



Executive neuropsychological functioning in individuals with Williams syndrome

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ABSTRACT

The present study investigated executive neuropsychological functioning in individuals with the neuro-developmental disorder Williams syndrome (WS) using a set of validated standardized neuropsychological tasks. Relatively few studies have examined frontal lobe related executive functions within the cognitive phenotype associated with the disorder. The present study compared participants with WS to typically developing participants who were individually matched for (1) chronological age and (2) verbal mental age ($N = 19$ each group) on tasks of attention-set shifting, planning and working memory from the Cambridge Neuropsychological Test Automated Battery (CANTAB). To address the specificity of executive function impairment, non-executive tasks of delayed short-term memory and short-term memory span were also administered. Individuals with WS (mean age 18 years) showed impaired executive functioning on tasks of attention set-shifting, working memory, and planning. Non-executive deficits were also observed in short-term delayed memory and memory span. Neuropsychological impairments were correlated with a range of behavioural problems assessed using parent-rated Questionnaires. Overall, these findings point to the role of a range of executive function impairments in WS but further suggest that cognitive impairments extend beyond executive dysfunction.

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Williams syndrome (WS) is a relatively rare neuro-developmental disorder with confirmed genetic origin (Ewart et al., 1993). The predicted prevalence of the disorder is generally accepted to be 1 in 20,000 births (Morris & Mervis, 1999) although there have been suggestions of prevalence as high as 1 in 7,500 (Strømme, Bjørnstad, & Ramstad, 2002). The discovery of the genetic nature of WS links its occurrence with a random deletion of approximately 25 genes on chromosome 7, specifically 7q11.23 (Ewart et al., 1993). The disorder has attracted a great deal of research attention due to unique aspects of its associated behavioural, social and cognitive phenotypes. The earliest research investigating the disorder was largely dedicated to unearthing the distinct cognitive profile, with claims of 'peaks and valleys' of performance (e.g. Bellugi, Wang, & Jernigan, 1994). However, more recent research has focused on elucidating the behavioural and social phenotypes that typically accompany the disorder, the interplay between these characteristics, and the importance of the underlying neural mechanisms that play a role in the WS phenotypes.

Cognitively, individuals with WS exhibit a distinct profile of relatively proficient skills within the verbal domain and more severe impairment associated with visuo-spatial processing (e.g. Hoffman, Landau, & Pagani, 2003; Jarrold, Baddeley, & Hewes, 1999; Mervis, Robinson, & Pani, 1999; Vicari, Bellucci, & Carlesimo, 2003; Wang & Bellugi, 1994), although this distinct profile of relative preservation and impairment in cognitive skills in WS has been challenged by Porter and Coltheart (2005, 2006). Importantly, performance within both these domains falls short of that expected by chronological age. Sensitive assessments have emphasised that processing within the verbal domain is far from 'intact' or 'typical' (e.g. irregular inflection errors Clahsen & Almazan, 1998; past tense formation deficits Thomas et al., 2001). However verbal performance remains more proficient than that observed within the non-verbal domain especially for visuo-spatial tasks. Although individuals with WS appear relatively competent at holding visual information such as objects in memory (Vicari et al., 2003), linking visual and spatial information such as the location of that object within an array is far more problematic (Jarrold, Baddeley, & Hewes, 1999; Vicari, Bellucci, & Carlesimo, 2006). Performance may not only be affected by the type of information to be remembered such as whether it is visual or spatial however, as recent research indicates that the length of delay between remembering and recalling information

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and the exact stimuli details are critical to performance (O'Hearn, Courtney, Street, & Landau, 2009). During longer delay periods (5 s) individuals with WS have been found to be impaired irrespective of whether the task assesses memory for object identity or location, and whether the stimuli are houses or faces (O'Hearn et al., 2009). The studies outlined here emphasise a range of atypicalities in the short term memory skills of individuals with WS. When information must be held and manipulated in memory further deficits are likely. Research investigating central executive aspects of working memory is however much more limited.

Relatively few studies have examined 'executive functions' in general in individuals with WS. 'Executive function' is a broad term encompassing a variety of higher order strategic/organizational cognitive functions including inhibition, working memory, attentional flexibility and planning (Hughes & Graham, 2002; Rhodes, Coghill, & Matthews, 2005). These abilities aid the successful completion of new and difficult situations (Hughes & Graham, 2002). Executive functioning is associated with the frontal lobe, particularly pre-frontal cortex; individuals with frontal lobe damage who are characteristically socially disinhibited exhibit impairment in executive function abilities (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). There is some evidence to suggest that individuals with WS are impaired in executive functions. The limited research available for individuals with WS has principally focused on the role of inhibition, a key executive component (Atkinson, 2000; Atkinson et al., 2003; Mobbs et al., 2006; Porter, Coltheart, & Langdon, 2007). Linking the cognitive and social phenotypes associated with WS, research has recently suggested that the hyper-social behaviours typically found in WS may relate to deficits inhibiting socially salient information (Porter et al., 2007). For example, a propensity towards assessing strangers with increased approachability (Frigerio et al., 2006; Jones et al., 2000) has been linked to this notion of inhibitory deficits for social responses (Porter et al., 2007). Neuroimaging analyses of fMRI data produced while individuals with WS completed a GoNoGo inhibition task has also shown reduced activity in brain areas known to be critically involved in behavioural inhibition namely the striatum, dorsolateral prefrontal and dorsal anterior cingulate cortices (Mobbs et al., 2006). There is therefore growing behavioural as well as neuroimaging evidence for impaired response inhibition in WS that may not only impact upon cognitive skills but may also extend to social behaviours.

Research exploring inhibition difficulties in other disordered populations has increasingly focused on the role of other executive functions with a profile of skills and deficits (e.g. Attention Deficit Hyperactivity Disorder, ADHD; Tourettes Disorder; Obsessive Compulsive Disorder, OCD). Reports that individuals with WS are four times more likely to meet criteria for ADHD than typically developing children (Finegan et al., 1994), a disorder known to be characterized by a range of executive function impairments, clearly suggests this area warrants further investigation. Research exploring executive functions in populations such as ADHD, OCD and Tourettes Disorder are marked by much more extensive literatures in line with the increased prevalence of the disorders. Interestingly, in these populations research has moved beyond focusing on response inhibition to examine other aspects of executive function as a potential explanation for the observed range of impairments. For example, theories of cognitive impairment in ADHD have historically focused on observed impulsiveness, with one popular theory postulating a primary deficit in inhibitory control leading to secondary deficits in other aspects of executive function (Barkley, 1997, 1998). This focus developed from the observation that children with ADHD show a range of difficulties in social inhibition: some examples of which include 'disturbs other children', has 'difficulty waiting his or her turn', and 'interrupts or intrudes on others' [ratings included on the Conners (1997),

Conners, Parker, Sitarenios, and Epstein (1998) ADHD Rating scale (CTRS-28)]. However, an extensive body of research over the last decade has provided no clear empirical evidence to support the primacy of inhibition deficits in ADHD. A wide range of executive function deficits, including inhibition (Barkley, 1997), working memory (Kempton et al., 1999; Rhodes, Coghill, & Matthews, 2004; Rhodes et al., 2005) attentional set shifting and planning (Kempton et al., 1999; Rhodes et al., 2005; Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008) have now been described. It would appear plausible therefore that some of the cognitive, behavioural and social characteristics that are related to WS are likely to be similarly accounted for by a range of executive function deficits, rather than being the result of isolated deficits of inhibition.

Although limited investigations have been conducted there is some evidence that individuals with WS show impairment in aspects of executive function beyond inhibition. Two studies report poor planning behaviour on a behavioural letterbox task (Arnold, Yule, & Martin, 1985; Bellugi, Bihrl, Jernigan, Trauner, & Doherty, 1990). It has also been reported that individuals with WS show impaired attentional set-shifting on a Point/Counter-Pointing Task (Atkinson, 2000). A recent study examined executive aspects of working memory (Kittler, Krinsky-McHale, & Devenny, 2008) and reported no difference in performance between a WS sample and a mixed aetiology group with developmental delay. The findings of the study may however have been limited in relation to sample size. Furthermore, an alternative explanation for Kittler et al.'s findings is that the executive aspects of working memory were tested within a specific task domain, and visuospatial dual tasks may have revealed important differences in WS when compared to the mixed etiology groups. Indeed, Atkinson et al. (2003) observed that children showed weaknesses in the executive component of inhibition within the visuospatial domain. Further assessment of executive aspects of working memory in a larger sample is clearly warranted. Overall, research investigating aspects of executive function in WS is limited.

The present study set out to investigate a range of executive functioning skills in individuals with WS using standardized and validated neuropsychological tasks with known neural correlates taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB). These computerized tasks, performed using a touch-screen, have been extensively used with child and patient populations in assessment of executive function (e.g. Coghill, Rhodes, & Matthews, 2007; Curtis, Lindeke, Georgieff, & Nelson, 2002; Luciana & Nelson, 1998; Matthews, Coghill, & Rhodes, 2008; Rhodes et al., 2004, 2005; Rhodes, Coghill, & Matthews, 2006; Robbins et al., 1994) and have been shown to be differentially sensitive to dysfunction in several brain regions; including frontal, temporal and amygdalo-hippocampal regions (Owen et al., 1995). They are chosen on the basis of their well established neural correlates and suitability for use with children and individuals with neuro-developmental disorders. The current study will specifically assess individuals with WS on tasks of planning, working memory and attention set-shifting, known to be sensitive to frontal lobe functioning (Owen et al., 1995) from this battery.

The primary aim of the current research was to consolidate and further expand knowledge of executive functioning in individuals with WS. This avenue of exploration may not only inform us of components of the WS cognitive profile but may provide further insights into behaviours associated with the disorder. The research will explore a range of aspects of executive functioning using standardized, validated tasks with known neural correlates that have not previously been applied to this population. A secondary aim was to examine the specificity of an executive impairment in explaining the cognitive deficits observed in WS through inclusion of additional non-executive short-term memory tasks. One of these tasks was chosen on the basis of enabling further exploration of the

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