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THE FITTS TASK REVEALS IMPAIRMENTS IN PLANNING AND ONLINE CONTROL OF MOVEMENT IN FRIEDREICH ATAXIA: REDUCED CEREBELLAR-CORTICO CONNECTIVITY?

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Abstract—Friedreich ataxia (FRDA) is the most common of the inherited ataxias. We have suggested that people with FRDA may have impairment in cognitive and/or psychomotor capacity either due to disturbance of projections of the cerebellum to the cortex, direct cortical pathology or perhaps both. To further explore this possibility, we used a movement task incorporating Fitts' Law, a robust description of the relationship between movement time and accuracy in goal-directed aiming movements. By manipulating task difficulty, according to target size and distance, we were able to quantify processes related to motor planning in 10 individuals with FRDA and 10 matched control participants. Compared to control participants, people with FRDA were significantly disadvantaged in terms of movement time to targets with an increasing index of difficulty. Successful completion of this task requires both preplanning of movement and online error detection and correction. The cerebellum and its connections to the frontal cortex via cerebro-ponto-cerebello-thalamo-cerebral loops are fundamental to both processes. These results lend further support to our contention that in FRDA these loops are impaired, reflecting a failure to access prefrontal/anterior regions necessary for effective management of preplanning of movement and online error correction.

Key words: Friedreich ataxia, Fitts law, index of difficulty, kinematics, movement.

Friedreich ataxia (FRDA) is the most common inherited ataxia, affecting approximately 1 in 29,000 individuals (Delatycki et al., 2000). The characteristic clinical features of this disease include progressive ataxia, spasticity, absent lower limb reflexes, impaired vibration sense and proprioception, scoliosis, foot deformity and cardiomyopathy (Harding, 1981; Delatycki et al., 2000). FRDA is due to mutations in the *FXN* gene. In 98% of mutant alleles, there is a homozygous expansion of a GAA trinucleotide repeat in intron one of the *FXN* gene (Campuzano et al., 1996). The other 2% are point mutations (Voncken et al., 2004). Onset of symptoms in FRDA is typically around the age of 10 (±6.4) years (Delatycki et al., 2000; Pandolfo, 2009). The major sites of pathology in FRDA include the dorsal root ganglia (DRG) and posterior columns of the spinal cord, spinocerebellar tracts, corticospinal tracts, dentate nucleus of the cerebellum and the heart (Junck et al., 1994; Pandolfo, 2008).

The hallmark symptom of FRDA is ataxia. Ataxia, meaning the "absence of order" (Klockgether, 2010), is apparent in the loss of muscle synergy, timing and thus smoothness of movement (Mariotti et al., 2005). Cerebellar pathology, sensory impairment and associated dysfunction in synergistic and temporally appropriate movement execution could thus be seen as underscoring the movement disorder associated with FRDA. However, this view does not take in account movement planning, as opposed to reflexive movement. Movement plans comprise factors such as the temporal order and synergy involved in activating individual and group muscles in conjunction with associated extrinsic environmental factors and importantly, the goals and intentions of the individual executing the movement. Movement thus comprises the selection of an appropriate movement plan and the seamless translation of this plan into the ongoing execution of movement. A challenge in understanding the movement disorder associated with FRDA is the impact of the cognitive control of movement and how the dynamics of planning move seamlessly into the execution of movement (Turvey and Fonseca, 2009).

There is now emerging evidence of significant and potentially debilitating cognitive changes associated with FRDA (Wollmann et al., 2002; Mantovan et al., 2006; de Nóbrega et al., 2007; Fielding et al., 2010; Hocking et al., 2010; Corben et al., 2010, 2011; Klopper et al., 2011). The nature of these changes, particularly in terms of the impact on movement, warrants an ongoing investigation in order to develop appropriate interventions and therapies.

The aim of this study was to utilize the robust Fitts' law in a reciprocal goal-directed aiming task in order to further examine how people with FRDA plan and execute move-

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Abbreviations: BDI, Beck Depression Inventory; DLPFC, dorsolateral prefrontal cortex; DT, dwell time; FARS, Friedreich ataxia rating scale; ID, index of difficulty; MT, movement time; NART, National Adult Reading Test; SD, standard deviation.

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ment. Fitts' law describes the relationship between movement time (MT) and the difficulty of the task (Fitts, 1954; Fitts and Peterson, 1964). Task difficulty is seen as a function of movement amplitude and the size of the target, with smaller targets at a greater distance having the greatest accuracy demands. Fitts' law expresses the scaling of MT in relation to movement amplitude (A) and target size (W) as follows: $MT = a + b\ [\log_2(2A/W)]$. Fitts devised an index of difficulty (ID) that specifies the minimum amount of information required to execute each movement (Fitts, 1954). Hence ID reflects the degree of task difficulty as a function of combining A and W and is calculated as the value of $\log_2$ (2 A/W) (Fitts, 1954).

The control of goal-directed aiming movements has historically been based on Woodworth's premise that goal-directed aiming movement comprises a two step process (Woodworth, 1899). The initial step entails a preplanned ballistic movement that brings the limb close to the target. The subsequent step involves the use of visual and proprioceptive feedback in order for the limb to accurately reach the target (Elliott et al., 2010). Elliott et al. (2010) expanded this model to include the development of a premovement action plan and the ongoing online comparison between the expected and the actual efferent and afferent motor and sensory information. Elliott et al. (2010) proposed this model as appropriate in the examination of the pathology underscoring the breakdown of goal directed movement.

Successful completion of Fitts' task involves the interplay of MT and the accuracy demands of the task, otherwise referred to as the speed-accuracy trade-off (Bogacz et al., 2010). In tasks with high accuracy demands, such as moving to smaller targets at greater distance, slowing down movement provides a greater opportunity for afferent-based error reduction, particularly in the final stages of the movement. Studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have indicated easier; as compared to more difficult, ID's invoke activity in different regions of the brain (Winstein et al., 1997; Boyd et al., 2009). In particular, increasingly difficult ID activates more anterior cortical and subcortical structures associated with complex motor planning and error detection. Not surprisingly, significant activation was also noted in the cerebellum. Previous studies of cognitive capacity in FRDA have reported impairment in functions usually ascribed to frontal and parietal cortices (Corben et al., 2010; Fielding et al., 2010; Hocking et al., 2010; Klopper et al., 2011) hence utilization of the Fitts' task, seen to also activate these regions, may also reveal important information about the function of these areas in FRDA.

As with previous studies, the challenge in examining cognitive or psychomotor function in FRDA is limiting the confounding effects of the motor impairment associated with the condition, while devising a strategy to examine the disturbance in psychomotor processing attributed to cerebellar dysfunction in FRDA. The Fitts' task provides an ideal opportunity to examine how people with FRDA plan and execute movement, particularly in the context of online error detection and correction. In particular, the Fitts' task provides a paradigm in which the psychomotor planning in respect to target size and distance can be teased apart. Moreover, given the significant role of the cerebellum in identifying differences between planned and actual movement (Ito, 2008), this task provides an opportunity to further explore the effects of deficits in cortico-ponto-cerebello-thalamo-cortical loops accessing critical cortical areas, in particular the frontoparietal circuitry, on psychomotor control in people with FRDA. Finally, to our knowledge, no previous studies have examined the kinematic components of planned movement in FRDA in order to further elucidate the effect of FRDA on movement planning and execution.

In view of the neuropathology associated with FRDA, particularly in the dentate nucleus of the cerebellum, we hypothesized that while participants with FRDA and control participants would show a log-linear relationship between MT and task difficulty, participants with FRDA would show greater MT as a function of an increment in task difficulty. Furthermore, we hypothesized that given the role of the cerebellum in error detection and correction, people with FRDA, compared with controls, would show greater difficulty in terminal accuracy under conditions associated with greater complexity.

EXPERIMENTAL PROCEDURES

Participants

Ten right handed individuals aged over 18 years and homozygous for a GAA expansion in intron one of the *FXN* gene participated in this study (see Table 1 for demographic, clinical and screening measure details). Ten right-handed individuals matched for age and gender participated as controls. There was no significant difference in mean age between individuals with FRDA (M=37.4, standard deviation (SD)=8.9) and control participants (M=38.11, SD=9.8). Clinical severity in individuals with FRDA was assessed by the Friedreich Ataxia Rating Scale (FARS) (Subramony et al., 2005). The FARS has a maximum score of 167, with lower scores indicating less impairment. All participants completed the National Adult Reading Test (NART), which provides an estimate of premorbid IQ; a one-way ANOVA confirmed that individuals with FRDA (M=117, SD=3.9) had a significantly lower NART score than control participants (M=121, SD=2.4) [$F(1,18)=6.09$, $P<0.05$]. To control for the effect of depression on speed of information processing, executive function, attention and memory (Elliot, 2002), all participants were screened for symptoms of depression at the time of testing using the Beck Depression Inventory (BDI (Beck et al., 1961). The maximum score for the BDI is 63 and the "normal" range is considered to be between 0 and 9 (Beck et al., 1961). To screen for impaired planning and inhibitory processes, participants also completed the Trail Making Test, parts A and B (Reitan, 1955) and all three conditions of the Stroop Interference Test (Golden, 2002). There was a significant difference between the groups for Trails B minus A [$F(1,18)=10.87$, $P<0.05$]; however, no significant differences were observed in the Stroop Interference Test or the BDI. Despite the presence of a significant difference between groups in the Trails B minus A, there were no significant correlations between scores on the Trails B minus A and movement execution parameters. It is therefore unlikely that performance on the Trails task significantly influenced the pattern of results in this study.

Approval for this study was obtained from the Southern Health Human Research Ethics Committee. All participants gave in-