mothers. C&B show that psychosis-proneness is associated with smaller, slower growing, less demanding babies, whereas autism-proneness is associated with the opposite. They also argue that the remote associations found in schizotypy and artistic creativity are a direct (and therefore unfakable) consequence of having a brain whose growth pattern is of the psychosis-prone – and therefore less costly for the mother – type.

This hypothesis is not implausible. Human reproduction makes extremely high metabolic demands on females. Rates of maternal death in pregnancy, and during or soon after birth, are as high as 2% per pregnancy in the poorest countries even today (World Health Organisation 2007), and would have been higher under ancestral conditions. The Haigian model of paternal–maternal conflict under multiple paternity predicts that paternal interests will tolerate a greater risk of harm or death to the mother than would be optimal from the point of view of the maternal genome. This tussle is partly carried out at the level of genetic imprints and counter-imprints, but can also be carried out in the arena of mate choice. If the female can find cues that discriminate males on the basis of how strongly their genotype is going to favour the patrilineal interest, she should exploit them. Such cues should be of *particular* interest in the short-term mating case, where genetic material is all that is being provided. In the long-term case, the additional costs of offspring of autistic-prone individuals could be offset by their propensity to make paternal behavioural investment.

The hypothesis, speculative as it is, could lead to testable predictions. Further investigation is needed into whether the young offspring of highly schizotypal or creative males are indeed smaller or less demanding than the babies of more autistic-prone individuals, and also of women's intuitions about the desirability of such men as partners. One prediction might be that women whose own somatic resources are limited (health problems, small size) should be especially keen on schizotypal-creative versus autism-prone males as partners. This would indicate that these traits are being used as mate-choice indicators for the reasons invoked.

It is a great testament to the breadth and importance of C&B's target article that it allows novel predictions to be generated about something so far removed from their initial concern.

Cortical plasticity: A proposed mechanism by which genomic factors lead to the behavioral and neurological phenotype of autism spectrum and psychotic-spectrum disorders

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Abstract: Crespi & Badcock (C&B) hypothesize that biases toward expression of paternally or maternally imprinted genes lead to the symptoms of autism spectrum disorders (ASD) and psychotic-spectrum disorders (PSD), respectively. We suggest that such genetic risk factors may act by inducing abnormalities in developmental and learning-related plasticity. We provide preliminary evidence of abnormal plasticity in ASD and suggest transcranial magnetic stimulation as a useful tool to investigate as well as influence cortical plasticity.

The target article suggests that the symptoms of autism spectrum disorders (ASD) and psychotic-spectrum disorders (PSD) are mediated by altered biases toward paternally or maternally expressed genes, respectively. This hypothesis fits well with the existing literature, and provides a potential genotype that acts together with brain development and environmental factors to create the complex phenotypes that define these disorders.

Though understanding the genetic underpinning of these disorders is of critical importance, diagnosis usually occurs around age 2–3 in ASD and during adolescence or later in PSD. Thus, the phenotypic presentation is a result of the complex interaction among genetic risk factors, brain development, and environment, and ultimately the manifestation of brain plasticity. It is worth considering whether the mechanisms of plasticity might be normal, simply acting upon a genetically determined abnormal substrate, or may themselves be pathological, thus contributing to progressively dysfunctional states.

There are several pieces of evidence to support abnormal plasticity in ASD. First, the developmental trajectory of brain size abnormalities suggests a dynamic underlying process. Second, studies have found decreased cortico-cortical and long-range connections and an increase in intracortical and superficial connections. Such patterns of abnormal connectivity might be the result of increased ability to form new connections and/or a decreased ability to prune superfluous ones. Abnormal plasticity is also consistent with the phenotype of PSD, which has also been reported to have abnormal connectivity patterns. Though there are inconsistencies in the findings, one study finds increased corpus callosum size with decreased local connections (Siekmeier & Hoffman 2002). Additionally, the lower levels of BDNF in schizophrenia (Moises et al. 2002; Palomino et al. 2006; Weickert et al. 2003) may also be related to abnormal plasticity. A recent study suggests that there is a relationship between having a specific polymorphism in the BDNF gene and experience-dependent motor plasticity (Kleim et al. 2006).

Abnormal plasticity provides a plausible, parsimonious, and testable mechanism, consistent with both the main proposal of the target article, as well as the core phenotypes of ASD and PSD. Studies are currently underway to evaluate the role of plasticity in the etiology of ASD using transcranial magnetic stimulation (TMS). TMS paradigms can capture aspects of homosynaptic and heterosynaptic plasticity (see Hallett 2007 for a review). A paradigm known as theta burst stimulation (TBS) is well-suited for investigating homosynaptic plasticity and allows a rapid conditioning of the motor cortex that produces controllable, consistent, and long-lasting effects on motor physiology and behavior. In typical individuals, TBS for 20–90 seconds results in suppression of the motor evoked potential (MEP) for up to 30 minutes. Preliminary data suggest this effect is greater in both degree and duration in individuals with ASD. (See Fig. 1.)

Paired associative stimulation (PAS) is well-suited for investigations of heterosynaptic plasticity and ability for the motor cortex to form long term potentiation (LTP) and long term depression (LTD) in response to sensory input. PAS involves stimulation of the median nerve combined with TMS over the motor cortex at variable interstimulus intervals (ISI). At 25 msec ISI the MEP shows facilitation, while an ISI of 10 msec inhibits the MEP. Both effects are amplified in individuals with ASD. (See Fig. 2.)

Abnormal patterns of plasticity may be leading to the abnormal connectivity in ASD, which in turn may be mediating the deficits in social and communicative skills (as these skills require synchronization of neuronal populations across relatively disparate regions of the cortex) as well as the restricted, repetitive, and stereotyped patterns of behaviors, interests, and activities. Abnormal plasticity may also lead to increased long-range connections in PSD, perhaps contributing to the complex social delusions, enhanced imagination and creativity, and "loose" associations between words and aspects of the environment in this population.

Though the genetic predisposition toward maternally or paternally expressed genes might predispose a child for developing these disorders, the recent increase in incidence can better be

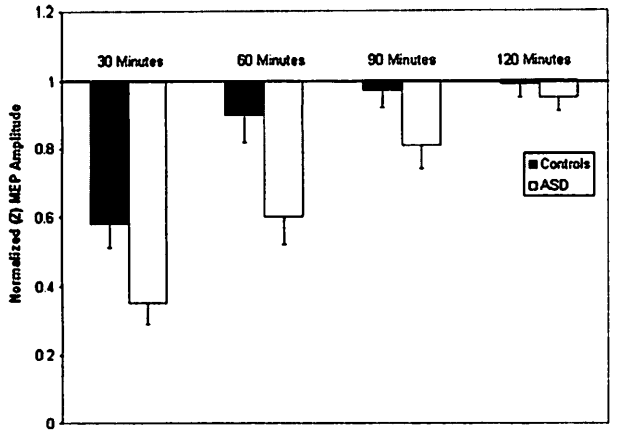

Figure 1 (Oberman & Pascual-Leone). Bars represent the standardized (Z score) MEP amplitude at 30, 60, 90, and 120 minutes following continuous theta burst stimulation (cTBS) for the control and ASD sample. cTBS induces an LTD-like phenomenon that can be quantified as a reduction in the amplitude of the MEP. Error bars represent the standard error of the mean. Note the greater degree and longer duration of suppression in the ASD group.

accounted for by a change in environment rather than an increase in the penetrance of the genetic risk factor. Children growing up in recent years are being exposed to an ever more diverse and stimulating environment packed with stimuli to process from very early on. In a child who is predisposed to increased plasticity, this overly stimulating environment could lead to deleterious consequences. In such a setting, ASD genetic risk factors may lead to a facilitated, insufficiently controlled reshaping of neural connections. The child may develop local hyperconnectivity, a surge in brain size, and an inefficient processing system for incoming sensory stimuli. If, however, this child is placed in a very structured environment and develops a specific interest, this enhanced plasticity may actually lead to savant abilities.

One can also consider the opposite scenario with a child who is genetically at risk for developing PSD with an increased bias toward effects of genes with maternal expression leading to uncontrollable increased global connectivity. Later in life when more associative long-range connections are maturing, abnormal plasticity in this population would lead to the characteristic positive symptoms of PSD.

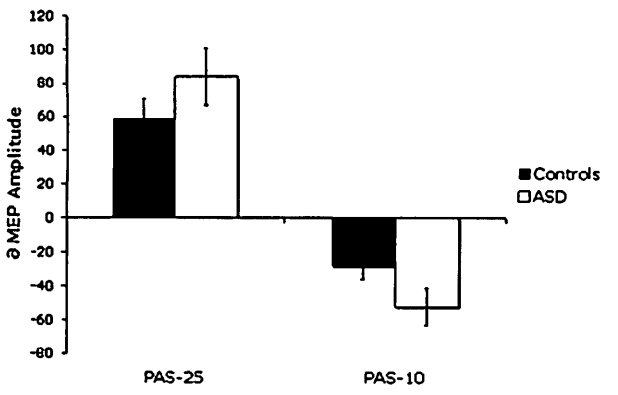

Figure 2 (Oberman & Pascual-Leone). Bars represent the average percent change in MEP amplitude following paired associative stimulation (PAS) (with an ISI of 25 msec and 10 msec) for the control and ASD sample. PAS_{25} results in facilitation, while PAS_{10} results in suppression of the MEP. Note the greater degree of both facilitation and suppression in the ASD group. Error bars represent the standard error of the mean.

TMS can be used not only to measure the degree of plasticity in a given system, but also as a valuable tool for clinicians developing therapeutic interventions for these disorders. Specifically, repetitive TMS (rTMS) has been shown to produce long-term (several-month) changes in cortical plasticity and has been effective in other brain diseases, for example, depression.

In conclusion, Crespi & Badcock (C&B) present an interesting hypothesis for genetic factors that may lead to ASD and PSD. We suggest that abnormal plasticity may be the common underlying mechanism that ultimately leads to many of the core behavioral deficits which define these disorders. The manifestation of the specific pattern of abnormal plasticity may lie in the timing of the hyperplastic response. Specifically, if hyperplasticity is promoted early in life, this may preferentially affect local circuits, resulting in ASD. However, PSD may result from abnormal plasticity during adolescence and young adulthood, leading to promotion of long-range hyperplasticity. Such conceptualization provides an appealing account for the increase in incidence of ASD and PSD in our highly stimulating society. Finally, modulation of plasticity may provide an effective means to treat these disorders.

A complete theory of psychosis and autism as diametric disorders of social brain must consider full range of clinical syndromes

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Abstract: We argue that autism and psychosis spectrum disorders cannot be conceptualized as polar extremes of mentalizing ability. We raise two main objections: (1) the autistic-psychotic continuum, as conceptualized by the authors, excludes defining features of schizophrenia spectrum: negative symptoms, which correlate more strongly with mentalizing impairments; and (2) little evidence exists for a relationship between mentalizing ability and positive symptoms.

Crespi & Badcock's (C&B's) novel and bold theory places autism spectrum disorders (ASD) and psychotic-spectrum disorders (PSD) on diametrically opposite ends of a spectrum, with underdeveloped social cognition in ASD and hyper-developed social cognition in PSD. The authors represent schizophrenia at the extreme end of PSD and discuss their genetic imprinting hypothesis of hyper-mentalizing in PSD mainly in the context of schizophrenia. However, although the authors *acknowledge* the multifaceted nature of the disorder, they fail to adequately *consider* it in the construction of their theory.

One underlying problem with placing schizophrenia and ASD at extreme poles is that the major symptoms of schizophrenia do not cohere with this method of distinction. Schizophrenia is characterized by positive symptoms such as delusions and hallucinations, and negative symptoms that reflect a diminution or loss of normal functions such as alogia, anergia, and anhedonia. Positive symptoms fluctuate over time and can be ameliorated by antipsychotic medication, but negative symptoms are treatment-resistant and enduring. C&B's theory focuses on schizophrenia to represent