



Cognition and lobar morphology in full mutation boys with fragile X syndrome

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ABSTRACT

The aims of the present study are twofold: (1) to examine cortical morphology (CM) associated with alterations in cognition in fragile X syndrome (FXS); (2) to characterize the CM profile of FXS versus FXS with an autism diagnosis (FXS + Aut) as a preliminary attempt to further elucidate the behavioral distinctions between the two sub-groups. We used anatomical magnetic resonance imaging surface-based morphometry in 21 male children (FXS $N = 11$ and age [2.27–13.3] matched controls [C] $N = 10$). We found (1) increased whole hemispheric and lobar cortical volume, cortical thickness and cortical complexity bilaterally, yet insignificant changes in hemispheric surface area and gyrification index in FXS compared to C; (2) linear regression analyses revealed significant *negative* correlations between CM and cognition; (3) significant CM differences between FXS and FXS + Aut associated with their distinctive behavioral phenotypes. These findings are critical in understanding the neuropathophysiology of one of the most common intellectual deficiency syndromes associated with altered cognition as they provide human in vivo information about genetic control of CM and cognition.

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1. Introduction

FXS is caused by the hypermethylation-mediated silencing of the FMR1 gene (no mRNA) deficiency of the fragile X mental retardation protein (FMRP), and occurrence of the FXS phenotype. The deficiency in production of FMRP leads to the dysregulation of synaptic development and plasticity (Devys, Lutz, Rouyer, Bellocq, & Mandel, 1993; Hagerman, 2008; Turner, Webb, Wake, & Robinson, 1996). Hallmark features of Fmr1 silencing (no FMRP) are dysregulation of dendritic spine morphogenesis and abnormal synaptic plasticity, that are reproduced in the Fmr1 KO mouse model as the most distinctive anatomical abnormality in humans with FXS (Comery, Stamoudis, Irwin, & Greenough, 1996; Harlow et al., 2010; Kaufmann & Moser, 2000; McKinney, Grossman, Elisseou, & Greenough, 2005; Nimchinsky, Oberlander, & Svoboda, 2001). Interestingly, this mechanism is restricted to precise

developmental windows (i.e., early post-natal) (Galvez & Greenough, 2005). FMRP expression peaks during the early postnatal period of cortical synaptic refinement (Khandjian et al., 1995; Tessier & Broadie, 2008). Specifically, Khandjian et al. stated that the widespread expression of the FMR1 is controlled by different mechanisms implicated in cell growth and differentiation during the early normal post-natal developmental period (Khandjian et al., 1995). Therefore, FMRP may be strong candidate for a molecule mediating activity-dependent synaptic refinement across age. Such refinement includes architectural and functional remodeling of a circuit in response to the use of neuronal activity, which is necessary to sculpt the final synaptic map necessary for normal cortical structure and function (Bassell & Warren, 2008; Verkerk et al., 1991). As for molecular abnormalities, maybe the most important alteration in protein expression due to the deficiency of FMRP is exaggerated group 1 metabotropic glutamate receptor (mGluR5) dependent long term depression (LTD), a cellular substrate of learning and memory (Bear, 2005). In this context, the relationship between aberrant cognition and the brain in FXS has been well documented (Barnea-Goraly et al., 2003; Eliez, Blasey, Freund, Hastie, & Reiss, 2001; Fahim, Meguid, & Evans, 2009; Gothelf

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et al., 2008; Haas et al., 2009; Hoefft et al., 2008, 2010; Kates, Folley, Lanham, Capone, & Kaufmann, 2002; Lee et al., 2007; Lightbody & Reiss, 2009; Meguid et al., xxxx; Mostofsky et al., 1998; Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995; Reiss, Lee, & Freund, 1994; Wilson, Tregellas, Hagerman, Rogers, & Rojas, 2009). These seminal papers concluded that the FXS behavioral phenotype is associated with abnormal development of specific brain regions, which may mediate the effects of FMR1 gene mutations on the FXS cognitive and behavioral features. Most of the authors reported significantly increased size of the caudate nucleus and decreased size of the posterior cerebellar vermis, amygdala, superior temporal gyrus. In this context, the aforementioned papers mainly focused on measuring sub-cortical volumetric structures.

From a clinical perspective, the full-mutation of the FMR1 gene results in a severe FMRP deficit (Hagerman et al., 2009), which is associated with a wide range of physical and neurobehavioral problems (Freund, Reiss, & Abrams, 1993; Hagerman & Hagerman, 2002; Hatton et al., 2002; Reiss & Freund, 1992). In terms of the former, facial dysmorphia (i.e., long and narrow face) is most prominent in postpubertal males, whereas young boys may only have large heads or no dysmorphia at all (Lachiewicz, Dawson, & Spiridigliozzi, 2000). Other characteristic physical (i.e., macroorchidism) (Oostra & Halley, 1995) and neurological (i.e., hypotonia) features are also components of the FXS phenotype (Hagerman et al., 2009). As for the latter, in addition to cognitive abnormalities (i.e., in particular deficits in executive function, visuo-spatial skills, and visuo-motor coordination), language and learning impairments, the vast majority of individuals with FXS display a wide range of behavioral abnormalities (i.e., attention deficit hyperactivity disorder, anxiety, and autism) (Hagerman et al., 2009). In this context (i) FXS provides a privileged venue for investigating gene-brain-behavior relationship; (ii) FXS is considered a portal for understanding a variety of neurobehavioral disorders (Hagerman & Hagerman, 2002). Of relevance to the present paper, the incidence of autism in FXS has been reported to be 15–60% (Bailey, Palferman, Heavey, & Le Couteur, 1998; Bailey et al., 1993; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004; Reiss & Dant, 2003). In this context, FXS research attempted to compare between FXS only and FXS with an autism diagnosis (FXS + Aut) and demonstrated (i) two distinct but interrelated social behavior abnormalities, one linked to impaired cognitive processes (delayed socialization) and the second to disturbance in limbic circuits (avoidance) (Budimirovic et al., 2006); (ii) relative to FXS, children with FXS + Aut display further severe cognitive and behavioral abnormalities (Budimirovic et al., 2006; Hernandez et al., 2009; Kau, Reider, Payne, Meyer, & Freund, 2000; Sabaratnam, Murthy, Wijeratne, Buckingham, & Payne, 2003).

Based on all of the above, the aim of the present study is two-fold: (1) determine the association between cortical anatomy and aberrant cognition and behavior in full mutation children with FXS compared to age matched healthy controls without FXS (C); (2) characterize the cortical anatomical profile in full mutation FXS versus full mutation FXS + Aut as a preliminary attempt to further elucidate the neurobehavioral distinctions between the two FXS sub-groups. To that end we used the most comprehensive fully automated anatomic magnetic resonance imaging Cortical-surface Based Morphometry (SBM) approach. Here we focus on the cerebral cortical morphology since (i) FMRP is highly expressed within the cerebral cortex and has a major role in its final morphology (Mercaldo, Descalzi, & Zhuo, 2009; Nimchinsky et al., 2001); (ii) the cerebral cortex is mostly involved in the human higher cognitive functions implicated in FXS. A priori we predicted (i) increased cortical volume (CV), cortical surface area (SA), cortical thickness (Cth), gyrification index (GI) and cortical complexity (CC) in FXS versus C, due in part to decreased pruning and increased dendritic

density; (ii) the increase in cortical morphology is negatively correlated with the verbal reasoning, abstract visual reasoning, quantitative reasoning and short term memory implicating the role of FMR1 and FMRP in an altered synaptic plasticity and genesis in FXS children; (iii) significant behavioral and cortical morphological differences between full mutation FXS and FXS + Aut associated with their distinctive behavioral phenotypes and pointing to the possible role of an altered postnatal environment, since both groups share the same FMR1 full mutation.

2. Methods

2.1. Participants

A total of 21 male children were recruited through the ongoing Swiss Canadian Egyptian Neurodevelopmental Study (SCENS) and divided into full mutation males with FXS ($N=11$) and age matched healthy controls C ($N=10$) age range (2.27–13.3), mean age, SD (9.16 ± 3.08 , 8.25 ± 3.82 respectively). The FXS group was then divided into FXS ($N=6$) and FXS + Aut ($N=5$). Noteworthy 4 of the 5 participants with FXS + Aut showed epileptogenic activity during the regular EEG clinical assessment. All patients were seen and scanned at one site (the National Research Centre, Cairo, Egypt). There were significant group differences in IQ (social and cognitive), however, there were no other significant differences. All participants' parents or legal guardians underwent thorough consent and assent procedures before commencing study procedures according to the declaration of Helsinki. Subjects' characteristics Table 1.

2.2. Cognitive assessment

Subjects were cognitively assessed using the Stanford-Binet Intelligence Scale-IV (SB-IV) (Thorndike, Hagen, & Sattler, 1986). The Stanford-Binet is a well-standardized instrument, with excellent reliability and validity, used with children and adolescents, ages 2–23 years. Table 1.

2.3. Standardized Arabic language assessment

The test utilizes colored picture cards. Raw scores of the test were used to obtain language age scores for semantics, receptive syntactic language, expressive syntactic language, pragmatics, prosody and total language age (Kotby, El-Sady, & Hegazi, 2010). Table 1.

2.4. Social adaptive behavior

We used the Vineland Social Maturity Scale (VSMS), which is systematically used in clinical settings because it focuses on different daily aspects of social competence and adaptive behavior (Eggert, 1974) (Table 1).

2.5. Autistic features assessment

The FXS + Aut met the Diagnostic and Statistical Manual for Mental Disorders, 4th Edition (APA., 1994) criteria for autism by an expert psychiatrist, in addition to the Childhood Autism Rating Scale (CARS) (Perry & Freeman, 1996; Sponheim, 1996). Here we use a score <30 to categorize the children as non-autistic (Table 1).

2.6. Fragile X syndrome DNA

A standard amplification protocol for CGG repeat region within the first exon of human FMR1 gene was performed as described

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