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ORIGINAL PAPER

# Associating Neural Alterations and Genotype in Autism and Fragile X Syndrome: Incorporating Perceptual Phenotypes in Causal Modeling

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**Abstract** We have previously described (see companion paper, this issue) the utility of using perceptual signatures for defining and dissociating condition-specific neural functioning underlying early visual processes in autism and FXS. These perceptually-driven hypotheses are based on differential performance evidenced only at the earliest stages of visual information processing, mediated by local neural network functioning. In this paper, we first review how most large-scale neural models are unable to address atypical low-level perceptual functioning in autism, and then suggest how condition-specific, local neural endophenotypes (described in our companion paper) can be incorporated into causal models to infer target candidate gene or gene clusters that are implicated in autism's pathogenesis. The usefulness of such a translational research approach is discussed.

**Keywords** Autism · Fragile X syndrome · Vision · Neural networks · Causal model · Genetics

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Autism and fragile X syndrome (FXS) are neurodevelopmental conditions that sometimes manifest shared neurocognitive and behavioral phenotypes (Clifford et al. 2007; Rogers et al. 2001). Conceptually, one condition is defined by the presence of a specific constellation of clinical symptoms (in the absence of a genetic diagnosis) and the second condition is defined by a distinct genetic mechanism that is "turned off" yet sometimes produces a similar behavioral phenotype to that of autism. The extent to which FXS can serve as a platform to understand one of possibly several mechanisms that leads to an autism diagnosis makes this a worthwhile comparison. However, we must also be cautious about assuming that so-called "commonalities" in phenotypic end-states actually reflect identical cognitive mechanisms or aetiology (Cornish et al. 2007).

Motivated by the suggestion that these genetically-defined conditions may be dissociated at a neural level (Belmonte and Bourgeron 2006), we have presented arguments suggesting that autism and FXS can be differentiated by neural alterations at a *local* network level only,

reflected by condition-specific perceptual signatures characterised by intact/enhanced static information processing in autism compared to decreased sensitivity to dynamic information in FXS (see companion paper, this issue). Based on these signatures, we have proposed biologically-plausible and testable working hypotheses proposing that spatial information processing in autism is best characterised by functional but altered lateral connectivity within primary visual areas. In addition, we argue that the perceptual consequence of altered integrative neural networks mediating more complex, texture-defined information processing are shared (or non-specific) between autism and FXS, demonstrated by decreased sensitivity to texture-defined information, whether static or dynamic, in both conditions. Although this hypothesis is based on decreased sensitivity to texture-defined stimuli, the same argument can be applied to other complex visual stimuli, most notably, global motion stimuli (Bertone and Faubert 2006).

In recent years, interest in information processing capabilities in autism and other neurodevelopmental conditions has increased, reflected by the number of recent review articles dedicated to this topic (i.e., Dakin and Frith 2005; Behrmann et al. 2006; Bertone and Faubert 2006; Mottron et al. 2006; Kaiser and Shiffrar 2009; Simmons et al. 2009).

The importance of early perceptual processing in autism's cognitive and behavioral phenotype has been previously outlined by others proposing that "perceptual features at low levels of processing are closer to autism's core than previously believed", suggesting that atypical information processing may be one of autism's core deficits (Belmonte et al. 2004, p. 1224). Nevertheless, lower-level perceptual processing in autism has until recently been overlooked as an important factor in higher-level cognitive impairments and behavioral manifestations relative to other neurodevelopmental conditions (i.e., developmental dyslexia). This is probably not surprising given the diagnostic and social relevance of autism's behavioral manifestations. Consequently, most research investigating visuo-perceptual processing in autism has for the most part been *symptom-driven*, predominantly concerned with functioning underlying atypical cognitive and/or social aspects (i.e., Courchesne and Pierce 2005; Schultz 2005; Mundy et al. 2009). Findings from these studies have been used to champion neurocognitive theories suggesting decreased integrative connectivity either within higher-level, specialized brain areas responsible for specific types of processing (i.e., fusiform face area, amygdala, etc.), or between functionally specialized networks comprising large-scale neural systems in autism (i.e., social brain network, mirror neuron system, executive function system, etc.; i.e., Castelli et al. 2002; Just et al. 2004; Rippon et al. 2007).

## Large-Scale Neural Models

Such large-scale hypotheses are congruous with neurocognitive theories explaining atypical perceptual functioning in autism by an impairment in global information processing, as exemplified by the Weak Central Coherence hypothesis (Frith and Happé 1994; Happé 1999; Happé and Booth 2008; Happé and Frith 2006). Most current theories based on impaired global processing suggest either atypical or reduced connectivity between functionally specialized neural networks, ultimately affecting either coherence, binding or integration throughout the brain. Specific neural mechanisms underlying such large-scale alterations in autism include reduced neural synchrony (temporal binding deficit hypothesis; Brock et al. 2002; Rippon et al. 2007), decreased functional connectivity between cortical regions during cognitive tasks (underconnectivity hypothesis; i.e., Just et al. 2004; Castelli et al. 2002), increased ratio of neural excitation/inhibition (noisy brain hypothesis; Rubenstien and Merzenich 2003), and abnormal binding-related $\gamma$ oscillations (Grice et al. 2001; Wilson et al. 2007). These models possess powerful explicatory power since many findings regarding atypical visual processing in autism, whether defined by atypical social (i.e., face perception) or non-social (i.e., global motion) complex information processing, are congruous with generalized neuro-integrative dysfunction. In addition, large-scale models are of interest in that they often implicate mechanisms closely related to autism's social phenotype, such as those involved in the social brain network.

Although the aforementioned theories have been influential for the advancement of behavior-contingent hypotheses, they do not provide plausible neural explanations concerning growing evidence of atypical low-level information processing in autism. Firstly, abnormal large-scale neural connectivity is not specific to autism. For example "underconnectivity" and atypical binding-related gamma-band oscillations have been evidenced in other conditions (i.e., Horwitz et al. 1998; Quaglino et al. 2008; Stanberry et al. 2006; Grice et al. 2001; Spencer 2008; Symond et al. 2005; see Phillips and Silverstein 2003 for review). In theory, comprehensive models of integrative dysfunction can also be applied and used to predict complex information processing (i.e., global motion) impairments in other conditions where pervasive neural alteration is suspected, including neurodevelopmental, neurodegenerative, affective and acquired conditions (Bertone and Faubert 2006). In addition, the majority of comprehensive models of autism are based on the premise that local neural networks, such as those underlying early information processing, are either intact or over-functioning (Belmonte et al. 2004; Brock et al. 2002; Frith 2003; Just et al. 2004;

Minshew et al. 1997). This notion can be challenged by recent behavioural and physiological findings that demonstrate that low-level perceptual anomalies in autism are the consequence of altered connectivity within early, local neural networks (i.e., Rubenstien and Merzenich 2003; Belmonte et al. 2004; Casanova et al. 2002; Bertone et al. 2003; 2005; Vandenbroucke et al. 2008; 2009; Milne et al. 2009; Tommerdahl et al. 2008).

Therefore, although the proposed causal origins may result in condition-specific perceptual signatures at one level of processing (i.e., mediated by local neural networks), they result in the same/shared perceptual consequence for information processing at a higher-level (mediated by larger-scale neural networks). It can therefore be suggested that a complexity-specific signature is most often expected, a priori, for any condition where neural dysfunction is suspected, regardless of the nature of neural alteration. This unidirectional prediction makes it difficult to advance a syndrome-specific neural etiology based on the complexity-specific perceptual signatures, given that it is presented not only in both autism and FXS, but in several other conditions where neural alteration is suspected (Bertone and Faubert 2006).

In the following section, we present a theoretical framework that demonstrates how distinct features of autism and FXS can be associated with local neural network alterations. Specifically, within the context of low-level information processing, we argue that it is only possible to dissociate etiologically distinct disorders at a local network level. Although neural connectivity alterations probably exists at both local and global levels in these and other neurodevelopment disorders, they should not be considered to be mutually exclusive (Geschwind 2008). Therefore, comprehensive models predicting atypical performance on tasks implicating higher-level, socially-driven information must also consider the implication of atypically functioning local, lower level networks. It is therefore imperative that the neural substrate of such local networks is well elucidated, and considered as a potentially contributing factor underlying larger-scale neural alterations since local changes may have significant effects on larger-scale network development. For example, an alteration in the architecture and functional connectivity of local circuits during infancy, such as those mediating the extraction of early sensory information, would over time alter the experience-dependent development and organization of long-range neural networks that mediate visually-related cognition and behavior in autism, such as those implicated in social brain network functioning.

## An Adapted and Extended Causal Model Based on Perceptual Phenotypes

Associations between genetic, neurocognitive and behavioral levels have in the past been outlined in causal models of autism (also applicable to other developmental disorders), which propose a framework within which the consequences of biological origins of autism can be defined at different levels of analysis or discourse (Morton and Frith 1995). For example, in a model such as that proposed by Morton and Frith's (1995), multiple genetic perturbations ($O_n$) result in abnormal brain conditions (Br), defined as non-specific or general brain anomalies that can affect a specific brain system (br). It is this specific brain system that is argued to mediate an identifiable and specific function, which if abnormal, will result in one or more characteristic autistic behaviors. Central to the authors' causal chain is the inclusion of an intervening cognitive level, linking the biological and behavioral levels of analysis in their framework. The inclusion of this level ultimately allows for the proposition that autism can be defined as a condition where particular aspects of cognitive functioning are absent, resulting from biological origins (Morton and Frith 1995).

Within the context of such a causal framework, we argue that it is advantageous to assess the neuromodulatory effects of biological alterations, whether mono- or polygenetic in nature ($O_n$), on local network functioning of a specific brain system (such as those mediating low-level information processing), rather than looking at how an abnormal brain condition (Br) impacts the neural functioning of specific brain systems (br). There are several compelling reasons for such an approach. First, operationally defining and dissociating biologically plausible neural networks underlying specific local, low-level information processing is easier to accomplish as compared to higher-level networks whose functioning is contingent on multiple origins (i.e., complex or multimodal information processing, social brain network functioning, etc.). It is more plausible to associate specific genetic perturbation with a local neural alterations (br) which are more proximal to the ultimate genetic cause using paradigms that target specific, well-defined visual information processing mechanisms (such as stimulus-driven mechanisms underlying visual orientation), rather than to the more distal global or non-specific network (abnormal brain condition or Br) involved in various types of processes (e.g., frontal lobe functioning). Second, an alteration in local connectivity specific to an information processing property (i.e., non-functioning brain systems (br)) would affect the functioning of larger neural networks they feed into (Br),

rather than vice-versa (Br → br) (i.e., Dakin and Frith 2005; Courchesne and Pierce 2005). Implementation of these requirements result in a genetically influenced, systems-driven type model (Herbert 2005), where emphasis is placed on associating genetic perturbation with altered local neural connectivity, rather than a specific region of brain dysfunction (or region of dysfunction model). For this reason, it is suggested that local neural alterations in autism (and other neurodevelopmental disorders) should be considered as a potential contributing *cause*, rather than collateral consequence, of large-scale neural dysfunction (see Bertone et al. 2003; Bertone et al. 2005; Rubenstien and Merzenich 2003; Belmonte et al. 2004; Herbert 2005; Tommerdahl et al. 2008).

These tenets provide the theoretical context for an adapted and extended causal model (see Fig. 1) within which previously described condition-specific perceptual signatures will be used to argue either a disorder-specific (or divergent) or shared (or convergent) neural etiology based on neural alterations underlying low-level information processing in autism and FXS. In addition, arguments regarding how such alterations may be associated to causal poly- (autism) or monogenetic (FXS) origins will also be presented. We further argue that the perceptual signatures approach may provide a very useful tool for defining the relationship between genotype and atypical neural networks mediating low-level information processing across neurodevelopmental disorders where emphasis is placed on perceptual, rather than cognitive endophenotypes (see Gerrard and Rugg 2009).

In the case of FXS, it is suggested that the defining monogenetic mutation selectively affects the functioning of local neural mechanisms involved in dynamic information processing (i.e., magnocellular dysfunction). Specifically, selective M-layer morphology changes in the thalamus and reduced sensitivity to low-spatial/high-temporal magnocellular-associated flicker stimuli results (Kogan et al. 2004b), accompanied with a reduction in sensitivity to both simple and complex motion information (Kogan et al. 2004a; Farzin et al. 2008) support this association at different levels of assessment or discourse. Although the genetic origins of autism are not defined (but are probably polygenetic, see Pinto et al. 2010), we argue that it is useful to use information regarding atypical local connectivity that (1) is possibly specific to autism (i.e., atypical lateral connectivity as discussed in companion paper) and (2) can be used to target candidate gene or gene clusters that are implicated in autism's genotype, as represented by the double-ended arrow between genetic and local neural network levels in the model.

As presented in their review, Persico and Bourgeron (2006) suggest three plausible neural consequences of various causal genetic alterations involved in the pathogenesis of autism; reduced cell migration, excitatory-inhibitory imbalance and abnormal synaptogenesis. Of these three possible neural endophenotypes, we propose that candidate genetic alterations leading to an imbalance of excitation/inhibition mediated by glutamate and GABA receptors respectively are most consistent with the aforementioned hypotheses of functionally altered local lateral connectivity in autism (Bertone et al. 2005; Vandenbroucke et al. 2008; Vandenbroucke et al. 2009; Tommerdahl et al. 2008; Keita et al. in press; see Rubenstien and Merzenich 2003; Vattikuti and Chow 2010).

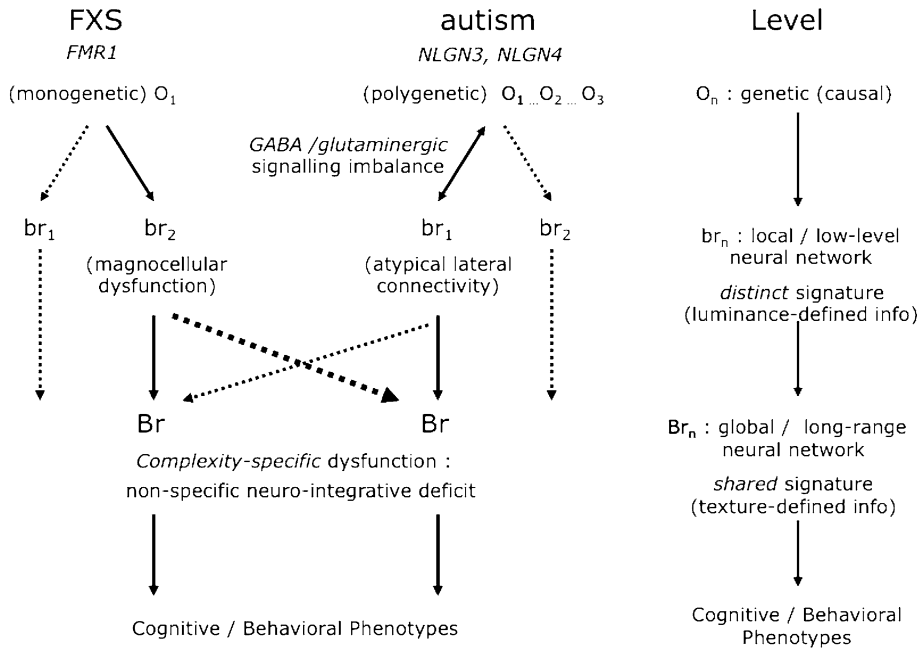


**Fig. 1** As shown in the proposed adapted and extended model, defining local and larger-scale neural alterations via perceptual signatures enables propositions to be advanced regarding how genetic factors (level O) may differentially impact local neural connectivity defined by information processing capabilities (levels br & Br) in FXS and autism

Genomic linkage, association, and mutation studies have identified a number of putative and known genes involved in the pathogenesis of autism that are also implicated in excitatory and inhibitory neural transmission (see Persico and Bourgeron 2006; Abrahams and Geschwind 2008 for reviews). For example, GABA has been linked to chromosome 15, a chromosome implicated in autism (Bundey et al. 1994; Schroer et al. 1998; Wolpert et al. 2000; Muhle et al. 2004; Veenstra-Vanderweele et al. 2004). This inhibitory neurotransmitter is involved in early brain development; disruption to this cluster is likely to impact on the maturation of local circuits involved in information processing, but also on complex cognitive behaviour. Findings both from linkage and association studies strongly implicate this region as housing one or more autism risk alleles (i.e., DeLorey et al. 2008; McCauley et al. 2004). Glutamate receptors on chromosome 6 have also been found to be in disequilibrium in patients with autism (Jamain et al. 2002). In addition, recent studies by Fatemi et al. (2009, 2010) have found atypical GABAergic signaling in different brain regions of persons with autism, suggesting that this dysfunction is widespread in their brains and may be implicated in the cognitive deficits present in this condition. Within the context of local synaptic connectivity consequent to an altered inhibitory-excitatory signaling disequilibrium, autism-associated mutations of neuroligins (NLGN3, NLGN4) cell-adhesion molecules are also proposed as candidate genes implicated in neural alteration affecting information processing in autism. Although these genes have been associated to a small fraction of autism cases within the context of pathogenesis or susceptibility to autism (Jamain et al. 2003; Laumonnier et al. 2004; Yan et al. 2005; but see Gauthier et al. 2005), we argue that they represent plausible origins of neural alteration underlying the aforementioned information processing characteristics in autism given their synaptogenetic involvement in GABAergic and glutamatergic transmission (i.e., Graf et al. 2004; Chih et al. 2005; Huang and Scheiffele 2008; see Gutierrez et al. 2009). Finally, the implication of the *NLGN autism pathway* (Persico and Bourgeron 2006) as the causal origin of AUTISM-specific altered neural connectivity is further supported by demonstrations of SHANK3 gene mutations (Durand et al. 2007; Moessner et al. 2007; Gauthier et al. 2009), a binding partner for NLGNs (Meyer et al. 2004).

Based on the perceptual signatures of autism and FXS, neural networks mediating low-level information processing are only dissociable, or syndrome-specific, at a local neural network level (simple information processed differently); the perceptual consequence of altered global or long-range neural networks (Br) mediating complex, texture-defined information are shared, defined by a complexity-specific dysfunction. In essence, we propose that if one is to infer on how genetic alteration differentially affects neural processes between two or more neurodevelopmental conditions, it is advantageous to assess functioning at local, in addition to long-range networks. This approach is most congruous with models such as the Enhanced Perceptual Functioning (EPF) model (Mottron et al. 2006), whose tenets are based on atypical perceptual functions mediated by local mechanisms operating within primary perceptual cortices in autism. Although the EPF model was originally presented as a descriptive model, recent empirical evidence supports the notion that atypical spatial information processing in autism, and possibly the autistic perceptual endophenotype in general, my originate from atypical lateral connectivity within early cortical areas (see companion paper, this issue). The idea that local neural perturbations should be considered as a contributing cause of autistic behaviour has also been advanced in a recent computational model suggesting a link between local neural alterations originating from excitatory/inhibitory synaptic imbalances and abnormal oculomotor behaviours in autism (Vattikuti and Chow 2010). Finally, another advantage of associating excitatory/inhibitory synaptic connectivity to local rather than large-scale neural networks is that the functional integrity of well-defined circuitry defining low-level feature extraction mechanisms (such as spatial filters in the primary visual cortex) has been demonstrated to be contingent on excitatory/inhibitory signaling (see Ferster and Miller 2000). The association between signaling and the efficacy of locally-mediated feature extraction has been recently demonstrated by Edden et al. (2009), who found that the ability of observers to discriminate orientation (oblique) was correlated with the resting GABA concentration in their primary visual cortex.

Although beyond the scope of the present paper, we also assert that defining and contrasting autism and FXS at a neural level may have important theoretical implications on a cognitive/behavioral level of analysis. As mentioned, FXS is manifested behaviorally with (shared phenotypes) and without autistic features (Clifford et al. 2007; Rogers et al. 2001). It is therefore plausible that genetically-related neural alterations specific to FXS (manifesting neurally by magnocellular dysfunction) may have important downstream implications regarding whether or not an autistic phenotype is manifested, possibly the result of an interaction with other neural alterations resulting from other genetic or environmental causes (as represented by the thick dotted arrow). In contrast, as represented by the thin dotted arrow, the opposite is less probable; atypical lateral connectivity may be less involved in FXS etiology, at both perceptual and behavioral levels. We are presently attempting to dissociate the underlying pathophysiology of the behavioral phenotypes in FXS using perceptual signatures. Specifically, we are examining whether perceptual

signatures of FXS affected children with a dual diagnosis of autism is more consistent with that of FXS or autism alone during development. If the perceptual signatures can be associated with the presence of autistic symptomology at a behavioral level, this approach may potentially play an important role in understanding how the FXS (neural and cognitive) may be implicated in autism. We expect that this information will help in appropriate remediation (clinical and academic) that targets an affected child's specific strengths and challenges.

From a clinical and educational perspective, we suggest that the presented and similar approaches be used to guide accurate diagnosis and interventions throughout development by providing a clearer understanding of perceptual profiles that are more reflective of underlying behavioral phenotypes. It is therefore important that future perceptual phenotypes be assessed within a developmental framework. In this manner, interventions need not be oriented around the behavioral end-state, but rather, such interventions can incorporate and optimize intact information processing abilities at different levels of analysis, specific to each condition and stage of development. To achieve this goal, perceptual phenotyping should beginning in infancy when the developing cortex is most susceptible to altered sensory input. It is also critical that educators and clinicians are made aware of the importance of targeting interventions as early as possible in development.

## Conclusion

Recent advances in the emerging field of developmental cognitive neuroscience have prompted researchers to try and understand neurodevelopmental disorders at varying levels of analysis: genetic, brain, cognitive and behavior. However, it has become increasingly apparent that attempts to articulate simple causal relationships, for example between the deletion of a single gene (as in FXS) and a specific behavioral outcome have been misguided. The shared phenotypic characteristics among diverse neurodevelopmental conditions with disparate genetic etiologies warrant a more appropriate level of analysis that does not underestimate the complexity of the relationship between genetic abnormalities and cognitive outcomes. The present paper outlines an intermediate level of analysis that can be used to propose functional links between genetic and neural alterations that are specific to autism and FXS. As argued by others, analysis at this level may be advantageous not only for suggesting condition-specific neural etiology, but also for guiding genetic research by restricting the search for candidate genetic origins most consistent with neural alterations underlying perceptual abilities, and possibly, cognition and behaviour.

If interpreted within the context of a systemic model where polygenetic perturbations alter neural connectivity, defining the neural substrate of condition-specific visual processes is best accomplished at the local neural network level. By using such a translational framework, we propose that attempting to link genotype with neural alterations using characteristics information processing capabilities is potentially a very useful systems-level approach for defining and dissociating mechanisms involved in the etiology of various neurodevelopmental conditions.

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## References

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

Behrmann, M., Thomas, C., & Humphreys, K. (2006). Seeing it differently: Visual processing in autism. *Trends in Cognitive Science, 10*, 258–264. Review.

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

Belmonte, M. K., Cook, E. H., Jr., Anderson, G. M., Rubenstein, J. L. R., Greenough, W. T., Beckel-Mitchener, A., et al. (2004). Autism as a disorder of neural information processing: Directions for research and targets for therapy. *Molecular Psychiarty, 9*, 646–663.

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

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2003). Motion perception in autism: A 'complex' issue. *Journal of Cognitive Neuroscience, 15*, 218–225.

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain, 128*, 2430–2441.

Brock, J., Brown, C. C., Boucher, J., & Rippon, G. (2002). The temporal binding deficit hypothesis of autism. *Development and Psychopathology, 14*, 209–224. Review.

Bundey, S., Hardy, C., Vickers, S., Kilpatrick, M. W., & Corbett, J. A. (1994). Duplication of the 15q11–13 region in a patient with autism, epilepsy and ataxia. *Developmental Medecine and Child Neurology, 36*, 736–742.

Casanova, M. F., Buxhoeveden, D. P., Switala, A. E., & Roy, E. (2002). Minicolumnar pathology in autism. *Neurology, 58*, 428–432.

Castelli, F., Frith, C., Happé, F., & Frith, U. (2002). Autism, asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain, 125*, 1839–1849.

Chih, B., Engelman, H., & Scheiffele, P. (2005). Control of excitatory and inhibitory synapse formation by neuroligins. *Science, 307*, 1324–1328.

Clifford, S., Dissanayake, C., Bui, Q. M., Huggins, R., Taylor, A. K., & Loesch, D. Z. (2007). Autism spectrum phenotype in males

and females with fragile X full mutation and premutation. *Journal of Autism and Developmental Disorders, 37*, 738–747.

Cornish, K., Turk, J., & Levitas, A. (2007). Fragile X syndrome and autism; common developmental pathways? *Current Pediatric Reviews, 3*, 61–68.

Courchesne, E., & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: Local over-connectivity but long-distance disconnection. *Current Opinion in Neurobiology, 15*, 225–230.

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

DeLorey, T. M., Sahbaie, P., Hashemi, E., Homanics, G. E., & Clark, J. D. (2008). Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: A potential model of autism spectrum disorder. *Behavioural Brain Research, 187*, 207–220.

Durand, C. M., Betancur, C., Boeckers, T. M., Bockmann, J., Chaste, P., Fauchereau, F., et al. (2007). Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nature Genetics, 39*, 25–27.

Edden, R. A., Muthukumaraswamy, S. D., Freeman, T. C., & Singh, K. D. (2009). Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. *Journal of Neuroscience, 29*, 15721–15726.

Farzin, F., Whitney, D., Hagerman, R. J., & Rivera, S. M. (2008). Contrast detection in infants with fragile X syndrome. *Vision Research, 48*, 1471–1478.

Fatemi, S. H., Reutiman, T. J., Folsom, T. D., & Thuras, P. D. (2009). GABA(A) receptor downregulation in brains of subjects with autism. *Journal of Autism and Developmental Disorders, 39*, 223–230.

Fatemi, S. H., Reutiman, T. J., Folsom, T. D., Rooney, R. J., Patel, D. H., & Thuras, P. D. (2010). mRNA and protein levels for GABA(A)alpha4, alpha5, beta1 and GABA (B)R1 receptors are altered in brains from subjects with autism. *Journal of Autism and Developmental Disorders, 40*, 743–750.

Ferster, D., & Miller, K. D. (2000). Neural mechanisms of orientation selectivity in the visual cortex. *Annual Review of Neuroscience, 23*, 441–471.

Frith, C. (2003). What do imaging studies tell us about the neural basis of autism. In G. Bock & J. Goode (Eds.), *Autism: Neural basis and treatment possibilities* (pp. 149–176). Chichester, UK: Wiley.

Frith, U., & Happé, F. (1994). Autism: Beyond "theory of mind". *Cognition, 50*, 115–132.

Gauthier, J., Bonnel, A., St-Onge, J., Karemera, L., Laurent, S., Mottron, L., et al. (2005). NLGN3/NLGN4 gene mutations are not responsible for autism in the Quebec population. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics., 132*, 74–75.

Gauthier, J., Spiegelman, D., Piton, A., Lafrenière, R. G., Laurent, S., St-Onge, J., et al. (2009). Novel de novo SHANK3 mutation in autistic patients. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 50*, 421–424.

Gerrard, S., & Rugg, G. (2009). Sensory impairments and autism: A re-examination of causal modelling. *Journal of Autism and Developmental Disorders, 39*, 1449–1463.

Geschwind, D. H. (2008). Autism: many genes, common pathways? *Cell, 135*, 391–395.

Graf, E. R., Zhang, X., Jin, S. X., Linhoff, M. W., & Craig, A. M. (2004). Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins. *Cell, 119*, 1013–1026.

Grice, S. J., Spratling, M. W., Karlimoff-Smith, A., Halit, H., Csibra, G., de Haan, M., et al. (2001). Disordered visual processing and oscillatory brain activity in autism and William's syndrome. *Neuroreport, 12*, 2697–2700.

Gutierrez, R. C., Hung, J., Zhang, Y., Kertesz, A. C., Espina, F. J., & Colicos, M. A. (2009). Altered synchrony and connectivity in neuronal networks expressing an autism-related mutation of neuroligin 3. *Neuroscience, 162*, 208–221.

Happé, F. (1999). Autism: Cognitive deficit or cognitive style? *Trends in Cognitive Sciences, 3*, 216–222.

Happé, F. G., & Booth, R. D. (2008). The power of the positive: Revisiting weak coherence in autism spectrum disorders. *Quarterly Journal of Experimental Psychology (Colchester), 61*, 50–63. Review.

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

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

Horwitz, B., Rumsey, J. M., & Donohue, B. C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy of Sciences USA, 95*, 8939–8944.

Huang, J. H., & Scheiffele, P. (2008). GABA and neuroligin signaling: Linking synaptic activity and adhesion in inhibitory synapse development. *Current Opinion in Neurobiology, 18*, 77–83.

Jamain, S., Betancur, C., Quach, H., Philippe, A., Fellous, M., Giros, B., et al. (2002). Linkage and association of the glutamate receptor 6 gene with autism. *Molecular Psychiatry, 7*, 302–310.

Jamain, S., Quach, H., Betancur, C., Råstam, M., Colineaux, C., Gillberg, I. C., et al. (2003). Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nature Genetics, 34*, 27–29.

Just, M. A., Cherkassky, V. L., Keller, T. A., & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high functioning autism: Evidence of under-connectivity. *Brain, 127*, 1811–1821.

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*, 761–777.

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

Kogan, C. S., Bertone, A., Cornish, K., Boutet, I., DerKaloustian, V. M., Andermann, E., et al. (2004a). Integrative cortical dysfunction and pervasive motion perception deficit in fragile X syndrome. *Neurology, 63*, 1634–1639.

Kogan, C. S., Boutet, I., Cornish, K., Zangenehpour, S., Mullen, K. T., Holden, J. A., et al. (2004b). Differential impact of the FMR1 gene on visual processing in fragile X syndrome. *Brain, 127*, 591–601.

Laumonnier, F., Bonnet-Brilhault, F., Gomot, M., Blanc, R., David, A., et al. (2004). X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. *American Journal of Medical Genetics, 74*, 552–557.

McCauley, J. L., Olson, L. M., Delahanty, R., Amin, T., Nurmi, E. L., Organ, E. L., et al. (2004). A linkage disequilibrium map of the 1-Mb 15q12 GABA(A) receptor subunit cluster and association to autism. *The American Journal of Human Genetics: B Neuropsychiatrtic Genetics, 131*, 51–59.

Meyer, G., Varoqueaux, F., Neeb, A., Oschlies, M., & Brose, N. (2004). The complexity of PDZ domain-mediated interactions at glutamatergic synapses: A case study on neuroligin. *Neuropharmacology, 47*, 724–733.

Milne, E., Scope, A., Pascalis, O., Buckley, D., & Makeig, S. (2009). Independent component analysis reveals atypical

electroencephalographic activity during visual perception in individuals with autism. *Biological Psychiatry, 65*, 22–30.

Minshew, N. J., Goldstein, G., & Siegel, D. J. (1997). Neuropsychologic functioning in autism: Profile of a complex information processing disorder. *Journal of the International Neuropsychological Society, 3*, 303–316.

Moessner, R., Marshall, C. R., Sutcliffe, J. S., Skaug, J., Pinto, D., Vincent, J., et al. (2007). Contribution of SHANK3 mutations to autism spectrum disorder. *American Journal of Human Genetics, 81*, 1289–1297.

Morton, J., & Frith, U. (1995). Causal modelling: A structural approach to developmental psychopathology. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology, volume 1, theory and methods* (Vol. 1, pp. 357–390). New York: Wiley.

Mottron, L., Dawson, M., Soulieres, I., Hubert, B., & Burack, J. (2006). Enhanced perceptual functioning in autism: An update, and eight principles of autistic perception. *Journal of Autism and Developmental Disorders, 36*, 27–43. Review.

Muhle, R., Trentacoste, S. V., & Rapin, I. (2004). The genetics of autism. *Pediatrics, 113*, 472–486.

Mundy, P., Sullivan, L., & Mastergeorge, A. M. (2009). A parallel and distributed-processing model of joint attention, social cognition and autism. *Autism Research, 2*, 2–21.

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

Phillips, W. A., & Silverstein, S. M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behavioural and Brain Sciences, 26*, 65–82.

Pinto, D., Pagnamenta, A. T., Klei, L., Anney, R., Merico, D., Regan, R., Conroy, J., Magalhaes, T. R., Correia, C., Abrahams, B. S., et al. (2010). Functional impact of global rare copy number variation in autism spectrum disorders. *Nature* [Epub ahead of print].

Quaglino, V., Bourdin, B., Czternasty, G., Vrignaud, P., Fall, S., Meyer, M. E., et al. (2008). Differences in effective connectivity between dyslexic children and normal readers during a pseudoword reading task: An fMRI study. *Neurophysiologie Clinique-Clinical Neurophysiology, 38*, 73–82.

Rippon, G., Brock, J., Brown, C., & Boucher, J. (2007). Disordered connectivity in the autistic brain: Challenges for the 'new psychophysiology'. *International Journal of Psychophysiology, 63*, 164–172.

Rogers, S. J., Wehner, D. E., & Hagerman, R. (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*, 409–417.

Rubenstien, J. L., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, Behavior, 2*, 255–267.

Schroer, R. J., Phelan, M. C., Michaelis, R. C., Crawford, E. C., Skinner, S. A., Cuccaro, M., et al. (1998). Autism and maternally derived aberrations of chromosome 15q. *American Journal of Medical Genetics, 76*, 327–336.

Schultz, R. T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience, 23*, 125–141.

Simmons, D. R., Robertson, A. E., McKay, L. S., Toal, E., McAleer, P., & Pollick, F. E. (2009). Vision in autism spectrum disorders. *Vision Research, 49*, 2705–2739.

Spencer, K. M. (2008). Visual gamma oscillations in schizophrenia: Implications for understanding neural circuitry abnormalities. *Clinical Electroencephalography and Neuroscience, 39*, 65–68.

Stanberry, L. I., Richards, T. L., Berninger, V. W., Nandy, R. R., Aylward, E. H., Maravilla, K. R., et al. (2006). Low-frequency signal changes reflect differences in functional connectivity between good readers and dyslexics during continuous phoneme mapping. *Magnetic Resonance Imaging, 24*, 217–229.

Symond, M. P., Harris, A. W., Gordon, E., & Williams, L. M. (2005). "Gamma synchrony" in first-episode schizophrenia: A disorder of temporal connectivity? *American Journal of Psychiatry, 162*, 459–465.

Tommerdahl, M., Tannan, V., Holden, J. K., & Baranek, G. T. (2008). Absence of stimulus-driven synchronization effects on sensory perception in autism: Evidence for local underconnectivity? *Behavioral and Brain Functions, 4*, 4–19.

Vandenbroucke, M. W., Scholte, H. S., van Engeland, H., Lamme, V. A., & Kemner, C. (2008). A neural substrate for atypical low-level visual processing in autism spectrum disorder. *Brain, 131*, 1013–1024.

Vandenbroucke, M. W., Scholte, H. S., van Engeland, H., Lamme, V. A., & Kemner, C. (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*, 1006–1016.

Vattikuti, S., & Chow, C. C. (2010). A computational model for cerebral cortical dysfunction in autism spectrum disorders. *Biological Psychiatry, 67*, 672–678.

Veenstra-Vanderweele, J., Christian, S. L., & Cook, E. H., Jr. (2004). Autism as a paradigmatic complex genetic disorder. *Annual Review of Genomics and Human Genetics, 5*, 379–405.

Wilson, T. W., Rojas, D. C., Reite, M. L., Teale, P. D., & Rogers, S. J. (2007). Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. *Biological Psychiatry, 62*, 192–197.

Wolpert, C. M., Menold, M. M., Bass, M. P., Qumsiyeh, M. B., Donnelly, S. L., Ravan, S. A., et al. (2000). Three probands with autistic disorder and isodicentric chromosome 15. *American Journal of Medical Genetics, 96*, 365–372.

Yan, J., Oliveira, G., Coutinho, A., Yang, C., Feng, J., et al. (2005). Analysis of the neuroligin 3 and 4 genes in autism and other neuropsychiatric patients. *Molecular Psychiatry, 10*, 329–332.