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Examining the neural correlates of emergent equivalence relations in fragile X syndrome

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ABSTRACT

The neural mechanisms underlying the formation of stimulus equivalence relations are poorly understood, particularly in individuals with specific learning impairments. As part of a larger study, we used functional magnetic resonance imaging (fMRI) while participants with fragile X syndrome (FXS), and age- and IQ-matched controls with intellectual disability, were required to form new equivalence relations in the scanner. Following intensive training on matching fractions to pie charts (A=B relations) and pie charts to decimals (B=C relations) outside the scanner over a 2- day period, participants were tested on the *trained* (A=B, B=C) relations, as well as emergent *symmetry* (i.e., B=A and C=B) and *transitivity/equivalence* (i.e., A=C and C=A) relations inside the scanner. Eight participants with FXS (6 female, 2 male) and 10 controls, aged 10–23 years, were able to obtain at least 66.7% correct on the *trained* relations in the scanner and were included in the fMRI analyses. Across both groups, results showed that the emergence of *symmetry* relations was correlated with increased brain activation in the left inferior parietal lobule, left postcentral gyrus, and left insula, broadly supporting previous investigations of stimulus equivalence research in neurotypical populations. On the test of emergent *transitivity/equivalence* relations, activation was significantly greater in individuals with FXS compared with controls in the right middle temporal gyrus, left superior frontal gyrus and left precuneus. These data indicate that neural execution was significantly different in individuals with FXS than in age- and IQ-matched controls during stimulus equivalence formation. Further research concerning how gene–brain–behavior interactions may influence the emergence of stimulus equivalence in individuals with intellectual disabilities is needed.

1. Introduction

The ability to associate a stimulus presented in one modality (e.g., a number) to an equivalent stimulus presented in another modality (e.g., a picture of a quantity) is a fundamental component of learning a new skill. For example, when teaching number skills, an instructor may use three sets of corresponding stimuli: numerals (set A), pictures of quantities (set B), and number words (set C). Children may first be taught to associate the numbers to their corresponding picture quantities (A=B training) and then to associate the picture quantities to the number words (B=C training). Interestingly, it has been shown that once A=B and B=C relations are trained, new stimulus relations can *emerge* without explicit training, for example, C=A (the ability to associate word numbers to numerals) and C=B relations (the ability to associate word numbers to picture quantities) (Sidman, 1971; Sidman and Cresson, 1973). These emergent relations have been suggested to occur due to the properties of *symmetry* (if A=B, then B=A) and *transitivity* (if A=B and B=C, then A=C). Thus, if the child can demonstrate proficiency on symmetry (B=A, C=B), and transitivity (A=C) as well as C=A relations, the child can be considered to have demonstrated "stimulus equivalence" (Sidman, 1994). The stimulus equivalence paradigm therefore offers a useful rubric to gauge an individual's capacity to form new concepts. Hence, the ability to achieve stimulus equivalence could be an important correlate or predictor of more advanced cognitive capacity.

Over the past few decades, several theories have been advanced concerning the potential behavioral and/or neuroanatomical mechanisms that may be involved in the emergence of stimulus equivalence relations. To test these theories, neuroimaging studies conducted with neurotypical individuals have investigated the neural correlates of emergent stimulus equivalence relations following training on arbitrary sets of pictures (Dickins et al.,

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2001), colored ellipsoid shapes (Heckers et al., 2004), sets of symbols (Schlund et al., 2007) and consonant–vowel–consonant triplets (Schlund et al., 2008). In each case, individuals were trained on these associations outside the scanner and were then tested for the emergence of new stimulus relations inside the scanner. Increased activation during tests of symmetry and/or transitivity/equivalence relations has been detected in the dorsolateral prefrontal cortex (DLPFC), posterior parietal regions, the insular cortex and the left caudate nucleus (Dickins et al., 2001), the right anterior hippocampus (Heckers et al., 2004), the right and left inferior frontal gyrus (dorsolateral), the inferior parietal lobule (Schlund et al., 2007), and the parahippocampal gyrus (Schlund et al., 2008). Overall, the results from neuroimaging studies of stimulus equivalence provide valuable, but mixed, information about the neural architecture involved in the emergence of derived stimulus relations in healthy adults.

Fragile X syndrome (FXS) – the most common known form of inherited intellectual disability (Crawford et al., 1999) – may provide a useful model for understanding the pathogenesis of learning impairments commonly shown by children with intellectual disabilities. FXS is caused by mutations to a single gene (*FMR1*), located on the long arm of the X chromosome at Xq27.3 (Verkerk et al., 1991) in which excessive methylation in the promoter region of the gene compromises production of the Fragile X Mental Retardation Protein (FMRP), the protein product of the gene. FMRP is thought to actively participate in the translational machinery that converts messenger RNA into protein (Verkerk et al., 1991; Brown et al., 2001), and low levels of FMRP therefore contribute to aberrant neuronal development and brain function. FXS is also a risk factor for autism spectrum disorder (ASD), accounting for up to 6% of cases of ASD (Freund and Reiss, 1991; Fombonne, 2005). A distinct cognitive profile that includes weaknesses in visual spatial processing, writing skills, spatial memory and mathematical reasoning, but strengths in verbal labeling and comprehension, has been demonstrated in both boys and girls with FXS (Freund and Reiss, 1991; Roberts et al., 2005; Schneider et al., 2009).

Mathematical reasoning impairments in FXS have been reported to begin in early childhood, with toddlers demonstrating significant deficits in processing ordinal numerical sequences when compared to typically developing toddlers (Owen et al., 2013). Problems with counting and number sense have also been reported in females with FXS during late elementary school (Murphy and Mazzocco, 2008a). For example, Murphy and Mazzocco (2008b) required high-functioning girls with FXS to rank-order sets of 10 fractions, pie charts, and decimals. They found that while girls with FXS were able to rank-order the set of pie charts at grade-level performance, they evidenced impaired performance when attempting to rank-order the fractions, suggesting that girls with FXS demonstrate a relative strength in rote memory of numerical operations, but an impaired ability to understand numerical concepts and applied mathematics. In a functional magnetic resonance imaging (fMRI) study of mathematical reasoning skills, Rivera and colleagues (Rivera et al., 2002) found that when female subjects with FXS, aged 10–23 years, were given subtraction and addition tasks to complete in the scanner, activation in the angular gyrus and bilateral prefrontal regions was significantly increased relative to typically developing controls. These authors suggested that individuals with FXS were either employing compensatory strategies or required greater neural resources to complete the task compared with controls.

In a recent study conducted by our group, we examined whether stimulus equivalence relations would emerge in individuals with FXS following training on matching fractions to pie chart and pie charts to decimals (Hammond et al., 2012). Participants comprised 11 individuals with FXS, aged 10–23 years, and 11 age- and IQ-matched controls who were taught to match these relations (A=B and B=C training) over a 2-day period. They were then tested for the emergence of symmetry (B=A, C=B) and transitivity/equivalence (A=C, C=A) relations. Results showed that performance improvements on the *symmetry* test were significantly correlated with performance improvements on the *transitivity/equivalence* test in controls, but not in individuals with FXS, suggesting that individuals with FXS demonstrated an impairment in forming equivalence classes. Further investigation of the neural components involved in the emergence of stimulus equivalence could provide important information about how the brain makes logical inferences (generalizability) about stimulus relations. However, to our knowledge, no studies have assessed the underlying neural mechanisms involved in the emergence of equivalence relations in children diagnosed with disorders associated with intellectual impairment such as FXS.

Additional information concerning the neurobiological processes underlying the emergence of stimulus equivalence in FXS may therefore add to our understanding of how gene–brain–behavior interactions contribute to learning problems in this unique genetic disorder associated with intellectual disabilities. In the present study, we examined the underlying neural mechanisms involved in the emergence of stimulus equivalence relations in individuals with FXS compared to age- and IQ-matched individuals. Given previous research, we predicted that activation would be significantly greater in individuals with FXS than in age- and IQ-matched controls during tests of emergent equivalence relations.

2. Methods

2.1. Participants

Participants with FXS were recruited nationally through postings on parent support group websites, the National Fragile X Foundation, and our lab's database. Control participants were recruited locally within a 50-mile radius from the Stanford University campus through online parent support groups and agencies serving individuals with developmental disabilities. The care providers of potential participants completed a phone screen and demographic questionnaire in order to determine whether their child/ward met initial inclusion criteria. The inclusion criteria were as follows: age between 10 and 23 years old, IQ > 50, ability to travel to Stanford, and the absence of possible MRI contraindications such as orthodontia or other metallic materials in the body. Eligible families were subsequently mailed a brief paper-and-pencil screening test containing fraction, pie chart, and decimal equivalencies using the stimuli shown in Fig. 1 to ensure that participants were unfamiliar with these stimuli before entering the study. Chance responding on this test was 33.3%, and individuals who obtained less than 50% correct on the test were invited to travel to Stanford for the study.

All participants were recruited as part of a larger study evaluating a brief 2-day intensive behavioral intervention for children with FXS (see Hammond et al., 2012; Hall et al., 2014). Participants with FXS had a confirmed genetic diagnosis (i.e., > 200 CGG repeats on the FMR1 gene and evidence of aberrant methylation) and all control participants either had a current clinical diagnosis or qualified for special education services under a diagnosis of developmental delay. None of the control participants had a known genetic basis for developmental delay or a history of seizures and/or premature birth. All participants demonstrated the ability to communicate verbally and were right-handed. Inclusion criteria were satisfied by 20 individuals with FXS and 20 controls. They received an 8-min resting-state scan (see Hall et al., 2013) before the functional scan. For the purpose of the present study,