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Contrast, motion, perceptual integration, and neurocognition in schizophrenia: The role of fragile-X related mechanisms

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ABSTRACT

Recent studies demonstrated a reduced expression of Fragile X Mental Retardation Protein (FMRP), an RNA binding protein and translation regulator, in the brain and peripheral lymphocytes of patients with schizophrenia. Low FMRP levels may be related to impaired neurodevelopmental processes and synaptic plasticity. Here, we studied the relationship between peripheral FMRP level, visual perception (contrast sensitivity, perceptual integration, motion/form perception), and neuropsychological functions in schizophrenia as measured with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Results revealed that patients with schizophrenia displayed lower FMRP levels in peripheral lymphocytes as compared to control individuals. We found significant correlations between FMRP levels and contrast sensitivity at low spatial and high temporal frequencies, perceptual integration, and motion perception. The relationship between FMRP level and neuropsychological functions was less pronounced than that seen in the case of visual perception, with the greatest effect for RBANS attention. FMRP level was not related to contrast sensitivity at high spatial and low temporal frequencies and form perception. This pattern of data is reminiscent to that observed in patients with Fragile X Syndrome (FXS). These results suggest that FMRP may be implicated in the pathogenesis of schizophrenia, possibly via the regulation of neurodevelopment, plasticity, GABA-ergic, and glutamatergic neurotransmission.

1. Introduction

Research during the past decades revealed a characteristic and significant perceptual and neurocognitive dysfunction in schizophrenia. Extensive evidence suggests that deficits in executive functions, attention, memory, social cognition, and visual perception markedly contribute to the psychosocial outcome of the illness (Roder & Medalia, 2010; Sharma & Harvey, 2000). However, the neurobiological mechanisms of neurocognitive and perceptual dysfunctions have not been clarified, and there is no satisfying treatment strategy.

Recently, we found preliminary evidence that molecular mechanisms implicated in intellectual and developmental disabilities may be related to cognition in schizophrenia, with a special reference to Fragile X Syndrome (FXS) (Kovács et al., 2013). In FXS, the Fragile X Mental Retardation Protein (FMRP) is absent because of an extensive nucleotide triplet expansion, leading to neurodevelopmental and cognitive anomalies. FMRP can be detected in the soma and dendritic spines of neurons serving as a translational suppressor for genes encoding proteins essential for synaptic plasticity (Bear et al., 2008; O'Donnell & Warren, 2002; Rousseau et al., 2011). There is increasing evidence that altered expression of FMRP and its mRNA characterizes various disorders, including premature ovarian insufficiency, fragile X-associated tremor/ataxia syndrome, autism, mood disorders, and schizophrenia (Bourgeois et al., 2009; Fatemi et al., 2010; Fatemi & Folsom, 2011; Hagerman et al., 2010). Fatemi et al. (2010) found reduced FMRP expression in the lateral cerebellum of patients with schizophrenia and mood disorders. We confirmed these findings in peripheral lymphocytes of schizophrenia patients (Kovács et al., 2013). In addition, low FMRP expression predicted earlier illness onset and decreased IQ, which may indicate the key role of FMRP in neurodevelopment and cognition (Kovács et al., 2013).

In the present study, we aimed to extend these findings by investigating the cognitive and perceptual correlates of reduced peripheral FMRP in schizophrenia. We assessed neuropsychological functions and different aspects of visual perception. First, we examined immediate and delayed memory, attention, language, and visuospatial functions using the Repeatable Battery for the Assessment of Neuropsychological

Abbreviations: ANOVA, analysis of variance; FMRP, fragile X mental retardation protein; FXS, fragile x syndrome; GABA, gamma-aminobutyric acid; HSD, honestly significant difference; M, magnocellular; P, parvocellular; PANSS, Positive and Negative Syndrome Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SF, spatial frequency; TF, temporal frequency.

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Status (RBANS) (Randolph et al., 1998). Second, we assessed multiple levels of visual perception as delineated in the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project (Butler et al., 2008, 2012). Specifically, we studied visual contrast sensitivity, perceptual integration, and motion/form perception. Our previous results indicated that in healthy volunteers contrast sensitivity for low spatial and high temporal frequency gratings (rough resolution and dynamic changes of stimuli) and motion perception were associated with FMRP expression, whereas contrast sensitivity for high spatial frequency/static gratings (fine resolution of stimuli) and form perception were not (Kéri & Benedek, 2011, 2012) (Fig. 1). This is consistent with the eminent role of FMRP in the development of the magnocellular retino–geniculo–striatal visual pathways (Kogan et al., 2004; Zangenehpour et al., 2009). Therefore, we hypothesized that reduced FMRP expression would be associated with an impaired processing of low spatial/high temporal frequency gratings and coherently moving patterns in patients with schizophrenia. We also investigated, for the first time, the possible relationship between FMRP expression and perceptual integration.

2. Materials and methods

2.1. Participants

We enrolled 50 patients with schizophrenia and 50 healthy controls with a negative family history for psychotic disorders at the National Institute of Psychiatry and Addictology, Budapest and Bács-Kiskun County Hospital, Kecskemét, Hungary. None of the patients was included in the Kovács et al.'s (2013) study. The diagnosis was based on structured clinical interviews (First et al., 1996). We had access to the complete medical record of the patients. Patients with schizophrenia received antipsychotic medications at the time of testing (risperidone, olanzapine, quetiapine, haloperidol, aripiprazole, zuclopenthixol, amisulpride). We converted the daily dose of antipsychotics to chlorpromazine-equivalent units (Woods, 2003). All patients received the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). All participants had normal or corrected-to-normal visual acuity. The clinical and demographic data are depicted in Table 1. The study was done in accordance with the Declaration of Helsinki. We obtained written informed consent from each participant. The study was approved by the institutional ethics committee.

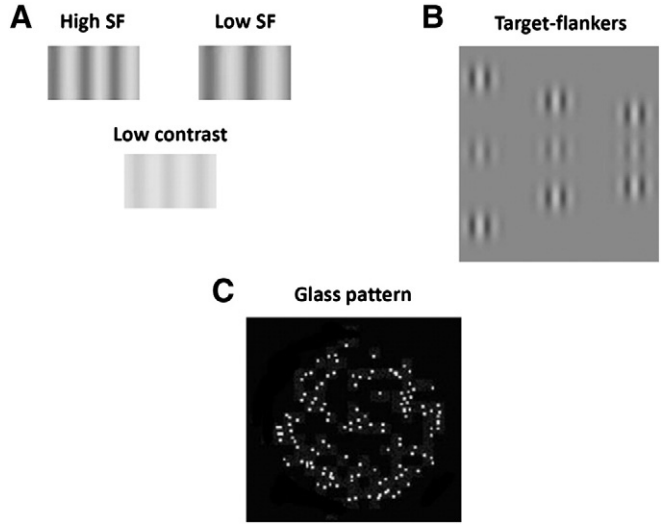

Fig. 1. Stimuli used in psychophysical tests of visual perception. A. Sinusoidal luminance-contrast gratings with different spatial frequencies and contrasts. Gratings were modulated using counterphase flickering (temporal frequency, Hz). B. Gabor patches with different target–flanker distances (target: low-contrast central patch; flankers: high-contrast lateral patches). C. Glass patterns used for form and motion coherence measurements.

Table 1
Demographic and clinical characteristics of the participants.

	Schizophrenia (n = 50)	Control (n = 50)
Male/female	31/19	31/19
Age (years)	42.7 (9.2)	44.1 (9.0)
Age of illness onset (years)	23.6 (6.6)	–
PANSS positive	21.2 (6.4)	–
PANSS negative	19.8 (7.5)	–
PANSS general	49.7 (10.0)	–
Antipsychotics (chlorpromazine-equivalent, mg/day)	455.0 (185.4)	–

Data are mean (standard deviation). PANSS — Positive and Negative Syndrome Scale.

2.2. Neuropsychological assessment

We used the RBANS comprising 12 tests classified according to five index scores (Gold et al., 1999; Juhász et al., 2003; Randolph et al., 1998). Each index score is standardized (normal mean: 100, $SD = 15$ based on a normative study group of 200 healthy Hungarian volunteers, 20–80 years of age). The RBANS index domains and tests are as follows: (1) immediate memory (word list learning [10 words repeated in four trials], story recall in two trials); (2) language (confrontation naming of 10 pictures, category fluency); (3) visuospatial functions (figure copy, line orientation); (4) attention (digit span, digit-symbol coding); and (5) delayed memory (delayed recall of the story, complex figure, and word list, recognition of the word list). The RBANS has two psychometrically matched forms. In this study, we used version "A".

2.3. Visual perception

2.3.1. Stimulus presentation and response collection

We used a VP2765-LED-27″ monitor (ViewSonic, Walnut, CA; refresh rate: 60 Hz, resolution: 1920 × 1080 pixel; viewing distance: 50 cm; output luminance: 65 cd/m^2; background luminance: 5 cd/m^2) controlled by a Dell XPS workstation. All experimental procedures have been extensively described in previous publications, and here only brief descriptions are provided with references to methodological details.

2.3.2. Contrast sensitivity

We undertook these measurements to evaluate early-stage, low-level visual information processing, including pathways stemming from the retina and projecting to the lateral geniculate nucleus and then to the primary visual cortex. We used two types of sinusoidal luminance-contrast gratings: stimuli with low spatial frequency (SF) and high temporal frequency (TF) (0.3 cycle/degree and 18 Hz, respectively) and stimuli with high SF and low TF (10 cycles/degree and 1 Hz, respectively) (Fig. 1a). Participants gave oral responses indicating whether they saw the grating or not, and the experimenter entered the responses on the keyboard. If the participant was not able to detect the grating, the contrast was increased and vice versa (reversals) using a staircase procedure. The contrast threshold was the average of the last 12 reversals. Contrast sensitivity was the inverse of contrast threshold (Halász et al., 2013; Kéri & Benedek, 2009; Kogan et al., 2004).

2.3.3. Perceptual integration

This procedure tests how early visual areas are able to bind and assemble basic perceptual details to create contours (Kéri et al., 2005a,b; Must et al., 2004; Polat & Sagi, 1993). Stimuli were Gabor patches (SF: 6.7 cycles/degree). There was a central Gabor patch (target) and two high-contrast flankers (Fig. 1b). The distance between target and flankers was 1 or 3λ (λ: reciprocal of SF). Trials without flankers were also presented. We measured contrast threshold for the target Gabor patch using a staircase procedure and determined threshold

changes at each target-to-flanker distance relative to targets presented without flankers (Kéri et al., 2005a,b; Must et al., 2004; Polat & Sagi, 1993).

2.3.4. Motion and form perception

We used Glass pattern stimuli to determine motion and form coherence threshold (Glass, 1969; Kéri & Benedek, 2012; McKendrick et al., 2006) (Fig. 1c). During the measurement of form coherence threshold, coherent dots were replaced with randomly positioned noise dots (e.g., 50% coherence means that half of the dots were positioned concentrically, whereas the other half of the dots was placed randomly). During the measurement of motion coherence threshold, a fraction of randomly chosen dots moved in the same signal direction, while all other dots moved in random (9 min arc/frame, 3°/s). We measured coherence thresholds (% of concentrically positioned and coherently moving dots necessary for stimulus detection) using a staircase procedure (Kéri & Benedek, 2012; McKendrick et al., 2006).

2.4. Measurement of FMRP

For the quantitative evaluation of FMRP level from peripheral blood lymphocytes, we followed the protocol of Iwahashi et al. (2009), an enzyme-linked immunosorbent assay (ELISA) method, which provides an accurate and standardized measurement of FMRP.

2.5. Statistical analysis

We used STATISTICA 11 (StatSoft, Inc., Tulsa) and Prism 6 (GraphPad, Inc., La Jolla) for data analysis. After the analysis of data distribution with Kolmogorov–Smirnov tests, we used analyses of variance (ANOVAs) followed by Tukey Honestly Significant Difference (HSD) tests. Where appropriate, measures were compared with two-tailed *t* test. We calculated Cohen's effect size values (*d*). To investigate the relationship between FMRP and neuropsychological and perceptual measures, we calculated Pearson's product moment correlation coefficients and used median-split analyses. Multiple comparisons were corrected according to the Bonferroni method. The level of statistical significance was $\alpha < 0.05$.

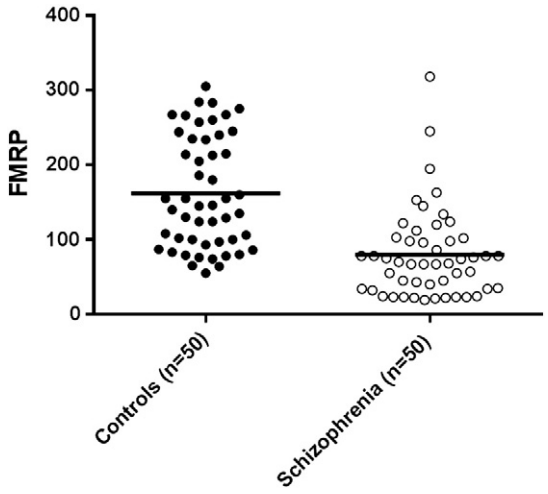

Fig. 2. Fragile X Mental Retardation Protein (FMRP) levels in patients with schizophrenia and healthy control volunteers. FMRP levels were calculated relative to a reference standard lymphocyte extract (Iwahashi et al., 2009). The dots show individual values, whereas the horizontal lines indicate mean in each group (for statistical details, see Results Section 3.1).

3. Results

3.1. Peripheral FMRP level

Patients with schizophrenia displayed a significantly reduced level of FMRP relative to controls (schizophrenia: 79.8 ($SD = 59.7$); controls: 162.1 ($SD = 74.6$); $t(98) = 6.10$, $p < 0.001$) (Fig. 2).

3.2. Neuropsychological performance

The results are depicted in Table 2. There was a generalized neuropsychological deficit in schizophrenia, which was the most pronounced in the case delayed memory. Language was relatively less affected.

3.3. Contrast sensitivity

The ANOVA indicated significant main effects of group (schizophrenia vs. controls) ($F(1,98) = 93.9$; $p < 0.001$; $\eta^2 = 0.49$) and stimulus type (low SF/high TF vs. high SF/low TF) ($F(1,98) = 126.14$, $p < 0.001$; $\eta^2 = 0.56$). There was a two-way interaction between group and stimulus type ($F(1,98) = 5.78$, $p < 0.05$; $\eta^2 = 0.06$). Patients with schizophrenia showed reduced contrast sensitivity for both stimulus types as compared with control individuals (Tukey HSD, $p < 0.001$). The two-way interaction appeared because the impairment was more severe in the case of stimuli with low SF/high TF relative to high SF/low TF (Table 3).

3.4. Perceptual integration

The ANOVA revealed significant main effects of group (schizophrenia vs. controls) ($F(1,98) = 5.61$; $p < 0.05$; $\eta^2 = 0.05$) and stimulus type (1λ vs. 3λ target–flanker distance) ($F(1,98) = 554.87$, $p < 0.001$; $\eta^2 = 0.85$). There was a significant two-way interaction between group and stimulus type ($F(1,98) = 12.34$, $p < 0.01$; $\eta^2 = 0.11$). The post-hoc analysis revealed less negative values at 3λ target–flanker distance in patients with schizophrenia relative to controls ($p < 0.001$). Patients and control showed similar values at 1λ target–flanker distance ($p > 0.5$) (Table 3).

3.5. Motion and form perception

There was a significant main effect of group ($F(1,98) = 46.81$; $p < 0.001$; $\eta^2 = 0.32$). The main effect of stimulus type (motion vs. form coherence) was not significant ($p > 0.5$). We found a significant two-way interaction between group and stimulus type ($F(1,98) = 6.93$; $p < 0.05$; $\eta^2 = 0.07$). Patients with schizophrenia had higher coherence thresholds than control individuals for form ($p < 0.05$) and motion ($p < 0.001$). As shown in Table 3, elevated threshold in schizophrenia patients, relative to control volunteers, was greater for motion than for form.

Table 2
RBANS results.

	Schizophrenia (n = 50)	Controls (n = 50)	*df*	*t*	*p*	*d*
Attention	80.9 (17.1)	96.3 (15.3)	98	4.73	<0.001	0.86
Immediate memory	80.3 (15.6)	98.7 (14.3)	98	6.16	<0.001	1.05
Delayed memory	77.7 (13.8)	99.1 (13.9)	98	7.73	<0.001	1.22
Visuospatial functions	82.6 (15.9)	95.9 (14.4)	98	4.36	<0.001	0.81
Language	89.2 (17.4)	98.1 (18.2)	98	2.50	0.01	0.49

Data are mean (standard deviation). Groups were compared with two-tailed *t* tests. Cohen's *d* values (effect size) are also shown. RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

Table 3
Results from the visual perceptual tests.

	Schizophrenia (n = 50)	Controls (n = 50)	*d*
Low SF/high TF contrast sensitivity	68.2 (10.0)	88.2 (9.9)	1.43
High SF/low TF contrast sensitivity	53.2 (11.8)	65.1 (15.0)	0.81
Form coherence (%)	32.9 (11.4)	26.6 (10.1)	0.56
Motion coherence (%)	38.7 (14.8)	23.4 (9.7)	1.05
Contrast threshold change at 1λ (log-unit)	0.23 (0.1)	0.25 (0.1)	0.18
Contrast threshold change at 3λ (log-unit)	−0.08 (0.1)	−0.18 (0.1)	0.83

Data are mean (standard deviation). SF: spatial frequency; TF: temporal frequency; Cohen's *d* values (effect size) are shown.

3.6. Correlations between neuropsychological and visual performance and FMRP levels

Table 4 shows the correlation coefficients. Patients and control individuals displayed a similar pattern of correlations, although these relationships were more robust in patients than in control individuals. FMRP levels were associated with better contrast sensitivity at low SF/high TF, RBANS attention, motion perception, and perceptual integration.

3.7. Median split analysis of RBANS and visual perceptual performance

We divided control participants and patients with schizophrenia into two groups using the median of the FMRP level (individuals with low and high FMRP level). In control individuals, there were significant differences between high and low FMRP groups in contrast sensitivity at low SF/high TF (high: 92.8 ($SD = 8.8$); low: 83.6 ($SD = 8.5$); $t(48) = -3.76$, $p < 0.005$) and in motion coherence (high: 20.2 ($SD = 5.5$); low: 26.5 ($SD = 11.8$); $t(48) = 2.41$, $p < 0.05$).

In patients with schizophrenia, we found significant differences between high and low FMRP groups in contrast sensitivity at low SF/high TF (high: 73.0 ($SD = 8.9$); low: 63.4 ($SD = 8.3$); $t(48) = -3.92$, $p < 0.001$), motion perception (high: 30.2 ($SD = 10.2$); low: 47.2 ($SD = 13.9$); $t(48) = 4.92$, $p < 0.001$), contrast threshold change at 3λ target–flanker distance (high: −0.14 ($SD = 0.1$); low: −0.03 ($SD = 0.09$); $t(48) = 4.16$, $p < 0.001$), and RBANS attention (high: 87.5 ($SD = 15.6$); low: 74.4 ($SD = 14.1$); $t(48) = -2.92$, $p < 0.05$).

3.8. Correlation with antipsychotic doses

We did not find a significant correlation between chlorpromazine-equivalent antipsychotic dose and FMRP levels. The antipsychotic dose did not correlate with the test performances ($-0.2 < rs < 0.2$, $ps > 0.1$).

4. Discussion

The findings of the present study suggest that reduced FMRP plays a key role in the visual dysfunction associated with schizophrenia. FMRP may also modulate visual perception in healthy individuals (Kéri & Benedek, 2011, 2012). We observed trend-level and consistent positive relationships between FMRP levels and neuropsychological functions, but even when it reached statistical significance (attention and immediate memory), it hardly passed the criteria of correction for multiple comparisons. Therefore, it seems that FMRP has a greater impact on particular domains of visual perception assessed by psychophysical tasks than on neuropsychological functions assessed by standard pen-and-paper tests.

The relationship between FMRP and perception was selective for certain visual functions, similarly to our previous data from healthy individuals (Kéri & Benedek, 2011, 2012). Specifically, we observed a correlation between FMRP level and contrast sensitivity for low SF/high TF gratings, motion perception, and perceptual integration. There was no such relationship between FMRP and contrast sensitivity at high SF/low TF and form perception. These findings can be interpreted in the framework of the magnocellular (M)/parvocellular (P) precortical visual pathways and their cortical recipients (dorsal occipito-parietal and ventral occipito-temporal streams, respectively). Low SF/high TF gratings are thought to preferably stimulate M pathways, whereas high SF/low TF gratings activate P pathways. M pathways provide essential information to dorsal stream areas responsible for motion perception and visuospatial coordination, whereas P pathways project to ventral stream areas participating in form and color perception (for an overview, see Gilbert, 2013; Nassi & Callaway, 2009). In schizophrenia, there is an impairment of both systems, but M pathways seem to be dominantly affected (Butler et al., 2008). The fact that FMRP might be implicated in the appropriate organization and functioning of M pathways, but not P pathways, is in well accordance with this model (Kogan et al., 2004; Zangenehpour et al., 2009).

However, this model has limitations. First, the selective stimulation and functional unity of M and P pathways have been debated (Goodbourn et al., 2012; Skottun & Skoyles, 2007). Second, M and P pathways interact in the primary visual cortex (Sawatari & Callaway, 1996), and therefore their strictly separate contribution to dorsal and ventral systems is dubious. Third, recent evidence suggests a "patchwork" organization of higher-level visual cortical areas instead of functionally separated dorsal and ventral streams (de Haan & Cowey, 2011). Nevertheless, there is substantial evidence from several studies that stimulus characteristics (e.g., spatial frequency, contrast, motion, and color) significantly and differentially affect behavioral performance and brain activation in schizophrenia (e.g., Butler et al., 2007; Calderone et al., 2013; Chen, 2011; Graham & Meng, 2011; Kéri et al., 2004, 2012; Martínez et al., 2008; McBain et al., 2010; O'Donnell et al., 1996, 2002; Schechter et al., 2005). Beyond generalized deficits in contrast sensitivity and coherence threshold, the present study demonstrated more severe impairments in patients for low SF and moving stimuli than for high SF and form stimuli, which is consistent with the above-discussed findings. Moreover, the differential effect of FMRP lends further support for the existence of separate systems for the processing of low SF/motion and high SF/form.

We also found a relationship between FMRP level and perceptual integration, which may be mediated by lateral connections between processing units in early visual cortical areas (Kovács, 1996; Polat & Sagi, 1993; for a review of perceptual integration and organization in schizophrenia, see Silverstein & Keane, 2011). At specific distances, these lateral interactions are inhibitory (e.g., 1λ target–flanker distance), whereas in other

Table 4
Correlations between FMRP level and neuropsychological and visual perceptual measures.

	CS1	CS2	Att	MemI	MemD	VSP	Lang	Form	Motion	1λ	3λ
Controls (n = 50)	0.69**	−0.20	0.32*	0.26	0.11	0.09	0.15	0.13	−0.41*	−0.05	−0.31*
Schizophrenia (n = 50)	0.67**	−0.28*	0.54**	0.30*	0.19	0.22	0.28	0.0	−0.57**	0.18	−0.61**

The table shows Pearson's correlation coefficients. CS1: contrast sensitivity at low spatial and high temporal frequencies; CS2: contrast sensitivity at high spatial and low temporal frequencies; Att: attention; MemI: immediate memory; MemD: delayed memory; VSP: visuospatial functions; Lang: language; Form: form coherence; Motion: motion coherence; 1λ: contrast threshold change at 1λ target–flanker distance; 3λ: contrast threshold change at 3λ target–flanker distance.
* $p < 0.05$.
** $p < 0.002$ (Bonferroni-corrected threshold).

distances it is excitatory (e.g., 3λ target–flanker distance). In the latter case, flankers enhance contrast detection at the target patch, and therefore contrast threshold is reduced relative to the scenario when the target stimulus is presented without flankers (Polat & Sagi, 1993). This excitatory effect is diminished in schizophrenia (Kéri et al., 2005a,b; Must et al., 2004). Data from the present study raise the possibility that FMRP may have an effect on the development and functional integrity of lateral connections in early visual cortical areas. This hypothesis must be confirmed by animal studies.

Our results must be interpreted with caution. Development and functional plasticity of neuronal circuits, such as domains of the visual system, are not regulated by a single molecular factor, and therefore FMRP cannot be considered as a sole master regulator. Nevertheless, the high expression of FMRP in M cells, but not in P cells, and the marked loss of certain visual function in FXS and premutation carriers strongly indicate its key role (Kéri & Benedek, 2009; Kogan et al., 2004). Although evidence suggests that in FXS FMRP is abnormally expressed in both brain tissue and peripheral lymphocytes (e.g., Devys et al., 1993; Kogan et al., 2004; Pieretti et al., 1991; Willemsen et al., 1997), the exact relationship between neuronal and peripheral changes in neuropsychiatric disorders must be directly verified.

FMRP is an RNA binding protein regulating the translation of hundreds of transcripts in the brain, with a special reference to subunits of gamma-amino butyric acid (GABA) and metabotropic glutamate receptors (Heulens & Kooy, 2011). Altered FMRP levels are not specific for schizophrenia: similar findings have been revealed in bipolar disorder, major depressive disorder, and autism without FXS (Fatemi & Folsom, 2011; Fatemi et al., 2010, 2011, 2013). The visual phenotype of mood disorders and autism is partly similar to that of schizophrenia (e.g., Dakin & Frith, 2005; Kéri et al., 2007; Laycock et al., 2007), but more data are indispensable to obtain conclusive evidence and to explore the shared role of FMRP. Overall, FMRP may be a missing link in the GABA and glutamate hypothesis of schizophrenia and other neuropsychiatric disorders and may provide new targets for pharmacological agents crossing the boundary of classic diagnostic categories.

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