

# Do women with fragile X syndrome have problems in switching attention: Preliminary findings from ERP and fMRI

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## Abstract

Fragile X syndrome (FXS) is a neurodevelopmental disorder that represents the most common known cause of developmental delay. Recent neuropsychological findings indicate that females with FXS present with a specific pattern of cognitive deficits and that these difficulties primarily involve skills requiring executive control. The present study is the first to examine the extent to which neural activity of females with FXS can be observed on a task that specifically taps two core deficits, namely switching and response inhibition. Brain activity was measured using both event-related electrical potentials (ERPs) and event-related functional MRI (fMRI) neuroimaging in separate studies using the same cognitive paradigm. Compared to controls, females with FXS were significantly slower and made more errors on trials that required an immediate response (Go) to stimulus onset but were comparable on trials that required a delayed response (Wait) to stimulus onset. At the brain level, several areas showed significantly greater activation for females with FXS compared with controls, including the cingulate cortex and left and right ventral prefrontal areas. In contrast, no areas were found to show significantly greater activation for controls compared with females with FXS.

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## 1. Introduction

Over the last decade there have been unparalleled advances in the application of molecular genetic analysis to the study of many medical disorders, including genetic disorders and disorders of brain function. Alongside this development there has been a substantial growth in the number of studies attempting to identify specific patterns of cognitive deficits that associate with a given genetic disorder, in essence to link genotype to phenotype. The rapid growth in neuroimaging techniques has potential to provide further delineation of this relationship by providing opportunities of studying how problems in brain structure might influence cognitive abilities and behaviour.

A neurodevelopmental disorder that has received much attention in recent years is FXS, not only because

its point of origin is the X chromosome but also because the syndrome represents a well recognised cause of learning disability and developmental delay in boys and to a lesser extent girls. The prevalence of FXS, however, has not been firmly established and figures vary from 1 in 1000, an older estimate, to more recent consensus of 1 in 4000 males.

The clinical manifestations of the disorder have been recognised since 1943 and the world literature is now extensive. A key aim of recent research, however, has been to elucidate more precisely the relationship between the genetic and molecular mechanisms in brain development and function in FXS. At a *molecular* level, it is now firmly established that the FMR1 gene is the only gene involved in the pathogenesis of the syndrome. It is the silencing of this gene which leads to a lack of messenger RNA (mRNA) and a lack of subsequent FMR-1 protein (FMRP) synthesis. Understanding how the absence of FMRP induces the cognitive phenotype has been extensively studied in the past several years.

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We are now much closer to understanding the physiological functions of FMRP and its potentially critical role in early brain development and subsequent lateralisation of function. There is certainly accumulating evidence to indicate a correlation between increased FMRP levels and a greater phenotypic effect (Tassone, Hagerman, Taylor, Mills, & Harris, 2000). When viewed at the *cognitive* level, accumulating evidence supports the conclusion that the fundamental deficit in FXS lies in poor attentional control of input and output information sequences (Munir, Cornish, & Wilding, 2000; Wilding, Cornish, & Munir, 2002). It is suggested that this control requires a balance of excitation and inhibition in various ways, to enable switching from one attentional focus to another or from one emitted response to the next response in a sequence. The nature and severity of this deficit appears to be specific to the condition, affecting a range of higher-level functions (e.g., speech, memory). One possibility is that damage to crucial neural pathways connecting areas involved in executive control processes could have resulted in many of the deficits witnessed in FXS. This might also explain why some cognitive skills (i.e., face processing, emotion recognition, and vocabulary) which are not so dependent upon executive control, are not as impaired as others.

Emerging evidence by Reiss and colleagues (e.g., Tamm, Menon, Johnston, Hessel, & Reiss, 2002) have provided the first published demonstration that fMRI can be sufficiently sensitive to measure the role of the FMR1 gene expression and neural activity. In a sample of females with FXS, they report significantly greater brain activation than controls in specific regions of the prefrontal cortex (anterior) and reduced brain activation in the left orbitofrontal gyrus during the performance on a Stroop interference task.

In the present study, we sought to extend these findings by investigating the extent to which we could observe differences in neural activity on a task that tapped two specific cognitive deficits in FXS—switching and response-inhibition (see Wilding et al., 2002). In the first published study to date, FXS participants' brain activity was measured using both event-related electrical potentials (ERPs) and event-related functional MRI (fMRI) neuroimaging in separate studies using the same cognitive paradigm. Our hypothesis was that by comparing neural activity on a task involving deficits known to be associated with FXS we will determine those areas associated with the differences between FXS and normals in performance on such tasks.

## 2. Methodology

Three women with the FMR1 full mutation (aged 19, 22, and 32 years, respectively) participated in the study.

The diagnosis of FXS was confirmed by DNA analysis. All participants performed within the mild-normal range of intellectual ability as measured by the Wechsler Intelligence Scale for Adults (WAIS III) with no reported neurological problems (i.e., epilepsy) or alcohol/substance abuse.

In the ERP study, eighteen healthy control participants also took part in the study (aged between 18 and 36 years (mean  $\pm$  SD: 24.9  $\pm$  5.73 years)) and in the MRI study, 12 healthy control participants (aged between 19 and 36 years (mean  $\pm$  SD: 25.9  $\pm$  5.6 years)) took part.

## 3. Behavioural task

Participants performed the same task switching task during both the fMRI and ERP phases of the study. In the fMRI phase stimuli were presented at a rate of one every 8000 ms, while in the ERP phase a variable interval of 1500–2000 ms between stimuli was used. The stimuli consisted of colored left or right-pointing arrows presented for 1000 ms. Participants were instructed to respond to each arrow by pressing a right or left key depending on the arrow's direction. If the arrow was green (Go task) participants were required to respond immediately. If the arrow were red (Wait task) participants responded at stimulus offset. The stimuli were presented in a predictable fixed predictable order. Trials were classified according to 5 event types: Go-Switch stimuli, Go-Repetition, Wait-Switch, Wait-Repetition, and Errors. Go errors were defined as responses made more than 200 ms after stimulus offset. Wait errors were defined as responses made more than 200 ms before stimulus offset.

## 4. fMRI Study

### 4.1. Image acquisition

Imaging was performed at the University of Nottingham (UK) Magnetic Resonance Center using a 3 T magnet (Oxford Magnet Technology, Whitney, UK), custom-built head gradient set, and high-performance head coil (Nova Medical, Wakefield, USA).

### 4.2. Data analysis

Image preprocessing and statistical analysis was performed using SPM99 (Friston et al., 1995). Image data for each participant were analysed individually at the first level using the general linear model as implemented in SPM99.

For control participants, contrast images for each event-type were entered into a second-level random-effects analysis using single-sample *t* tests. For FXS

participants, a separate first-level fixed-effects model including all 3 subjects with the same covariates per subject as above was calculated. Statistical parametric maps for each event-type were then obtained using conjunction analyses in order to maintain high statistical power. For all group analyses, regions showing a peak activation of  $Z > 3.89$ ,  $P_{\text{uncorrected}} < .00005$  were considered to be significant.

## 5. Results

### 5.1. Task performance

Mean reaction times and proportions of Go and Wait errors for FXS and control participants are shown in Fig. 1. Compared with controls, FXS participants showed significantly slower reaction times for Go trials overall (Mann–Whitney:  $Z = 2.60$ ,  $P < .01$ ), but no significant difference for Wait trials (Mann–Whitney:  $Z = 1.59$ ,  $P > .05$ ). The FXS group showed an equiva-

lent reaction time cost to the control group (Mann–Whitney:  $Z = 1.59$ ,  $P > .05$ ) in switching from delayed to immediate responses (Go-Switch trials) compared with the repetition of immediate responses (Go-Repetition trials; switch costs of 75, 88, and 94 ms, respectively, for each of the FXS participants).

Control participants made very few errors on Go trials (only one subject made two of these errors on Go trials), made significantly more errors responding too early on Wait trials (Wilcoxon Signed Ranks;  $Z = 2.86$ ,  $P < .01$ ), and significantly more errors when switching to Wait trials compared with Wait repetition trials (Wilcoxon Signed Ranks;  $Z = 2.23$ ,  $P < .05$ ). This switch cost in errors on Wait trials mirrored the switch cost in reaction times found for Go Trials.

In contrast, FXS group compared with controls showed significantly more errors on Go trials (Mann–Whitney:  $Z = 2.37$ ,  $P < .05$ ) and a trend towards less errors on Wait trials (Mann–Whitney:  $Z = 1.91$ ,  $P = .064$ ). As with control, FXS participants showed a switch cost in errors on Wait trials which was not

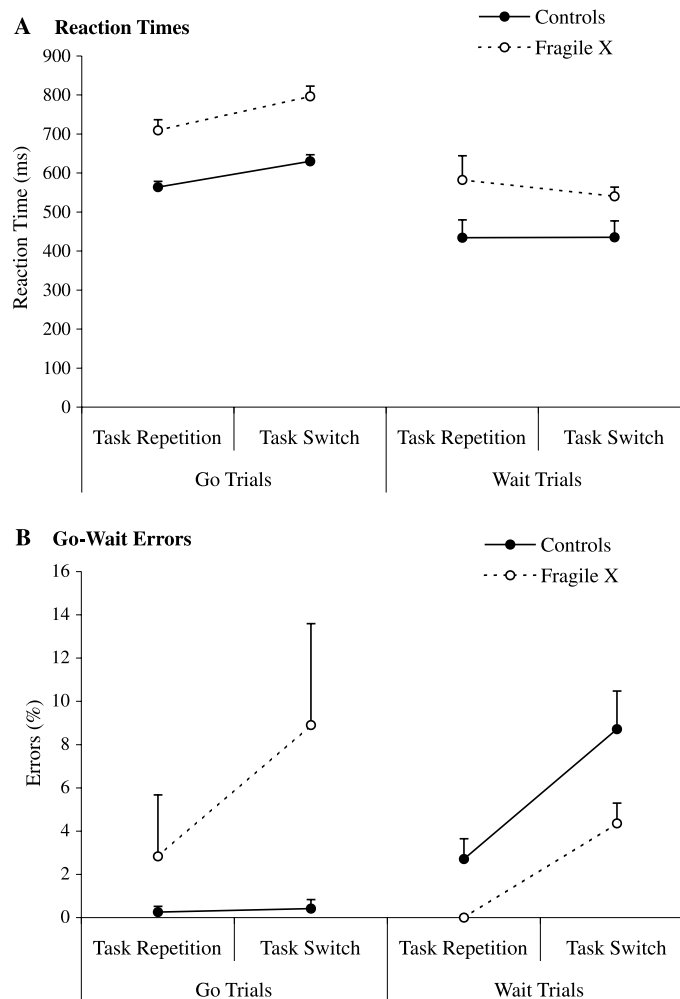


Fig. 1. (A) Reaction times and (B) proportions of Go-Wait errors (means and standard errors) for controls (solid line) and fragile X subjects (dotted lines).

significantly different to that of controls (Mann–Whitney:  $Z = .73$ ,  $P > .05$ ), but also showed a switch cost in errors on Go trials which was significantly different from controls (Mann–Whitney:  $Z = 2.37$ ,  $P < .05$ ).

### 5.2. Functional imaging results

For the control group, highly consistent activation across all conditions (Wait/Go and Switch/Repetition trials) was found in a network of areas involving the anterior cingulate, left lateral premotor cortex, bilateral primary motor cortex, right cerebellum, right ventral prefrontal cortex, and regions of both right and left inferior parietal cortex. Significant activation was also found in the presupplementary motor area and bilaterally within the thalamus for Wait Switch trials.

The FXS group showed highly consistent activation across all conditions within right lateral premotor cortex, bilateral ventral prefrontal cortex, and regions of the left inferior parietal cortex. Unlike controls, the FXS group showed significant activation within the anterior cingulate only on Wait Switch trials in a region more caudal than that found for controls, bordering on cingulate and presupplementary motor areas. Activation within the right ventral prefrontal cortex was in the identical location to that found in controls, bordering on the inferior frontal insula cortex; however, FXS participants also showed strong activation in the equivalent region of left ventral prefrontal cortex for all conditions, as well as significant activation within right middle prefrontal and left dorsal prefrontal areas for Wait Switch trials.

In the inferior parietal cortex, FXS participants showed activation bilaterally in the region of the supramarginal gyrus (although on the right side this was significant only for Wait-Switch trials). The location of this activity was consistent with the left side inferior parietal activation found for control subjects. The FXS group also showed significant activation across all conditions more ventrally within the left inferior parietal lobe, close to the intraparietal sulcus. This activation was in the equivalent contralateral region to that found in the right inferior parietal cortex in controls.

Several areas showed significantly greater activation for FXS participants compared with controls, as assessed by nonparametric permutation tests. These included the cingulate cortex and left and right ventral prefrontal areas. No areas were found to show significantly greater activation for control participants compared with FXS participants in any condition.

## 6. ERP study

Participants EEG was measured using a 128-channel geodesic sensor net.

### 6.1. Task performance

These results largely replicated the effects found in the fMRI phase, except that both the control and FXS group made less errors on WAIT trials. For both groups errors on WAIT trials were less than 4%. Compared with controls, fragile X subjects responded more slowly both on GO trials ( $Z = 2.31$ ,  $P = .017$ ) and on WAIT trials ( $Z = 2.51$ ,  $P = .006$ ). The RT cost of switching in the Go task did not differ significantly from those of controls ( $Z = .70$ ,  $P = .53$ ). Fragile X subjects did not differ significantly from controls in terms of either Go or Wait errors (Go trials,  $Z = 1.69$ ,  $P = .22$ ; Wait trials,  $Z = .97$ ,  $P = .36$ ).

### 6.2. ERP data analysis

The N2 ERP was examined at the midline frontal scalp site (Fz; sensor 11 in the EGI system) collapsed across the time window 300–340 ms (early N2) and 360–400 ms (late N2).

### 6.3. ERP results

For control subjects there was a significant increase in negativity for WAIT compared with GO switch trials on during the early N2 time window. The FXS groups' early N2 mean amplitudes fell within the range of the control participants'. During the late N2 time window for controls there was a significant increased negativity for switch compared with WAIT repetition trials. The FXS group show a similar pattern on WAIT trials to the controls. However for switch GO trials their mean amplitudes were at the more negative end of the controls' distribution.

## 7. Discussion

The present study sought to examine the extent we could observe neural differences on a task designed to tap two core cognitive deficits reported in individuals with FXS—namely set-switching and response inhibition (Cornish, Munir, & Cross, 2001; Wilding et al., 2002). At a behavioural level, the ERP and fMRI findings indicate that the FXS group had significantly slower response time on all “GO” trials. This was the case even when the FXS group performed a “pure” block of GO trials which did not require any switching between tasks or response suppression. In the fMRI study the FXS group made significantly more Go errors than the control group. An examination of Fig. 1 shows that these errors were mainly on switch trials. This is suggestive of a problem in switching from a task involving task suppression.

Interestingly, on the “wait” trials, the number of errors is comparable to the controls indicating that the

FXS group are responding in much the same way to the “wait” trials as the normal comparison group. Though rather slower than the control group, they cut their times compared with “go” trials by almost exactly the same amount, indicating that they are managing to anticipate the disappearance of the stimulus—in other words, they can inhibit a prepotent response. Although this finding was unexpected it is possible that the task employed in the present study was not sufficiently complex to elicit a more robust behavioural deficit. However, the similar pattern of reaction times and errors across both ERP and fMRI is encouraging and suggests that the task is tapping stable phenomena. Future studies need to develop tasks that require a greater attentional load between trials for example by making the sequence unpredictable. Another possibility would be to reduce inter-trial intervals. Crucially, further exploration is needed to deconstruct what the critical features of a task are which make switching difficult in FXS.

One further possibility is that even though response inhibition appears relatively normal in the FXS group it might well be, for example, that the cognitive processes by which the FXS individuals have reached this behavioural outcome are very different from those of the normal controls. Specifically, there is some indication from brain recordings that brain activity is less differentiated in the FXS group for the two types of trials (Go and Wait) suggesting of a weakness in inhibiting the activation of the wrong type of response in each case. This is reflected in errors for Go but not for Wait where the normally slow responding of the FXS participants would actually benefit, reducing the actual occurrence of errors on the Wait trials. Analysis at the *brain* level suggests, as indicated by the fMRI findings, that even on

non-switch Go trials the FXS group are activating response suppression areas (bilateral ventral prefrontal) and on non-switch Wait trials response conflict areas (anterior cingulate). Thus, proficient performance by the FXS group may be achieved, despite basic deficits, by developing non-standard strategies and procedures to compensate for the deficits.

Undoubtedly, the approach to understanding atypical development at its various levels: the genetic and brain levels, the cognitive level and the behavioural level holds out an exciting promise for future research in FXS and other developmental disorders.

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