03	–
ECD	9	10	80	−2.23*	−0.39
VE	8	9	81	−2.04*	−0.35
ECR	4.5	9	40	−3.51**	−0.61
Lottery	9.5	10	68	−3.27**	−0.57

Note. FRDA = Friedreich ataxia; EC = Elevator Counting subtest; ECD = Elevator Counting with Distraction subtest; VE = Visual Elevator subtest; ECR = Elevator Counting with Reversal subtest.
*$p < .05$ (two-tailed). **$p < .01$ (two-tailed).

coordination, and peripheral nervous system function. One participant did not undergo FARS examination.

Data Analysis

Due to skewed distributions, Mann-Whitney *U* tests statistically compared the FRDA and control groups' accuracy scores on the TEA subtests. Correlational analyses using Spearman's rho assessed the relationships between the subtests and clinical characteristics of people with FRDA (age of disease onset, disease duration, GAA repeat number on shorter *FXN* allele, and FARS scores). Effect size was judged as small, medium, or large according to Cohen (1992).

RESULTS

Median values of the TEA subtest accuracy scores for FRDA and control groups, and Mann-Whitney *U* tests statistically comparing performance, appear in Table 1.

Given the ceiling effect on EC subtest performance it will not be considered further. The significantly lower accuracy scores of the FRDA group on the ECD and VE subtests were small effects, while the significantly lower scores by the FRDA group on the ECR and Lottery subtests were both large effects (Cohen, 1992).

Table 2. Spearman rho correlations between clinical characteristics of FRDA group ($n = 16$) and TEA subtest accuracy scores

	Age disease onset	Duration of disease	GAA1	FARS
ECD	−.26	.01	.31	−.18
VE	.22	−.14	−.27	−.61*
ECR	.15	−.15	−.74**	−.49
Lottery	−.32	.45	−.10	−.24

Note. FRDA = Friedreich ataxia; TEA = Test of Everyday Attention; ECD = Elevator Counting with Distraction subtest; VE = Visual Elevator subtest; ECR = Elevator Counting with Reversal subtest; GAA1 = GAA repeat length on short allele of *FXN* gene; FARS = Friedreich Ataxia Rating Scale score.
*$p < .05$ (two-tailed); **$p < .01$ (two-tailed).

Spearman's rho correlational analyses determined if performance on TEA subtests was related to FRDA clinical characteristics. As seen in Table 2, VE subtest accuracy scores were significantly negatively correlated with FARS scores. The ECR accuracy scores were significantly negatively correlated with GAA repeat length on the shorter *FXN* allele.

DISCUSSION

Subtests of the TEA (Robertson et al., 1994) investigated sustained volitional attention and working memory function of individuals with FRDA, to establish whether performance was significantly related to clinical characteristics. As predicted, people with FRDA were significantly less accurate on all TEA subtests except EC, where there was a ceiling effect. Furthermore, performance on the ECR and VE subtests of the TEA correlated significantly with disease parameters.

Results indicate that sustained volitional attention and working memory deficits significantly affect individuals with FRDA. The ceiling effect of the EC subtest in both participant groups is consistent with performance in the normative population (Robertson et al., 1994), highlighting its relative simplicity. However, the clinically significant lower accuracy scores of participants with FRDA on the Lottery subtest, which arguably gives the most pure indication and places the highest demand on sustained volitional attention, demonstrates deficits in this domain. Significantly lower scores on the ECD subtest further support deficits in sustained volitional attention in people with FRDA and, together with results from the ECR and VE subtests, highlight the clinically significant impairment in working memory evident in this patient group. Indeed, accuracy scores as dependent variables confirm that poorer performance characterizes sustained volitional attention and working memory deficits independent of motor impairments central to FRDA. Moreover, evidence of these impairments, in a relatively small clinical sample of 16, supports the high sensitivity of the TEA subtests in revealing such deficits.

This is the first study to administer the TEA to people with FRDA, and the first to determine any relationship between

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TEA subtest scores and clinical characteristics. The relationship between ECR and FRDA genetics is consistent with previous research demonstrating a positive relationship between GAA repeat length on the shorter *FXN* allele and disease severity (Delatycki et al., 2000). Overall, the significant correlation between VE and ECR subtests and clinical parameters suggests that more serious disease, as indicated by higher GAA repeat number on the shorter *FXN* allele and higher FARS scores, respectively, is related to greater impairments in working memory. In noting that ECD subtest performance was not related to clinical parameters, results suggest that perhaps only tasks with greater working memory demands correlate significantly with FRDA characteristics. Furthermore, the lack of a significant relationship between Lottery subtest performance and clinical characteristics suggests that sustained volitional attention deficits, although statistically significant with a large effect size, may not be related to disease parameters in a simple way. It is also possible, however, that our inability to demonstrate a significant relationship between performance on this subtest and disease parameters is related to our small clinical sample. As frataxin deficiency likely underpins the relationship between GAA repeat length on the shorter *FXN* allele and disease severity (Lodi, Tonon, Calabrese, & Schapira, 2006), the working memory deficits observed may stem from reduced frataxin levels in critical brain areas.

Sustained attention is associated with activation of the anterior cingulate, dorsolateral prefrontal cortex, and parietal regions; brain areas also active during working memory tasks (Ortuno et al., 2002). Of note is the alerting network, which is associated with sustained volitional attention, and engages thalamic, frontal, and parietal areas (Wang & Fan, 2007). The deficits evident in people with FRDA may relate to alterations of this neural network, and/or to the significant cerebellar degeneration evident in FRDA, in combination with disruption to its afferent and efferent connections. Future investigation of the functional brain changes in people with FRDA, such as through functional MRI, will help elucidate the underlying neuropathology and how it relates to the observed working memory and sustained volitional attention impairments.

A limitation was that additional cognitive variables, possibly influencing attention and working memory function (e.g., information processing speed), were not directly examined. A pure measure of information processing speed (e.g., an Inspection Time Task, see Phillips et al., 1999) would ensure that performance on tasks such as the ECD subtest is not confounded by this variable. Note also that no correction for multiple comparisons was made and that covarying for the contributions of short-term and working memory would remove their possible effects upon attentional processes, enabling a more in-depth analysis of attention function in FRDA.

In summary, we document for the first time clinically significant impairment in sustained volitional attention and working memory in FRDA, likely implicating a network of brain regions modulating and subserving attention and working memory function. Measures of sustained volitional attention did not correlate with disease parameters, indicating that, although clinically significant, the impairment does not represent disease related deficits. Correlations between GAA repeat length on the shorter *FXN* allele and working memory, as measured by the ECR subtest of the TEA, indicate the effect of decreased levels of frataxin upon developing brain and cognitive function. This finding, together with the documented relationship between the VE subtest and disease severity, suggests that deficits in working memory may provide a sensitive marker of not only disease severity but also disease progression, which may be useful for future clinical drug trials as surrogate end points.

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