Brain and Cognition 78 (2012) 206–217

Contents lists available at SciVerse ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Attentional set-shifting in fragile X syndrome

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ARTICLE INFO

Article history:
Accepted 20 December 2011
Available online 18 January 2012

Keywords:
Fragile X syndrome
CANTAB
Attentional set-shifting
Reversal learning
IED

ABSTRACT

The ability to flexibly adapt to the changing demands of the environment is often reported as a core deficit in fragile X syndrome (FXS). However, the cognitive processes that determine this attentional set-shifting deficit remain elusive. The present study investigated attentional set-shifting ability in fragile X syndrome males with the well-validated intra/extra dimensional set-shifting paradigm (IED) which offers detailed assessment of rule learning, reversal learning, and attentional set-shifting ability within and between stimulus dimensions. A novel scoring method for IED stage errors was employed to interpret set-shifting failure in terms of repetitive decision-making, distraction to irrelevance, and set-maintenance failure. Performance of FXS males was compared to typically developing children matched on mental age, adults matched on chronological age, and individuals with Down syndrome matched on both mental and chronological age. Results revealed that a significant proportion of FXS males already failed prior to the intra-dimensional set-shift stage, whereas all control participants successfully completed the stages up to the crucial extra-dimensional set-shift. FXS males showed a specific weakness in reversal learning, which was characterized by repetitive decision-making during the reversal of newly acquired stimulus–response associations in the face of simple stimulus configurations. In contrast, when stimulus configurations became more complex, FXS males displayed increased distraction to irrelevant stimuli. These findings are interpreted in terms of the cognitive demands imposed by the stages of the IED in relation to the alleged neural deficits in FXS.

1. Introduction

Fragile X syndrome (FXS) is the most frequent inherited type of intellectual disability with a prevalence of 1:4000 in males and 1:8000 in females (Turner, Webb, Wake, & Robinson, 1996). FXS is most often caused by silencing of the fragile X mental retardation 1 (*FMR-1*) gene, which results in reduced or absent FMR-1 protein (FMRP) levels (Oostra & Chiurazzi, 2001; Verkerk et al., 1991). FMRP plays an important role in early brain development by regulating the translation of proteins important for cortical network formation (Greenough et al., 2001; Irwin et al., 2001; Oostra & Chiurazzi, 2001). FXS males are typically characterized by a general impairment in intellectual functioning (Dykens, Hodapp, & Leckman, 1987; Hagerman & Hagerman, 2002), as well as by pronounced attentional dysfunction (Cornish, Munir, & Cross, 2001; Cornish, Sudhalter, & Turk, 2004; Munir, Cornish, & Wilding, 2000b; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004, 2007; Scerif et al., 2005). In particular, FXS males show a weakness in the ability to flexibly respond to the rapidly changing demands of the environment (Munir et al., 2000b; Scerif et al., 2007; Wilding, Cornish, & Munir, 2002), also referred to as an impairment in cognitive flexibility or attentional set-shifting (Miller, 2000; Miller & Cohen, 2001). To date, the cognitive mechanisms that underlie this attentional set-shifting deficit in FXS remain poorly understood.

Attentional set-shifting is generally defined by two key aspects. The first aspect refers to the predisposition to selectively respond or attend to a particular stimulus dimension (e.g., the shape or color of a particular stimulus). This response bias has been established on the basis of reinforcing feedback, and is referred to as the stimulus–response 'set'. The second aspect consists of the disengagement of attention from the previously correct stimulus dimension to the newly correct stimulus dimension, indicating an attentional 'shift' (Owen, Roberts, Polkey, Sahakian, & Robbins, 1991). Studies on attention in FXS have demonstrated that switching attention between alternating target stimuli is characterized by a weakness in inhibiting a previously successful response (Cornish

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doi:10.1016/j.bandc.2011.12.008

et al., 2001; Munir et al., 2000b; Scerif et al., 2007; Wilding et al., 2002; Woodcock, Oliver, & Humphreys, 2009). For example, Cornish et al. (2001) compared attentional set-shifting ability in FXS with that of intellectually disabled (Down syndrome) and typically developing adults, using the Wisconsin Card Sorting Test (WCST), a widely used neuropsychological measure of attentional set-shifting. Results showed that FXS males committed significantly more perseverative errors than the other control groups. This perseverative behavior has been interpreted to suggest an inability to refrain from responding to a previously learned sorting rule when it is no longer appropriate (Cornish et al., 2001; Cornish et al., 2004), indicative of a primary deficit in *shifting* attentional set in FXS individuals.

An important critique of the WCST, however, is that this task only assesses *extra-dimensional set-shifting* (ED) and fails to assess *intra-dimensional set-shifting* (ID set-shifting) (Owen et al., 1991; Owen et al., 1993). ED set-shifting refers to shifting an attentional set *between* stimulus dimensions (e.g., switching stimulus–response mappings from the stimulus dimension 'color' to 'shape'), whereas ID set-shifting refers to the engagement of an attentional shift towards new stimuli within the same stimulus dimension (e.g., shape) (Owen et al., 1991). In addition, recent WCST investigations have found that besides perseverative behavior, impairments in attentional set-shifting can also reflect an underlying weakness in *maintaining* an attentional set (i.e., set-maintenance failure) (Barceló & Knight, 2002). In turn, this set-maintenance failure could interfere with continued responding to a previously reinforced stimulus (Barceló & Knight, 1999; Barceló & Knight, 2002). Based on the substantial literature reporting working-memory deficits in FXS (Baker et al., 2010; Munir, Cornish, & Wilding, 2000a; Ornstein et al., 2008; Van der Molen et al., 2010; Wilding et al., 2002), it could be hypothesized that, next to perseverative behavior, set-maintenance failure contributes to the observed attentional set-shifting weaknesses in FXS males.

In addition to these rule-based types of attentional set-switching, Ravizza and Carter (2008) recently proposed that attentional set-shifting also comprises perceptual switching, which entails switching visuospatial attention between sets of features of presented stimuli. For example, Kogan and colleagues (2009) investigated the more perceptual aspects of attentional set-shifting in males with FXS and Down syndrome (DS) employing a two-stimulus object discrimination-learning and reversal-learning paradigm. Results revealed that FXS males showed increased difficulty with learning the correct rule, as well as with reversal of the rule. In addition, the analysis of the committed error types in the object reversal stage showed that FXS males committed more random errors (i.e., performance on chance-level) than perseverative errors (Kogan et al., 2009). Interestingly, these findings indicate that attentional set-shifting abilities within a single-stimulus dimension show a different pattern of errors than across multiple stimulus-dimensions (Cornish, Scerif, & Karmiloff-Smith, 2007). Within this context, random errors suggested perceptual weaknesses (Ravizza & Carter, 2008), which subsequently interfere with efficient object discrimination, as well as impaired learning of stimulus-reward associations.

This notion of a perceptual impairment in FXS is in accordance with recent electrocortical findings, showing exaggerated sensory responses to stimulus perception (Castrén, Paakkonen, Tarkka, Ryynanen, & Partanen, 2003; Ferri et al., 1994; Rojas et al., 2001; Van der Molen et al., 2011a, 2011b) as well as neuroimaging findings reporting dysfunction in a widespread neural network including the frontostriatal brain circuitry (Barnea-Goraly et al., 2003; Haas et al., 2009; Hallahan et al., 2011; Hessl, Rivera, & Reiss, 2004; Hessl et al., 2009; Hoeft et al., 2007; Hoeft et al., 2008; Kwon et al., 2001; Lee et al., 2007; Lightbody & Reiss, 2009; Menon, Leroux, White, & Reiss, 2004; Reiss & Dant, 2003) and hippocampal formation (Hoeft et al., 2007; Lightbody & Reiss, 2009; Menon et al., 2004). These brain regions are frequently associated with stimulus discrimination and reversal learning, as well as attentional set-shifting (Kehagia, Murray, & Robbins, 2010; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000; Schoenbaum, Chiba, & Gallagher, 2000).

Based on the abovementioned findings of Cornish et al. (2001) and Kogan et al. (2009), weaknesses in attentional set-shifting ability in FXS males seem to be differentially expressed during discrimination learning and reversal (i.e., random search behavior), and extra-dimensional set-shifting (i.e., perseverative behavior). However, as different experimental paradigms were employed, caution is warranted when comparing results between these studies. Moreover, it remains elusive whether FXS males show attentional set-shifting deficits in ID set-shifting, and if so, what cognitive processes characterize these deficits. To address this question, a paradigm should be employed that could aid in investigating attentional set-shifting ability in the face of simple stimulus discrimination, as well as ID and ED set-shifting.

A paradigm widely used to investigate both ID and ED set-shifting, as well as simple discrimination learning and reversal, is the intra-extra dimensional set-shifting paradigm (IED). The IED is a subtest from the well validated Cambridge Neuropsychological Test Automated Battery (CANTAB) (De Luca et al., 2003; Lowe & Rabbitt, 1998; Robbins et al., 1994; Robbins et al., 1998), a neuropsychological assessment battery that has been successfully used in children from up to 4 years of age to adulthood (Luciana, 2003; Luciana & Nelson, 2002) and in a variety of neurodevelopmental disorders, including FXS (Van der Molen et al., 2010), Down syndrome (Visu-Petra, Benga, Tincas, & Miclea, 2007), and Williams syndrome (Rhodes, Riby, Matthews, & Coghill, 2011; Rhodes, Riby, Park, Fraser, & Campbell, 2010). The IED is administered via a computer touch screen and comprises nine stages with increasing difficulty. The first two stages involve basic stimulus discrimination within a single stimulus dimension (e.g., shape), rule acquisition and reversal, as well as learning to benefit from feedback. Stages 3-to-5 assess the ability to ignore irrelevant multidimensional compound stimuli, while selectively responding to the previously reinforced stimulus dimension (e.g., shape). Two critical shifts are introduced at stages six and eight, which assess the ability to adequately shift attentional set to new stimuli from the same stimulus dimension (e.g., shape) (intra-dimensional shift), and to shift attentional set to new stimuli from a different stimulus dimension (e.g., lines) (extra-dimensional shift) (Downes et al., 1989; Roberts, Robbins, & Everitt, 1988).

The present study sets out to investigate the underlying cognitive processes that give rise to the weak attentional set-shifting abilities in FXS males by using the IED paradigm. To this end, the IED was considered a suitable paradigm for the following reasons: (1) the IED is a computerized attentional set-shift paradigm with an appealing stimulus configuration, and excludes concurrent scoring procedures; (2) the IED incorporates abstract patterns instead of meaningful stimuli, thereby minimizing the confound of focusing on detail. Preoccupation with parts of objects is frequently observed for persons with FXS (Hagerman & Hagerman, 2002), and presenting abstract rather than meaningful stimuli could minimize attentional bias towards specific (parts of) stimuli; (3) the IED includes stages with varying levels of difficulty, or cognitive demand. This allows for isolating both lower-level (e.g., visual–perceptual abilities, sustained visual attention) as well as higher-level cognitive processes (e.g., switching attention within or between stimulus dimensions) (Bertone, Hanck, Kogan, Chaudhuri, & Cornish, 2010; Ravizza & Carter, 2008) which could differentially impact on attentional set-shifting abilities in FXS; (4) the IED is a validated measure of attentional set-shifting ability at both a behavioral (Lowe & Rabbitt, 1998; Wild, Howieson, Webbe, Seelye, & Kaye,