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ORIGINAL PAPER

Using Perceptual Signatures to Define and Dissociate Condition-Specific Neural Etiology: Autism and Fragile X Syndrome as Model Conditions

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Abstract The functional link between genetic alteration and behavioral end-state is rarely straightforward and never linear. Cases where neurodevlopmental conditions defined by a distinct genetic etiology share behavioral phenotypes are exemplary, as is the case for autism and Fragile X Syndrome (FXS). In this paper and its companion paper, we propose a method for assessing the functional link between genotype and neural alteration across these target conditions by comparing their *perceptual signatures*. In the present paper, we discuss how such signatures can be used to (1) define and differentiate various aspects of neural functioning in autism and FXS, and subsequently, (2) to infer candidate causal (genetic) mechanisms based on such signatures (see companion paper, this issue).

Keywords Autism · Fragile X syndrome · Vision · Perception · Perceptual signatures · Neural networks

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Commonalities in perceptual, cognitive and behavioral profiles are often manifested across different neurodevelopmental conditions despite each having arisen from disparate genetic causes. This can obscure unique, condition-specific pathways, leading to shared phenotypes at different levels of assessment. Such is the case for autism and Fragile X syndrome (FXS), the latter being the most common hereditary cause of developmental delay in males. The condition is caused by the silencing of a single gene on the long arm of the X chromosome at q27.3. The gene, named the Fragile X Mental Retardation Gene - 1 (FMR1), is "turned off" in affected individuals. It is now well established that FMR1 is the only gene involved in the pathogenesis of FXS and that the lack of encoded protein, FMRP, and the subsequent impact of its absence on early brain development causes FXS (Cornish et al. 2008).

Although a number of gender, twin and family studies suggest an important biological component in autism, its genetic origin remains elusive with an estimated 90% of autism cases considered idiopathic (Muhle et al. 2004; Persico and Bourgeron 2006; Abrahams and Geschwind 2008; Losh et al. 2008; Steyaert and De la Marche 2008). However, approximately 10% of autism cases are considered syndromic since the autism phenotype can be explained by single-gene syndromes and/or chromosomal

abnormalities defined by specific genetic mutations (including FMR1). Although still controversial, approximately 2–6% of children with autism will have the FMR1 mutation (Wassink et al. 2001; Reddy 2005), and between 33 and 67% of children with fragile X will fulfill the diagnostic criteria for autism (Rogers et al. 2001; Clifford et al. 2007). Similarities across core social and language domains define the link between autism and FXS, and it therefore seems highly plausible that both conditions share neurobiological networks.

As suggested by (Belmonte and Bourgeron 2006), in order to study convergent (and/or divergent) neurocognitive phenotypes between genetically dissociable syndromes, analysis at a neural network level must be considered. For instance, the susceptibility to autism in FXS may at least in part arise from a significant amount of commonalities with respect to atypical neural network functioning (and other interactive modifying aspects such as environmental factors) that is shared between the two conditions. This theoretical framework is shared by others who champion a genetically-influenced, systemic model of autism where causal genetic perturbations alter neural connectivity (and also tissue morphology), leading to atypical information processing capabilities which may at least in part define neurocognitive phenotypes in autism (Herbert 2005). In essence, although poly- (autism) or monogenetic (FXS) perturbation is the defining cause of autism and FXS, consequent similarities and/or differences at the neurocognitive level may be defined, and therefore dissociable at a neural network level (neural endophenotypes; (Muller 2007). We have chosen autism and FXS as model neurodevelopmental conditions because both manifest low-level perceptual deficits. However, whereas FXS is a well-defined genetic syndrome that often manifests an autistic phenotype (as described above), the genetic origin of autism remains undefined. Additionally, similar perceptual assessments are available for both conditions, using two different experimental paradigms, allowing for a direct comparative to be made with limited methodological constraints.

The focus of the present paper is therefore to introduce a theoretical framework that includes the assessment of neural network functioning across autism and FXS (but may be applicable to other conditions), defined by characteristic information processing abilities, referred to as *perceptual signatures* (Bertone and Faubert 2006). Such information may serve not only to differentiate neurodevelopmental conditions from each other, but can also provide an understanding of plausible causal mechanisms that drive phenotypic signatures. Rather than conducting an exhaustive review of this literature, we will present pertinent experimental evidence useful for comparing and contrasting autism and FXS at a neural network level, based on their characteristic perceptual signatures that reflect the integrity of local neural connectivity mediating specific visual information processing abilities. We also discuss how the choice of experimental paradigm for defining perceptual signatures is crucial for advancing condition-specific neural etiology underlying perceptual capabilities for each condition. Finally, in order to strengthen the functional link between genotype, subsequent neural alteration, and ultimately neuro-cognitive abilities/behavior within target condition, it is useful to investigate and compare network-based differences and similarities across target conditions (Belmonte and Bourgeron 2006), as reflected by their perceptual signatures. Based on such comparisons, we are proposing the use of a novel and expanded (cross-condition) causal framework whereby perceptual signatures can be used to argue either divergent or convergent etiology at different levels of connectivity (i.e., local vs large-scale networks) in autism and FXS, as presented in our companion paper.

Perceptual Signatures: The Importance of Experimental Paradigm

The hypothesis that atypical behavior in neurodevelopmental conditions may be the result of atypical low-level information processing is relatively recent (Belmonte et al. 2004; Cornish et al. 2004; Bertone et al. 2005; Belmonte and Bourgeron 2006; Eckert et al. 2006; Mottron et al. 2006; Karmiloff-Smith 2007). With the use of applied psychophysical, experimental cognitive paradigms, electrophysiological and brain imaging approaches, the direction of research has recently been directed towards information processing capabilities in various clinical populations, including autism and FXS. This direction is not surprising given the increased interest in associating characteristic impairments related to social cognition with atypical sensory processing in autism and other neurodevelopmental conditions such as William's syndrome and dyslexia (Wilmer et al. 2004; Dakin and Frith 2005; Behrmann et al. 2006; Eckert et al. 2006; Simmons et al. 2009). This being said, such associations are not novel, as lower-level visuo-perceptual abilities have been assessed and hypothesized to be implicated in higher-level or cognitive functioning in other neurodevelopmental conditions, most notably dyslexia (Skottun 2000).

The most common behavioral method of evaluating low-level visual information processing in different atypical populations has been a variety of adapted global motion/global form paradigms (Atkinson et al. 1997). In these paradigms, sensitivity to global motion (adapted random dot kinematogram stimuli (RDK) detection task) and global form (adapted circular pathfinder detection task)

are measured, and have been argued to reflect the functional integrity of dorsal and ventral visual stream mechanisms, respectively (Atkinson et al. 1997). This reasoning is motivated by findings of specialized processing of global motion and global form mechanisms believed to selectively reflect extra-striate functioning in either visual stream by specialized visual areas (e.g., global motion: MT, dorsal stream versus global form: V4, ventral stream) (Braddick et al. 2003). Performance on these tasks, measured in terms of sensitivity, reflect the neural integrity of specialized neural networks underlying their processing. Based in part on studies that employ such stimuli, Braddick and colleagues have advanced an influential hypothesis, referred to as the *dorsal-stream vulnerability* hypothesis, which posits that the dorsal visual stream is more vulnerable to genetic and environmental factors, which in turn selectively affects the dorsal stream development relative to its ventral counterpart (Braddick et al. 2003).

As shown in Fig. 1 (left panel), a similar pattern of performance—or perceptual signature—is obtained using the same global motion/global form paradigm for autism (Spencer et al. 2000) and FXS (Kogan et al. 2004b); a decreased sensitivity to global motion [represented by ⇓ in Fig. 1; left panel] alongside preserved sensitivity to global form information [represented by = in Fig. 1; left panel]. Consistent with the dorsal-stream vulnerability hypothesis, we refer to these results as being *stream-specific* (Bertone et al. 2005; Bertone and Faubert 2006; Bertone et al. 2008) since the results are interpreted as a neural dysfunction selectively affecting dorsal stream-related dynamic information processing.

It is to note that in addition to autism and FXS, similar perceptual signatures have been demonstrated in other populations including William's syndrome, developmental dyslexia, children of parents with schizophrenia and cerebral palsy (Atkinson et al. 1997; Hansen et al. 2001; Gunn et al. 2002; O'Brien et al. 2002; Atkinson et al. 2006; Keri et al. 2006). Consequently, it is difficult to argue that the neural network functioning mediating low-level dynamic and static information processing differs across these two genetically divergent model conditions, or for that matter, among other conditions sharing the same perceptual signature. In addition, the resulting stream-specific interpretation is not fully supported by recent studies suggesting intact magnocellular-related functioning (spatio-temporal contrast sensitivity or flicker) in autism (Bertone et al. 2005; Pellicano et al. 2005; Pellicano and Gibson 2008). Furthermore, it is to note that dorsal-stream related spatio-temporal contrast sensitivity has been demonstrated to be selectively affected in FXS (Kogan et al. 2004b).

Recently, Bertone et al. (2005) and Bertone and Faubert (2006) suggested that these shared stream-specific perceptual signatures (impaired dorsal/preserved ventral functioning) might be at least in part due to the paradigm used to assess static and dynamic information processing for different syndromes. Although the stream-related interpretations are consistent with decreased global motion/unaffected global form results, an alternative explanation based on the complexity of the dynamic stimuli used in these experiments should not be ruled out. For example, according to their *complexity-specific* interpretation, decreased sensitivity to complex motion may have resulted

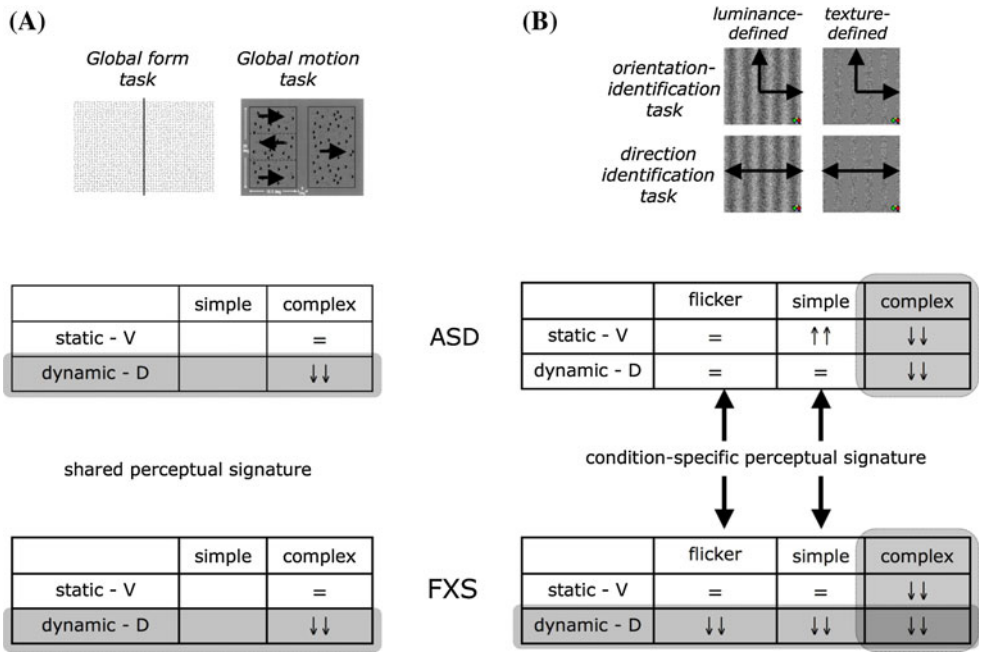

Fig. 1 Top. Using global motion/form (*left panel*) and static/dynamic (*right panel*) experimental paradigms (**a**), perceptual signatures (**b**) summarizing characteristic information processing abilities can derived for autism (ASD) and fragile-x syndrome (FXS)

from reduced neural integrative processing, not necessarily specific to a dorsal-stream vulnerability. Other arguments related to the differential neural processing demands between the global (circular) form/global (non-circular) motion stimuli have been forwarded, but will not be discussed in the present paper.

In an attempt to dissociate between stream-specific and complexity-specific interpretations across target neurodevelopmental conditions, static and dynamic information processing was assessed by measuring direction- and orientation-identification thresholds to luminance-defined (simple or first-order) and texture-defined (complex or second-order) stimuli (Chubb and Sperling 1988; Cavanagh and Mather 1989; Sperling et al. 1994). Whether presented in static or dynamic forms, luminance- and texture-defined information is initially processed by separate feed-forward mechanisms, exemplified by filter-rectify-filter analysis, using similar principles of detection at similar stages along each stream (Chubb and Sperling 1988; Wilson et al. 1992; Sperling et al. 1994; Sutter et al. 1995; Nishida et al. 1997; Smith et al. 1998; Baker 1999). Whereas luminance-defined motion and orientation information is initially extracted by standard analysis within the primary visual cortex, texture-defined information requires additional neural processing before being extracted within extra-striate visual areas (Dumoulin et al. 2003; Nishida et al. 2003; Larsson et al. 2006; Ashida et al. 2007). Using such a paradigm, it is possible to simultaneously assess static and dynamic information processing at various levels of complexity using stimuli that are processed in a similar manner, whether in dynamic or static forms. We argue that this approach is advantageous because it allows for the possibility to define and dissociate visual information processing in terms of either static/dynamic (stream-specific) or simple/complex (complexity-specific) variables. This is an important feature given the recent demonstration that the maturation of mechanisms mediating static and dynamic information processing is differentially affected by stimulus complexity in typically developing children (Bertone et al. 2008; Armstrong et al. 2009).

In the sections that follow, the perceptual signatures characterizing autism and FXS (Fig. 1, right panel) will be used to argue either a condition-specific or shared neural etiology underlying low-level information processing. We will base our arguments on the perceptual signatures presented in the right panel of Fig. 1 because (1) they are the only signatures to date that reflect static and dynamic processing at different levels of complexity using stimuli that are processed in a similar manner and (2), the same experimental paradigm was used for both FXS and autism, allowing for a comparison that minimizes differences due to experimental procedure and parameters. Supporting behavioral and physiological evidence from other studies will also be presented.

Using Perceptual Signatures to Dissociate Neural Etiology in Autism and FXS

Autism as a Model Condition

Perceptual Findings

In general, autism differs from other neurodevelopmental conditions because of recurrent demonstration of superior performances on several cognitive and lower-level auditory and perceptual tasks (Heaton et al. 1999; Mottron et al. 2000; Bonnel et al. 2003; O'Riordan and Passetti 2006) where local or detailed information processing is advantageous (Dakin and Frith 2005; Behrmann et al. 2006; Happe and Frith 2006; Mottron et al. 2006). As demonstrated in Fig. 1 (right panel), the ability of high-functioning individuals with autism for identifying the orientation of a static grating was found to be superior compared to neurotypical participants when the grating was defined by simple, luminance-defined information but inferior when defined by complex, texture-defined information (Bertone et al. 2005). This finding suggests that the same atypical local neural system mediating static information processing in autism may have two opposite perceptual consequences, depending on the physical attributes defining the complexity of the visual information being analyzed. Enhanced sensitivity to static visual information is a characteristic performance that is specific to autism (Dakin and Frith 2005; Behrmann et al. 2006; Baron-Cohen et al. 2009; Mottron et al. 2009). It has not been documented in other developmental conditions or for that matter, behavioural phenotypes often associated with autism, such as fragile x syndrome (Kogan et al. 2004a, b).

Other studies assessing static information processing in autism have for the most part used different varieties of circular global form (i.e., Glass patterns, pathfinder stimuli, etc.) stimuli argued to selectively target extra-striate mechanisms within the ventral stream. These studies have resulted in mixed findings, suggesting either unaffected (Spencer et al. 2000; Blake et al. 2003; Del Viva et al. 2006; Koldewyn et al. 2009) or decreased (Spencer and O'Brien 2006; Tsermentseli et al. 2008) sensitivity to circular global form stimuli in autism. Based on these and previous results, it can be argued that static (non-circular), texture-defined information processing is either deficient or altered in autism since it necessitates the involvement of extra-striate analysis (not processed by standard mechanisms operating with the primary visual cortex) before being detected (Vandenbroucke et al. 2008; Pei et al.

2009). In a recent study, the ability of high-functioning children with autism to discriminate the orientation of a boundary was decreased when its orientation was defined uniquely by a difference in chromaticity, which like texture, is an equiluminant stimulus attribute (contains no luminance information); no between-group differences was evidenced when boundaries were luminance-defined (Franklin et al. 2010).

The autistic perceptual signature also reflects unaffected sensitivity to simple, *dynamic* information processing while sensitivity to complex, texture-defined motion was decreased. Although decreased sensitivity to complex motion stimuli has been demonstrated in most autism studies (Spencer et al. 2000; Milne et al. 2002; Bertone et al. 2003; Blake et al. 2003; Pellicano et al. 2005; Del Viva et al. 2006; Spencer and O'Brien 2006; Freitag et al. 2008; Tsermentseli et al. 2008; Koldewyn 2009), simple luminance-defined motion mediated by standard analysis was found to be intact when assessed in autism (Bertone et al. 2003). Although the study remains the only assessment, and demonstration of intact simple motion processing in autism (Kaiser and Shiffrar 2009; Simmons et al. 2009), it is congruent with findings of unaffected sensitivity to spatio-temporal contrast sensitivity targeting M-pathway (magnocellular) functioning, suggesting that atypical dynamic information processing in autism has later (extra-striate), rather than early (primary) cortical origins (Bertone et al. 2005; Pellicano et al. 2005; Pellicano and Gibson 2008).

Although perceptual deficits in autism seem to be restricted to complex-type stimuli, similar results have been demonstrated in numerous other developmental, degenerative and affective conditions and therefore, is not enough to suggest autism-specific neural etiology if assessed in isolation (Bertone and Faubert 2006). The choice of experimental paradigm is therefore of important interpretive consequence, especially given the fact that when simple (i.e., local) dynamic information is indeed assessed in different patient populations, it is most often found to be either less affected, or unaffected when compared to complex (i.e., global) motion information (i.e., amblyopia (Simmers et al. 2003); schizophrenia (Chen et al. 2003; Kim et al. 2005); non-pathological aging (Habak and Faubert 2000); Migraine (McKendrick and Badcock 2004); mild traumatic brain injury (Brosseau-Lachaine et al. 2008). To our knowledge, enhanced sensitivity to simple motion stimuli has never been documented in autism, or for any other neurodevelopmental condition.

In conclusion, the perceptual signature presented in autism is more consistent with a complexity-specific interpretation where complex (non-luminance-defined) information processing, whether static or dynamic, is selectively affected in autism. In addition, enhanced sensitivity to simple (luminance-defined) information is evidenced for static, but not dynamic information. A plausible neural etiology underlying autism-specific information processing will be discussed in the following section.

Plausible Neural Mechanisms Consistent with an Autistic Perceptual Signature

In addition to advantages for local pattern detection and manipulation, as in visual search and the processing of hierarchical stimuli, autistic performance on tasks assessing stimulus-driven mechanisms mediating a variety of lower-level stimulus properties is both enhanced and diminished, often depending on the physical attribute of the information being extracted (Dakin and Frith 2005; Behrmann et al. 2006; Mottron et al. 2006; Simmons et al. 2009). Bertone et al.'s (2005) demonstration of both enhanced and diminished extraction of spatial information was interpreted as the result of atypical neural connectivity within the primary visual cortex (or V1), and interactions with adjacent early cortices. Among the available neural computational models suggesting hypersensitivity in autism (Cohen 1994; McClelland 2000), they argued that the most biologically plausible type of atypical local connectivity congruent with their results is that of strong or excessive lateral inhibition (Gustafsson 1997a, b; Gustafsson 2004), resulting in the inadequate formation of cortical feature maps consisting of neural columns as feature detectors (presented within the context of Kohonen-type (Kohonen 1995), self-organizing maps). Such atypical lateral connectivity would in theory (1) alter early spatial filtering characteristics in autism (i.e., increase tuning of orientation-selective mechanism in V1) and (2) enhance detection capabilities for luminance-defined information by minimizing the signal strength (i.e., luminance-modulation) needed to perceive a stimulus within noise (the implication of short-range feedback connectivity also discussed in Bertone et al. 2005). To our knowledge, it is the only data-driven and testable neural model that can account for both enhanced and diminished perceptual performance in autism to date that is contingent on the physical attributes defining the information being processed (see also "Neural Noise "hypothesis presented by Simmons et al. 2009).

This suggestion of functional but altered lateral connectivity within primary visual areas has been recently supported by (Vandenbroucke et al. 2009), whose behavioral and ERP data suggested strong evidence for atypical inhibition through horizontal connections in low-level visual areas in autism (associated with impaired object boundary detection; see also Pei et al. (2009). Presented within the context of the minicolumnar hypothesis of autism (Casanova et al. 2002), altered local connectivity between proximal neural mechanisms has been proposed to

explain the altered effects of somatosensory stimulation in autism (Tommerdahl et al. 2008). Finally, studies demonstrating the altered detection of crowded spatial targets at both lower (Keita et al. in press) and mid-level (Baldassi et al. 2009) visuo-spatial analysis also support the suggestion that atypical lateral interactions may best characterise spatial information processing in autism. More recently, a computational model sharing the aforementioned concept of atypical lateral interaction within local neural circuitry has been advanced to explain certain oculomotor behaviors reported in autism (Vattikuti and Chow 2009).

FXS as a Model Condition

Perceptual Findings

The majority of research studies on FXS have focused on delineating specific cognitive and behavioral strengths and weaknesses in this population. Although this strategy has been beneficial in providing a clearer understanding of the learning, memory, and attentional impairments in FXS, little is known about the contribution of perceptual abnormalities to the profile of intellectual disability observed in affected individuals. The latter is particularly important because a central impairment in FXS is poor visual-spatial abilities (Theobald et al. 1987; Loesch et al. 1993; Cornish et al. 1999), which may result from early visual perceptual processing deficits. The notion of an early perceptual deficit as either accounting for or being associated with cognitive and behavioural symptomatology of FXS is a novel concept. Therefore, few studies have addressed this question directly (Kogan et al. 2004a, b; Farzin et al. 2008; Keri and Benedek 2009).

Evidence for a selective impairment in visual perceptual processing in FXS comes from the results of neuropsychological testing that targeted a broad range of abilities within the visual domain (Cornish et al. 1999). FXS affected males were reported to perform worse than both age- and developmental-matched control groups on a variety of visual-motor tasks but exhibit largely spared performance on a visual-perceptual task. These data confirm earlier claims of visual-spatial and visual-motor abnormalities in FXS. Furthermore, these findings appear to coincide with the known organization of the visual system in which the magnocellular/dorsal pathway is devoted to processing visual-spatial information and the parvocellular/ventral visual pathway is devoted to processing visual-perceptual information (Ungerleider and Mishkin 1982; Milner and Goodale 1995). This compelling conjecture was tested by Kogan et al. (2004a, b).

In Kogan et al's study (2004a, b), performance of adult men with FXS were compared to that of verbal mental age matched and chronologically age matched comparison participants. The results showed that the FXS group consistently had greater difficulty detecting dynamic stimuli that were either defined by luminance (first-order) or by texture (second-order). Furthermore, a similar deficit was observed for more complex, second-order defined dynamic stimuli that presumably engages dorsal stream processing. In contrast, no differences were found between groups for detecting stimuli known to engage the parvocellular pathway, including those defined by color. However, when more complex, second-order static stimuli were presented, the FXS group exhibited a significant reduction in sensitivity. Taken together, these data suggest a pervasive deficit for perceiving dynamic stimuli in FXS that can be attributed to subcortically-mediated processing abnormalities. These deficits occur in conjunction with a global, perceptual integration impairment that affects all forms of visual input at cortical levels. Similar results have been found for female carriers of the FXS genotype using similar simple stimuli alongside stimuli presumed to demand more complex cortical processing (Keri and Benedek 2009).

More recently, (Farzin et al. 2008) have employed the same psychophysical paradigm to examine whether the pattern of spared and impaired visual function exists in infants affected by FXS. Interestingly, whereas the authors replicated the adult findings of a deficit for complex, second-order dynamic stimuli, they reported that affected infants were able to detect simple (first-order) dynamic and static stimuli and more complex (second-order) static stimuli as well as comparison infant observers. These data raise the interesting possibility for a process by which magnocellular function and integrative abilities deteriorate across development. A plausible biological explanation based on the known developmental milestones for the development of the subcortical lateral genicular nucleus and primary visual cortex is discussed below.

In summary, these findings provide compelling support of the notion that the visual-motor and visual-spatial impairments exhibited on neuropsychological tasks are attributable to a specific perceptual signature. Furthermore, they highlight the utility of probing the visual system at different levels of complexity. In the context of the model we are advocating here, the FXS perceptual signature is consistent with both stream- and complexity-specific interpretations.

Plausible Neural Mechanisms Consistent with FXS Perceptual Signature

Unlike other forms of intellectual disability, FXS has a well-identified monogenic etiology. Thus, observations of neuroanatomical abnormalities in the brains of affected individuals can most parsimoniously be explained by the

lack of *FMR1* gene expression. Additionally, brain areas identified as expressing high levels of *FMR1* protein in unaffected individuals can be hypothesized to be those most reliant on the protein for normal functioning and therefore the most susceptible to its absence as occurs in FXS. This logic has been tested with a plausible neural mechanism consistent with the FXS perceptual signature (Kogan et al. 2004b).

Kogan et al. (2004b) reasoned that the observed reduction in sensitivity for low spatial/high temporal frequency psychophysical stimuli among affected individuals likely reflects a pathophysiologic process within the subcortical magnocellular pathway of the lateral geniculate nucleus (LGN). That is, that those neurons comprising this pathway depend more greatly on *FMR1* protein for normal function than corresponding parvocellular neurons. Further, they speculated that with lack of protein expression as occurs in FXS, magnocellular neurons are not able to transmit dynamic visual information in a typical manner. Inspection of histological preparations of autopsied brains of unaffected and affected individuals revealed support for the authors' conjecture as well as a more complex picture (Kogan et al. 2004b). First, in the LGN of an unaffected individual, *FMR1* protein is expressed in greater amounts within the magnocellular neurons irrespective of overall neuronal size differences. Second, LGN from both left and right hemispheres of an affected individual were observed to lack the expected six-layer organization. Furthermore, cells within the LGN were approximately 5 μm in diameter as compared to 25 μm for magnocellular neurons and 15 μm for parvocellular neurons. Although both magnocellular and parvocellular neurons were equally affected, (Kogan et al. 2004b) proposed that small-sized neurons in the LGN would result in a greater loss of function to the magnocellular pathway, which depends on large neurons for rapid cycling of depolarization and repolarization in order to encode dynamic information (Derrington and Lennie 1984).

The psychophysical data suggesting decreased sensitivity for all types of complex, second order stimuli among observers affected by FXS suggests an additional neural mechanism beyond the reported subcortical abnormalities in the LGN. (Kogan et al. 2004a) proposed that this could be explained by a general, non-perception specific, process by which all neural networks requiring integration of information are impaired in FXS. Therefore, higher cortical processes in the visual brain are expected to demonstrate greater degrees of impairment dependent on the number of neuronal connections involved. More specifically, the nature of the integrative deficit is likely related to the role that the *FMR1* protein normally plays in synaptic formation. A variety of studies describe abnormalities in dendritic spine formation and pruning in the absence of *FMR1* protein, both in a knock-out mouse model of FXS and in post-mortem brains from FXS patients (Comery et al. 1997; Irwin et al. 2000; Greenough et al. 2001; Irwin et al. 2001; Churchill et al. 2002; Irwin et al. 2002). These studies reveal that in the absence of *FMR1* protein, neurons in the cortex have immature dendritic spines and are morphologically similar to those found in neurons from animals deprived of sensory experience. Furthermore, in FXS patients, the density of immature spines is elevated when compared with normal control brains, suggesting a lack of appropriate synaptic elimination.

In summary, there are two plausible neural mechanisms that can explain the observed perceptual signature of FXS. The first is a subcortically driven impairment that arises because of the loss of large caliber neurons in the lateral geniculate that can optimally process dynamic information, in accordance with the stream-specific hypothesis. The second is a generalized integrative deficit that results from deficient integration of information across multiple synapses due to the lack of the *FMR1* protein and subsequent disruption to normal dendritic spine maturation, manifesting perceptually by performance consistent with the complexity-specific hypothesis.

Conclusion

In the present paper, arguments have been presented suggesting that autism and FXS may be dissociated by syndrome-specific alterations at a *local* neural network level, defined by functional but altered lateral connectivity mediating spatial information processing in autism, compared to less efficient M-related neural functioning in FXS. However, the perceptual consequence of altered extrastriate neural networks mediating complex, texture-defined information processing are shared between autism and FXS, demonstrated by decreased sensitivity to texture-defined information (static and dynamic) in both conditions. Such cross-condition dissociations, in addition to the neural hypotheses derived from them, are only manifested using certain experimental paradigms. A similar consequence of paradigm selection has been recently demonstrated by (Pellicano and Gibson 2008), who showed that condition-specific perceptual abilities in autism and dyslexia are contingent on the level of information processing assessed.

The signature-driven neural hypotheses presented here are presented specifically within the context of low-level information processing in autism and FXS. In our companion paper, we describe how the aforementioned signature-driven neural hypotheses can be incorporated into causal models in order to infer target candidate gene or gene clusters that are implicated in autism's pathogenesis.

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References

Abrahams, B. S., & Geschwind, D. H. (2008). Advances in autism genetics: On the threshold of a new neurobiology. *Nature Reviews. Genetics, 9*(5), 341–355.

Armstrong, V., Maurer, D., et al. (2009). Sensitivity to first- and second-order motion and form in children and adults. *Vision Research, 49*(23), 2774–2781.

Ashida, H., Lingnau, A., et al. (2007). FMRI adaptation reveals separate mechanisms for first-order and second-order motion. *Journal of Neurophysiology, 97*(2), 1319–1325.

Atkinson, J., Braddick, O., et al. (2006). Dorsal-stream motion processing deficits persist into adulthood in Williams syndrome. *Neuropsychologia, 44*(5), 828–833.

Atkinson, J., King, J., et al. (1997). A specific deficit of dorsal stream function in Williams' syndrome. *Neuroreport, 8*(8), 1919–1922.

Baker, C. L., Jr. (1999). Central neural mechanisms for detecting second-order motion. *Current Opinion in Neurobiology, 9*(4), 461–466.

Baldassi, S., Pei, F., et al. (2009). Search superiority in autism within, but not outside the crowding regime. *Vision Research, 49*(16), 2151–2156.

Baron-Cohen, S., Ashwin, E., et al. (2009). Talent in autism: Hyper-systemizing, hyper-attention to detail and sensory hypersensitivity. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 364*(1522), 1377–1383.

Behrmann, M., Thomas, C., et al. (2006). Seeing it differently: Visual processing in autism. *Trends in Cognitive Sciences, 10*(6), 258–264.

Belmonte, M. K., & Bourgeron, T. (2006). Fragile X syndrome and autism at the intersection of genetic and neural networks. *Nature Neuroscience, 9*(10), 1221–1225.

Belmonte, M. K., Cook, E. H., Jr., et al. (2004). Autism as a disorder of neural information processing: Directions for research and targets for therapy. *Molecular Psychiatry, 9*(7), 646–663.

Bertone, A., & Faubert, J. (2006). Demonstrations of decreased sensitivity to complex motion information not enough to propose an autism-specific neural etiology. *Journal of Autism and Developmental Disorders, 36*(1), 55–64.

Bertone, A., Hanck, J., et al. (2008). Development of static and dynamic perception for luminance-defined and texture-defined information. *Neuroreport, 19*(2), 225–228.

Bertone, A., Mottron, L., et al. (2003). Motion perception in autism: A "complex" issue. *Journal of Cognitive Neuroscience, 15*(2), 218–225.

Bertone, A., Mottron, L., et al. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain, 128*(Pt 10), 2430–2441.

Blake, R., Turner, L. M., et al. (2003). Visual recognition of biological motion is impaired in children with autism. *Psychological Science, 14*(2), 151–157.

Bonnel, A., Mottron, L., et al. (2003). Enhanced pitch sensitivity in individuals with autism: A signal detection analysis. *Journal of Cognitive Neuroscience, 15*(2), 226–235.

Braddick, O., Atkinson, J., et al. (2003). Normal and anomalous development of visual motion processing: Motion coherence and 'dorsal-stream vulnerability'. *Neuropsychologia, 41*(13), 1769–1784.

Brosseau-Lachaine, O., Gagnon, I., et al. (2008). Mild traumatic brain injury induces prolonged visual processing deficits in children. *Brain Injury, 22*(9), 657–668.

Casanova, M. F., Buxhoeveden, D. P., et al. (2002). Minicolumnar pathology in autism. *Neurology, 58*(3), 428–432.

Cavanagh, P., & Mather, G. (1989). Motion: The long and short of it. *Spatial Vision, 4*(2–3), 103–129.

Chen, Y., Levy, D. L., et al. (2003). Effects of typical, atypical, and no antipsychotic drugs on visual contrast detection in schizophrenia. *American Journal of Psychiatry, 160*(10), 1795–1801.

Chubb, C., & Sperling, G. (1988). Drift-balanced random stimuli: A general basis for studying non-Fourier motion perception. *Journal of the Optical Society of America. A Optics and Image Science, 5*(11), 1986–2007.

Churchill, J. D., Beckel-Mitchener, A., et al. (2002). Effects of Fragile X syndrome and an FMR1 knockout mouse model on forebrain neuronal cell biology. *Microscopy Research and Technique, 57*(3), 156–158.

Clifford, S., Dissanayake, C., et al. (2007). Autism spectrum phenotype in males and females with fragile X full mutation and premutation. *Journal of Autism and Developmental Disorders, 37*(4), 738–747.

Cohen, I. L. (1994). An artificial neural network analogue of learning in autism. *Biological Psychiatry, 36*(1), 5–20.

Comery, T. A., Harris, J. B., et al. (1997). Abnormal dendritic spines in fragile X knockout mice: Maturation and pruning deficits. *Proceedings of the National Academy of Sciences of the United States of America, 94*(10), 5401–5404.

Cornish, K. M., Munir, F., et al. (1999). Spatial cognition in males with Fragile-X syndrome: Evidence for a neuropsychological phenotype. *Cortex, 35*(2), 263–271.

Cornish, K. M., Turk, J., et al. (2004). Annotation: Deconstructing the attention deficit in fragile X syndrome: A developmental neuropsychological approach. *Journal of Child Psychology and Psychiatry, 45*(6), 1042–1053.

Cornish, K., Turk, J., et al. (2008). The fragile X continuum: New advances and perspectives. *Journal of Intellectual Disability Research, 52*(Pt 6), 469–482.

Dakin, S., & Frith, U. (2005). Vagaries of visual perception in autism. *Neuron, 48*(3), 497–507.

Del Viva, M. M., Igliozzi, R., et al. (2006). Spatial and motion integration in children with autism. *Vision Research, 46*(8–9), 1242–1252.

Derrington, A. M., & Lennie, P. (1984). Spatial and temporal contrast sensitivities of neurones in lateral geniculate nucleus of macaque. *Journal of Physiology, 357*, 219–240.

Dumoulin, S. O., Baker, C. L., Jr., et al. (2003). Cortical specialization for processing first- and second-order motion. *Cerebral Cortex, 13*(12), 1375–1385.

Eckert, M. A., Galaburda, A. M., et al. (2006). The neurobiology of Williams syndrome: Cascading influences of visual system impairment? *Cellular and Molecular Life Sciences, 63*(16), 1867–1875.

Farzin, F., Whitney, D., et al. (2008). Contrast detection in infants with fragile X syndrome. *Vision Research, 48*(13), 1471–1478.

Franklin, A., Sowden, P., et al. (2010). Reduced chromatic discrimination in children with autism spectrum disorders. *Developmental Science, 13*(1), 188–200.

Freitag, C. M., Konrad, C., et al. (2008). Perception of biological motion in autism spectrum disorders. *Neuropsychologia, 46*(5), 1480–1494.

Greenough, W. T., Klintsova, A. Y., et al. (2001). Synaptic regulation of protein synthesis and the fragile X protein. *Proceedings of the National Academy of Sciences of the United States of America, 98*(13), 7101–7106.

Gunn, A., Cory, E., et al. (2002). Dorsal and ventral stream sensitivity in normal development and hemiplegia. *Neuroreport, 13*(6), 843–847.

Gustafsson, L. (1997a). Excessive lateral feedback synaptic inhibition may cause autistic characteristics. *Journal of Autism and Developmental Disorders, 27*(2), 219–220.

Gustafsson, L. (1997b). Inadequate cortical feature maps: A neural circuit theory of autism. *Biological Psychiatry, 42*(12), 1138–1147.

Gustafsson, L. (2004). Comment on "disruption in the inhibitory architecture of the cell minicolumn: Implications for autism". *Neuroscientist, 10*(3), 189–191.

Habak, C., & Faubert, J. (2000). Larger effect of aging on the perception of higher-order stimuli. *Vision Research, 40*(8), 943–950.

Hansen, P. C., Stein, J. F., et al. (2001). Are dyslexics' visual deficits limited to measures of dorsal stream function? *Neuroreport, 12*(7), 1527–1530.

Happe, F., & Frith, U. (2006). The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 36*(1), 5–25.

Heaton, P., Hermelin, B., et al. (1999). Can children with autistic spectrum disorders perceive affect in music? An experimental investigation. *Psychological Medicine, 29*(6), 1405–1410.

Herbert, M. R. (2005). Autism: A brain disorder, or a disorder that affects the brain. *Clinical Neuropsychiatry, 2*, 354–379.

Irwin, S. A., Galvez, R., et al. (2000). Dendritic spine structural anomalies in fragile-X mental retardation syndrome. *Cerebral Cortex, 10*(10), 1038–1044.

Irwin, S. A., Idupulapati, M., et al. (2002). Dendritic spine and dendritic field characteristics of layer V pyramidal neurons in the visual cortex of fragile-X knockout mice. *American Journal of Medical Genetics, 111*(2), 140–146.

Irwin, S. A., Patel, B., et al. (2001). Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: A quantitative examination. *American Journal of Medical Genetics, 98*(2), 161–167.

Kaiser, M. D., & Shiffrar, M. (2009). The visual perception of motion by observers with autism spectrum disorders: A review and synthesis. *Psychonomic Bulletin & Review, 16*(5), 761–777.

Karmiloff-Smith, A. (2007). Atypical epigenesis. *Developmental Science, 10*(1), 84–88.

Keita, L., Mottron, L., & Bertone, A. (in press). Far visual acuity is unremarkable in autism: Do we need to focus on crowding? *Autism Research.*

Keri, S., & Benedek, G. (2009). Visual pathway deficit in female fragile X premutation carriers: A potential endophenotype. *Brain and Cognition, 69*(2), 291–295.

Keri, S., Must, A., et al. (2006). Development of visual motion perception in children of patients with schizophrenia and bipolar disorder: A follow-up study. *Schizophrenia Research, 82*(1), 9–14.

Kim, J., Doop, M. L., et al. (2005). Impaired visual recognition of biological motion in schizophrenia. *Schizophrenia Research, 77*(2–3), 299–307.

Kogan, C. S., Bertone, A., et al. (2004a). Integrative cortical dysfunction and pervasive motion perception deficit in fragile X syndrome. *Neurology, 63*(9), 1634–1639.

Kogan, C. S., Boutet, I., et al. (2004b). Differential impact of the FMR1 gene on visual processing in fragile X syndrome. *Brain, 127*(Pt 3), 591–601.

Kohonen, K. (1995). *Self-organizing maps*. Springer: New-York.

Koldewyn, K., Whitney, D., et al. (2009). The psychophysics of visual motion and global form processing in autism. *Brain*.

Larsson, J., Landy, M. S., et al. (2006). Orientation-selective adaptation to first- and second-order patterns in human visual cortex. *Journal of Neurophysiology, 95*(2), 862–881.

Loesch, D. Z., Huggins, R., et al. (1993). Genotype-phenotype relationships in fragile X syndrome: A family study. *American Journal of Human Genetics, 53*(5), 1064–1073.

Losh, M., Sullivan, P. F., et al. (2008). Current developments in the genetics of autism: From phenome to genome. *Journal of Neuropathology and Experimental Neurology, 67*(9), 829–837.

McClelland, J. L. (2000). The basis of hyperspecificity in autism: A preliminary suggestion based on properties of neural nets. *Journal of Autism and Developmental Disorders, 30*(5), 497–502.

McKendrick, A. M., & Badcock, D. R. (2004). An analysis of the factors associated with visual field deficits measured with flickering stimuli in-between migraine. *Cephalalgia, 24*(5), 389–397.

Milne, E., Swettenham, J., et al. (2002). High motion coherence thresholds in children with autism. *Journal of Child Psychology and Psychiatry, 43*(2), 255–263.

Milner, A. D., & Goodale, M. A. (1995). *The visual brain in action*. New York: Oxford University Press.

Mottron, L., Dawson, M., et al. (2006). Enhanced perceptual functioning in autism: An update, and eight principles of autistic perception. *Journal of Autism and Developmental Disorders, 36*(1), 27–43.

Mottron, L., Dawson, M., et al. (2009). Enhanced perception in savant syndrome: Patterns, structure and creativity. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 364*(1522), 1385–1391.

Mottron, L., Peretz, I., et al. (2000). Local and global processing of music in high-functioning persons with autism: Beyond central coherence? *Journal of Child Psychology and Psychiatry, 41*(8), 1057–1065.

Muhle, R., Trentacoste, S. V., et al. (2004). The genetics of autism. *Pediatrics, 113*(5), e472–e486.

Muller, R. A. (2007). The study of autism as a distributed disorder. *Mental Retardation and Developmental Disabilities Research Reviews, 13*(1), 85–95.

Nishida, S., Ledgeway, T., et al. (1997). Dual multiple-scale processing for motion in the human visual system. *Vision Research, 37*(19), 2685–2698.

Nishida, S., Sasaki, Y., et al. (2003). Neuroimaging of direction-selective mechanisms for second-order motion. *Journal of Neurophysiology, 90*(5), 3242–3254.

O'Brien, J., Spencer, J., et al. (2002). Form and motion coherence processing in dyspraxia: Evidence of a global spatial processing deficit. *Neuroreport, 13*(11), 1399–1402.

O'Riordan, M., & Passetti, F. (2006). Discrimination in autism within different sensory modalities. *Journal of Autism and Developmental Disorders, 36*(5), 665–675.

Pei, F., Baldassi, S., et al. (2009). Neural correlates of texture and contour integration in children with autism spectrum disorders. *Vision Research, 49*(16), 2140–2150.

Pellicano, E., & Gibson, L. Y. (2008). Investigating the functional integrity of the dorsal visual pathway in autism and dyslexia. *Neuropsychologia, 46*(10), 2593–2596.

Pellicano, E., Gibson, L., et al. (2005). Abnormal global processing along the dorsal visual pathway in autism: A possible mechanism for weak visuospatial coherence? *Neuropsychologia, 43*(7), 1044–1053.

Persico, A. M., & Bourgeron, T. (2006). Searching for ways out of the autism maze: Genetic, epigenetic and environmental clues. *Trends in Neurosciences, 29*(7), 349–358.

Reddy, K. S. (2005). Cytogenetic abnormalities and fragile-X syndrome in Autism Spectrum Disorder. *BMC Medical Genetics, 6*, 3.

Rogers, S. J., Wehner, D. E., et al. (2001). The behavioral phenotype in fragile X: Symptoms of autism in very young children with

fragile X syndrome, idiopathic autism, and other developmental disorders. *Journal of Developmental and Behavioral Pediatrics, 22*(6), 409–417.

Simmers, A. J., Ledgeway, T., et al. (2003). Deficits to global motion processing in human amblyopia. *Vision Research, 43*(6), 729–738.

Simmons, D. R., Robertson, A. E., et al. (2009). Vision in autism spectrum disorders. *Vision Research, 49*(22), 2705–2739.

Skottun, B. C. (2000). The magnocellular deficit theory of dyslexia: The evidence from contrast sensitivity. *Vision Research, 40*(1), 111–127.

Smith, A. T., Greenlee, M. W., et al. (1998). The processing of first- and second-order motion in human visual cortex assessed by functional magnetic resonance imaging (fMRI). *Journal of Neuroscience, 18*(10), 3816–3830.

Spencer, J. V., & O'Brien, J. M. (2006). Visual form-processing deficits in autism. *Perception, 35*(8), 1047–1055.

Spencer, J., O'Brien, J., et al. (2000). Motion processing in autism: Evidence for a dorsal stream deficiency. *Neuroreport, 11*(12), 2765–2767.

Sperling, G., Chubb, C., et al. (1994). Full-wave and half-wave processes in second-order motion and texture. *Ciba Foundation Symposium, 184*, 287–303. discussion 303-8, 330-8.

Steyaert, J. G., & De la Marche, W. (2008). What's new in autism? *European Journal of Pediatrics, 167*(10), 1091–1101.

Sutter, A., Sperling, G., et al. (1995). Measuring the spatial frequency selectivity of second-order texture mechanisms. *Vision Research, 35*(7), 915–924.

Theobald, T. M., Hay, D. A., et al. (1987). Individual variation and specific cognitive deficits in the fra(X) syndrome. *American Journal of Medical Genetics, 28*(1), 1–11.

Tommerdahl, M., Tannan, V., et al. (2008). Absence of stimulus-driven synchronization effects on sensory perception in autism: Evidence for local underconnectivity? *Behavioral and Brain Functions, 4*, 19.

Tsermentseli, S., O'Brien, J. M., et al. (2008). Comparison of form and motion coherence processing in autistic spectrum disorders and dyslexia. *Journal of Autism and Developmental Disorders, 38*(7), 1201–1210.

Ungerleider, L. G., & Mishkin, M. (1982). *Analysis of visual behavior*. Cambridge, MA: MIT.

Vandenbroucke, M. W., Scholte, H. S., et al. (2008). A neural substrate for atypical low-level visual processing in autism spectrum disorder. *Brain, 131*(Pt 4), 1013–1024.

Vandenbroucke, M. W., Scholte, H. S., et al. (2009). A new approach to the study of detail perception in Autism Spectrum Disorder (ASD): Investigating visual feedforward, horizontal and feedback processing. *Vision Research, 49*(9), 1006–1016.

Vattikuti, S., & Chow, C. C. (2009). A computational model for cerebral cortical dysfunction in autism spectrum disorders. *Biological Psychiatry*.

Wassink, T. H., Piven, J., et al. (2001). Chromosomal abnormalities in a clinic sample of individuals with autistic disorder. *Psychiatric Genetics, 11*(2), 57–63.

Wilmer, J. B., Richardson, A. J., et al. (2004). Two visual motion processing deficits in developmental dyslexia associated with different reading skills deficits. *Journal of Cognitive Neuroscience, 16*(4), 528–540.

Wilson, H. R., Ferrera, V. P., et al. (1992). A psychophysically motivated model for two-dimensional motion perception. *Visual Neuroscience, 9*(1), 79–97.