In *Evolutionary Developmental Anthropology*, edited by **Julia Boughner** and **Campbell Rolian, Wiley, 2013**

The evolutionary biology of human neurodevelopment: evo-neuro-devo comes of age

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Introduction

The field of evolutionary developmental biology arose from the joining of two research traditions: century-old conceptualizations of how embryonic development has evolved, and recent discoveries of how genes orchestrate changes and variation in development. The goals of this field are manyfold, and famously include the roles of pleiotropy and 'constraints' in evolutionary change compared to unconstrained polygenic inheritance, the extent and control of modularity in developmental-genetic phenotypes, and the importance of heterochrony in evolutionary-developmental trajectories.

Most applications of evolutionary-developmental research have centered on morphological or life-historical timing phenotypes, probably due to ease of quantification. However, some of the most interesting traits that have evolved through changes in development are behavioral, and ultimately in a mechanistic sense, neurological. Such phenotypes are more challenging to measure due to the complexities of brain development and function. Recent, accelerating progress in the study of human

neurodevelopment, in the contexts of both typical and atypical brain development, are making possible the first tripartite connections between evolutionary biology, developmental biology, and neurological phenotypes. These connections are especially important because they allow the joint study of how humans evolved, how the human brain develops, and how variation among individuals in human brain development can manifest as neurodevelopmental conditions, most prominently autism and schizophrenia. In turn, such studies can dovetail with anthropological, paleontological, and comparative-primatological data on human evolution, to uncover convergent lines of evidence that lend rigor to the intrinsically challenging goal of inferring how modern human brain development and cognition have evolved.

In this article, we seek to inaugurate the field of evo-neuro-devo, the study of how neurodevelopment evolves. We focus on humans, the species for whom most salient data are available.

Our general approach is straightforward. Segregating genetic variation, and *de novo* mutations, provide novel insights into human neurodevelopmental gene functions, including effects from pleiotropy, polygenic inheritance, and developmental-genetic convergence. Neurogenetic phenotypes, including phenotypes characterizing psychiatric conditions mediated by neurodevelopment, are generated via gene-environment interactions, which have been more or less highly canalized by effects of selection whose impacts are expected to decrease with past evolutionary time from the present. Current phenotypic effects from genetic variation thus allow direct insights into psychiatric conditions, typical neurogenetic architecture, and evolutionary histories of neurodevelopment: how modularity, connectivity, timing, and information-processing trajectories have evolved. This methodology is akin to using experimental alterations of genes, proteins, or pathways to infer functions and tradeoffs, in the context of phenotypic, evolutionary trajectories inferred from independent sources of information.

We address two main questions. First, how are the causes and phenotypes of the primary human neurodevelopmental conditions, especially autism and schizophrenia, related to recent neurodevelopmental and cognitive changes in human evolutionary history? In this context, how have risks for particular neurodevelopmental psychiatric

conditions, as constellations of associated phenotypes, evolved, as extremes of normal variation? We refer to these psychiatric reifications as 'conditions', more than 'disorders', to emphasize that their psychological and neurological phenotypic spectra grade continuously into so-called normality, and to pre-empt consideration of psychiatric conditions as 'diseases' that solely involve dysfunction.

Second, to what degree does variation in specific sets of evo-neuro-devo phenotypes underlie the causes and phenotypes of neurodevelopmental conditions? In particular, we focus on how genetic factors that cause changes in the rate and timing patterns of neurodevelopmental events, and associated psychological phenotypes, are involved in autism spectrum conditions and schizophrenia. We thus put forward a 'developmental heterochronic' model for helping to explain the genetic bases of these two conditions, and connect the model with heterochronic change in human ancestry. This question generates a new perspective on how typical development is related to atypical development in autism and schizophrenia, in the general framework of how recently-evolved human neurological and psychological traits have generated liability to particular extremes of variation.

The genetical evolution of neurodevelopment

The evolutionary genetics of human neurodevelopment can be studied from two perspectives, that we call 'genes-up' and 'phenotypes-down'. The genes-up approach involves analyses of specific genes with documented functional roles in both human evolution and human neurodevelopment. The best examples of such genes are those that mediate the evolutionary tripling of human brain size since our divergence from the chimpanzee lineage: so-called 'microcephaly genes'.

Human-genetic pedigree-based studies, and neurological analyses, indicate that loss of function for 'microcephaly' genes leads to a brain about one-third the size of normal, but typical in shape. Molecular-biological studies indicate that these genes, which include ASPM, CDK5RAP2, CENPJ, CEP152, DUF1220, KCTD13, MCPH1, STIL and WDR62, among others) (Mahmood et al. 2011; Dumas et al. 2012; Golzio et al. 2012) exhibit convergent functions in cell-cycle dynamics during early brain

development, which increase numbers of neural progenitor cells and thus increase the overall size of the brain (Megraw et al. 2011). Moreover, molecular-evolutionary studies have shown that the evolution of microcephaly genes tends to be characterized by episodes of functional amino-acid evolution - so-called positive selection - along the human lineage as well as among our primate relatives (e. g., Ponting and Jackson 2005; Montgomery et al. 2011).

Based on these independent lines of molecular, developmental, and evolutionary evidence, we can describe a 'microcephaly paradigm' for evol-neuro-devo change: humans undergo a series of naturally-selected allelic substitutions that led to the evolution of human-specific phenotypes via changes in development. In turn, genetic alterations to the resultant human-evolved developmental pathways (for microcephaly, losses of function in key regulators) generate phenotypes with evolutionary structure - architecture - that links the human disorder with human evolutionary change and with development. Other sorts of large alterations to microcephaly genes, such as duplications (involving *de novo* mutations), may result in opposite-direction phenotypes: larger brain size, apparently through opposite alterations, gains of function, in the relevant developmental pathway (e. g., Golzio et al. 2012). In turn, small-scale variation in brain size has been linked with allelic variation in single nucleotide polymorphisms for several microcephaly genes (Rimol et al. 2010), indicating that small, polygenic effects on brain size development may also reflect phylogenetic history. To the extent that such segregating allelic variation is maintained in human populations due to trade-offs (as opposed to genetic drift, or as opposed to alleles changing in frequency due to selection; Crespi 2011a), there should be both costs and benefits to the alternative alleles at a locus; for example, larger brains are energetically much more costly, but have been associated with increased scores on tests of 'intelligence' (Schoenemann 2006).

[Figure 1]

The 'microcephaly paradigm' (Figure 1) involves a simple phenotype (overall brain size), and relatively-simple mechanisms (such as extensions of the proliferation stages of early brain growth). A second, more-specialized human-evolved phenotype, speech and language, also appears to fit the paradigm. Thus, the FOXP2 gene has

evolved under positive selection in humans, loss of function in the gene results in a reduced human-specific phenotype (here, in speech, language and articulation skills), and segregating allelic variation in the gene is associated with speech and language related phenotypes (in autism spectrum conditions and in schizophrenia). Here, the molecular-developmental mechanism involves localized neural-growth effects on neurodevelopment, in speech-related regions of the brain (Vernes et al. 2011). The cognitive effects of alternative segregating alleles on brain development and language remain to be investigated in detail, although for two SNPs, one allele has been reported to increase risk of autism spectrum disorders, whereas the alternative allele increases risk of schizophrenia with auditory hallucinations (Gong et al. 2004; Sanjuan et al. 2005; Casey et al. 2012). In theory, alternative alleles at single nucleotide polymorphisms (SNPs) of FOXP2 may thus involve tradeoffs in language-related cognitive functions among non-clinical populations, as described in more detail below.

Can the microcephaly paradigm be expanded, to encompass not just brain size and structure, but also major patterns of human cognitive variation underlain by neurodevelopment? To do so, we must adopt a 'phenotypes down' perspective, as the genetic, genomic and developmental underpinnings of complex human cognitive phenotypes are insufficiently known to start usefully and comprehensively from genes.

The evolution of human cognition and its disorders

Humans evolved large brains in conjunction with a spectacular constellation of new abilities for complex cognition. Let us therefore expand the microcephaly paradigm to a large suite of human-evolved (uniquely human) and human-elaborated (enhanced and more complex in humans) neurodevelopmental, cognitive phenotypes (Figure 2). Each of these phenotypes has evolved in the human lineage, each has a polygenic basis (so far as known), and each undergoes some trajectory of development as humans mature throughout infancy, childhood, adolescence, and young adulthood. Thus, (1) language is unique to humans, (2) humans exhibit highly-developed social cognition, social emotionality and social behavior (the so-called social brain), which is commonly manifest in complex, highly regulated goal pursuit, (3) human technical, mechanical and systematic-thinking skills far exceed those of our close primate relatives, and (4) we

show much better developed abstract, so-called 'fluid' intelligence, defined as pure problem-solving ability independent of learned, cuturally-based knowledge (Reader and Laland 2002; Saxe 2006; Suddendorf et al. 2011; Frith and Frith 2012; Nisbett et al. 2012; Reader et al. 2011).

[Figure 2]

These human-evolved and human-elaborated phenotypes are certainly associated with, and potentiated by, large absolute brain size, but they also involve specializations, as indicated, for example, by the notable degree of neuroanatomical and functional modularity in social-brain (Frith and Frith 2012) and non-social-brain (Stout et al. 2008) regions. Moreover, although large suites of human cognitive abilities that depend on general intelligence show strong pairwise positive correlations (embodied by the latent factor 'g', which appears to reflect some measure of general information-processing skills; Johnson and Bouchard 2005), some sets of human cognitive abilities show negative correlations with one another, with or without statistical adjustments for general intelligence (Table 1). In particular, extensive evidence has accumulated, especially in the literature on autism spectrum conditions, for negative associations of social, verbal phenotypes with visual-spatial, perceptual, and mechanistic phenotypes. These findings are indicative of tradeoffs between different sets of human cognitive traits, such that abilities in one large domain, verbal and social skills, tend to negatively covary with abilities in another domain, non-social skills. Different skills also, of course, tend to recruit different sets of regions of the brain, involving social-brain areas including midline areas, the temporoparietal junction, language processing in Broca's and Wernicke's areas, and the orbitofrontal cortex (e. g., Saxe 2006; Frith and Frith 2012), in contrast to parietal and occipital regions, and some additional areas, for non-social skills (e. g. Schoenenmann 2006; Stout et al. 2008; Hoppe et al. 2011).

[Table 1]

A central role for cognitive tradeoffs in human brain development and functioning is also concordant with the current best-supported model for the architecture of human intelligence, the verbal-perceptual-rotational model (Major et al. 2012), which involves a

negative correlation between verbal skills and visual-spatial abilities, when the general factor 'g' is parcelled out (Johnson and Bouchard 2009).

Why are cognitive tradeoffs important? In Figure 2, each of the human-evolved and human-elaborated phenotypes can vary in either of two directions, towards a lower or higher level of development and expression. Reduced expression of social and verbal phenotypes, with concomitant enhanced expression of visual-spatial, mechanistic, technical, and perceptual abilities, characterize autism spectrum conditions, especially among individuals with a higher general level of intellectual functioning (Mottron et al. 2006; Caron et al. 2006; Crespi and Badcock 2008). By contrast, relatively-higher expression of social and verbal phenotypes, concomitant to reduced abilities in visual-spatial, mechanistic, technical, and perceptual domains, characterizes the psychotic-affective spectrum, which the includes related, overlapping conditions schizophrenia, bipolar disorder, major depression, borderline personality, and schizotypal personality disorder (e. g., Crespi and Badcock 2008; Crespi et al. 2009; Crespi 2011b). This diametric difference between the autistic spectrum and the psychotic-affective spectrum is notably demonstrated by the enhanced empathic skills, compared to non-clinical individuals, reported among individuals with borderline personality disorder (Dinsdale and Crespi 2012); by contrast, reduced empathic skills and interests are specifically characteristic of autism (Baron-Cohen 2010).

Are cognitive tradeoffs genetically based? A study by Kravariti et al. (2006) documented that pedigree-based genetic risk of schizophrenia was highly significantly correlated, among non-clinical individuals, with high verbal skills relative to visual-spatial skills: having more alleles predisposing to schizophrenia was thus associated with a higher disparity between verbal and visual-spatial abilities. Similarly, Leach et al. (2013) showed that higher genetic risk of schizophrenia, as determined from genotyping 32 of the best-supported schizophrenia risk loci (single nucleotide polymorphisms), was associated with lower scores on a test of mental rotation; by contrast, several autism-risk alleles were associated with higher scores on the same test (Leach and Crespi, unpublished data). And comparably, mice knocked out for Shank1, a putative autism-

risk gene, have shown enhanced abilities at spatial learning relative to control mice (Hung et al. 2008).

A strong prediction that follows from these considerations is that tradeoffs between verbal-social and visual-spatial skills should be mediated by allelic variation at loci that also underlie risk of autism, and risk of psychotic-affective conditions such as schizophrenia. We have evaluated this prediction in a non-clinical population by genotyping a well-documented schizophrenia risk locus, the SNP rs3916971 in the DAOA (D-amino acid oxidase activator) gene, and testing for associations of genotype with scores on a test of verbal skills (vocabulary), and a test of visual-spatial skills (mental rotation) (Leach et al. 2013). The DAOA gene is of particular interest because: (1) it has apparently evolved recently in primates, with its full-length protein product found only among humans (Chumakov et al., 2002), (2) it is one of the best-documented risk genes for schizophrenia, as well as for bipolar disorder (Detera-Wadleigh and McMahon 2006); (3) its functional roles include modulation of the NMDA receptor, which mediates symptoms of schizophrenia; and (4) SNPs in the gene have been associated with better performance on several cognitive tasks, including verbal skills (Goldberg et al. 2006; Jansen et al. 2009a,b; Opgen-Rhein et al. 2008).

We found that males bearing two risk alleles for the SNP rs3916971 in the DAOA gene showed significantly better vocabulary performance, but significantly lower mental rotation performance, than males with one or no risk alleles (Figure 3). These results require replication, but they suggest that, as suggested by the findings of Kravariti et al. (2006), some schizophrenia risk genes mediate tradeoffs between higher verbal skills, and lower visual-spatial skills. Documenting additional loci that show such effects would help to close the loop between phenotypes-down and gene-up approaches, initially with single threads, but progressively strengthening as more and more data accumulate on neurodevelopment and neurocognitive function.

[Figure 3]

The upshot of what we can call the 'evo-neuro' model in Figures 1 and 2 is that each of the two major sets of so-called disorders of human sociality and cognition, the

autism spectrum and the psychotic-affective spectrum, can be considered to involve extremes of tradeoffs, specifically for traits that have become elaborated in recent human evolutionary history. Given that each of these two spectra grades continuously, in its constituent phenotypes, into populations of typically-developing individuals (Crespi and Badcock 2008; Crespi 2011b), this model for the architecture of human social-cognitive disorders also represents a simple, testable model for understanding cognitive variation among all human populations (Figure 4). The primary usefulness of this model is that it can direct research along promising paths by suggesting specific data to collect, and provide a unifying framework for existing results, such as familial associations of autism spectrum conditions with technical interests and abilities, and psychotic-affective conditions with literature and the humanities (Baron-Cohen 2012; Campbell and Wang 2012; Wei et al. 2012).

[Figure 4[

Most broadly, the evo-neuro model can be conceptualized as a generalization of the 'microcephaly paradigm', whereby recent human-evolutionary trajectories have structured the variation among humans in cognitive phenotypes, and in doing so, potentiated risk for psychiatric conditions with particular sets of phenotypes. The causes and correlates of psychiatric conditions may thus provide direct insights into normal human cognitive variation, as well as its evolutionary history. How well, then, is the model supported by the available data that connects genetic variation and perturbations, in two opposite directions, with diametric variation in cognitive phenotypes?

Diametric disorders of neurodevelopment

Autism spectrum and psychotic-affective conditions as discussed above are usually 'idiopathic' in causation, which means simply that the causes - genetic, environmental, or both - are unknown. For the best-studied conditions, autism and schizophrenia, a polygenic basis has recently been well established for 'explaining' some subset of genetic risk, which is consistent with the high heritabilities of both sets of conditions (Corvin et al. 2012). Thus, for both, segregating allelic variation from hundreds or thousands of single nucleotide polymorphisms, each of which influences risk to a tiny yet

estimable degree, contributes to distinguishing case from control populations (ISC 2009; Skafidas et al. 2012; Vorstman et al. 2013). These are not genes 'for' autism or schizophrenia at all, *per se* - they are genes with different alleles that cause slight differences in neurodevelopment, with differential impacts on social compared to non-social cognition (Kendler 2005).

In our evo-neuro model, effects of an 'autism risk' allele could be represented by a small vector pointed left and up at some angle (Figure 4). This vector can be conceptualized as the direction and magnitude of change in position on the plot caused by 'replacing' one allele with the other - essentially the same as Fisher's 'additive effects'. The alternative allele at this locus would, of course, be protective against autism - and also move brain development towards the psychotic-affective zone, usually ever so slightly. The position of any individual on this plot, (which ignores effects from the environment, and interactive effects of alleles), can be imagined as a summation of hundreds or thousands of small genetic vectors, which include effects from the alleles inherited from mother and father, plus any new mutations. The existence of tradeoffs between social and nonsocial cognition suggests that some notable proportion of vectors orient between upper left and lower right. Autism spectrum conditions may thus result, in part, from harboring 'too many' alleles for nonsocial, compared to social, cognitive functions, and psychotic-affective conditions result, in part, from the converse. A notable feature of this model is that it is fully compatible with the other major psychological models for autism, including Baron-Cohen's model of high systemizing relative to empathizing (Baron-Cohen 2010), Happé and Frith's (2006) model based on relatively weak central coherence, and Mottron's model of enhanced perceptual functioning (Mottron et al., 2006).

The genetic framework that we have described is simple, polygenic, and incomplete, because we also know that some subset of autism cases, and schizophrenia cases, are mediated by genetic alterations of larger effect. These large vectors are extremely useful for evaluating the evo-neuro model, because they commonly involve large genetic or genomic changes in two opposite directions from normality. Thus, to the extent that the model corresponds with our cognitive nature, if

changes in one direction predispose to autism spectrum conditions, then changes in the other direction should predispose to psychotic affective conditions.

[Figure 5]

Three main forms of large, diametric genetic perturbation have been associated with risk of autism and schizophrenia: (1) genomic copy number variants, (2) imprinted gene effects, and (3) X chromosome gains versus losses (Figure 5). Each form of perturbation involves *de novo* (not inherited) gains or losses of gene expression, genetic composition, or gene activity, involving the same regions of DNA. As such, each represents a sort of natural 'experiment' in changing gene dosages, for some stretch of DNA, from 2 to 1 or 3, or from 1 to 0 or 2. The primary drawback of such 'experiments' is that in humans they are, of course, uncontrolled, and usually engender effects from multiple genes, such that determining causation from the gene to phenotype levels is especially challenging; large changes also tend to be relatively pathological, variable, and syndromic in their effects, which can obscure relative cognitive deficits and enhancements. By contrast, mice can readily be engineered with higher or lower gene copy numbers, or doses of specified gene products, commonly resulting in opposite effects on neurological phenotypes and behavior (Crespi 2013a).

[Table 2]

Table 2 summarizes currently-available information on the prevalence of autism and schizophenia in association with opposite alterations in genomic copy number variants, imprinted gene regions, and X chromosome numbers. These data demonstrate clear, overall support for the diametric model, in that opposite genetic or genomic alterations are commonly associated with autism spectrum conditions versus psychotic-affective conditions as well as other manifestations of over-developed social cognition and behavior. Moreover, some sets of syndromes, such as Angelman syndrome, Rett syndrome and Pitt-Hopkins syndrome (all associated with the autism spectrum), and Prader-Willi syndrome, Smith-Magenis syndrome, and Kleine-Levin syndrome (all associated with the psychotic affective spectrum), involve phenotypic canalization, such that for each set a range of different genetic alterations gives rise to

notably-overlapping physical, behavioral and psychiatric phenotypes (Table 3 in Crespi 2008a). Such canalization reflects the patterns observed in idiopathic autism and schizophrenia (myriad highly-diverse genetic alterations, but similar endpoint phenotypes)(Happé 1994), and demonstrates that human neurodevelopment is structured, at least in part, along a canalized axis from autism spectrum to psychotic-affective cognition.

The dawn of evo-neuro-devo

Our evo-neuro model conceptually links the study of human cognitive evolution with the analysis of human psychiatric conditions. As such, it generates a non-subjective, non-arbitrary medical model for organizing the semi-chaotic plethora of named 'disorders' reified by the Diagnostic and Statistical Manual. Thus, psychiatric conditions, like all other medical conditions, can be understood strictly in terms of what evolved, adaptive biological system has become dysfunctional, and how (Johnson et al. 2012; Nesse and Stein 2012). The only problem with our model is that it lacks an essential component - perhaps *the* essential component - development.

Human brain and cognitive development have been studied in two largely-disparate domains: (1) neuroscience (including neurogenetics), which focuses bottom-up on neural mechanisms that orchestrate neurodevelopment, and (2) developmental psychology, which typically involves the top-down application of sequential-stage models for how cognitive development proceeds from birth to adulthood. Both of these domains have been applied, albeit separately, to the study of psychiatric, neurodevelopmental conditions. However, neither has been used, systematically, to connect processes and patterns of human brain and cognitive development with trajectories of recent human evolution.

Thus far, we have discussed how the human brain has evolved to be large overall, and to specialize in aspects of social as well as non-social cognition. From a developmental perspective, however, the evolution of the human brain and cognition is most strikingly characterized by heterochronic extension: temporal lengthening of all of the fundamental neural processes that brains undergo from early growth to adulthood.

This extension, sometimes associated with slowing of developmental times, has been reported for humans in neurological traits ranging from brain gene expression (Somel Franz et al. 2009; Liu et al. 2012), to synaptic plasticity (Bufill et al. 2011), synaptic spine generation and development (Huttenlocher and Dabholkar 1997; Petanjek et al. 2011; Charrier et al. 2012), expansion of neocortical surface area (Rakic 2009; Lui et al. 2011), and myelinization (Miller et al. 2012). These manifestations of neurodevelopmental extension are, apparently, integral to the life-history shift, along the human lineage, towards extension of the period of preadult development (Bogin and Smith 1996; Bjorklund et al. 2009; Zollikofer and de Leon 2010; Bogin 2012), though with an earlier time of weaning. Evolutionary expansion of the human childhood stage, with resultant more child-like human adult phenotypes, has, of course, usually been described in terms of neoteny - the retention of juvenile characteristics in adults due to evolutionary changes in rates and timing of development (Godfrey and Sutherland 1996; Brüne 2000).

The concept of neoteny has a long history in the study of human development and evolution (Brüne 2000), yet has seldom been subject to systematic study using data from different disciplines. We will use neurodevelopmental conditions, especially autism and schizophrenia (the conditions for which most data are available), as windows to analyze patterns of change in rates and timing of human neurological and cognitive development. This approach is predicated on the assumption that sets of genes and pathways that underlie neurodevelopment should be expected to overlap between: (1) human evolutionary-developmental changes (and evolutionary changes earlier in primate and mammalian development) and (2) genetic alterations, as well as segregating variation, that distinguish typically-developing individuals of different ages from individuals with autism, or with schizophrenia. This approach represents the microcephaly paradigm writ neurodevelopmental, over the largest neurological scales from perception and cognition to behavior. The primary previous deployment of this perspective comes from work by Crow (1997), Horrobin (2001) and Burns (2007) who have described extensive evidence regarding the hypothesis that schizophrenia represents 'the illness that made us human', because it centrally involves the suite of human neurodevelopmental and cognitive phenotypes that are most highly elaborated,

or unique (such as language), along the human lineage. This perspective, of course, is exemplified in our Figure 2, for a set of broad psychological phenotypes. As such, we are now adding a neurodevelopmental, heterochronic dimension to the variation in Figure 2 (and its neurological and psychological underpinnings), as each of the phenotypes shown must be a product of some time-dependent trajectory as ontogeny proceeds.

Developmental heterochrony and variation in human neurodevelopment

We will evaluate perhaps the simplest possible heterochronic model for the links of typical human neurodevelopment with human neurodevelopment in autism or in schizophrenia: shifts in the timing and rates of typical development, towards either slowing or lengthening (or both) (which may include non-completion of a typical trajectory), or acceleration or shortening (or both) (which may involve early differentiation). An initial treatment of this question, which focused mainly on autism, was described in Crespi (2013b); here, we expand on the model and link it more directly to human evolutionary history.

Two general types of perceptual, cognitive, behavioral, psychological and neurological developmental phenotypes will be considered. First, some phenotypes involve progressive, sequential, largely-quantitative increases in complexity and maturity as development progresses from infancy through adolescence or some period therein. Bjorklund et al. (2009) refer to these as 'deferred adaptations', and language skills represent a clear example. Second, some childhood phenotypes instead represent stage-specific adaptations (from Bjorklund et al. 2009, 'ontogenetic adaptations') that change qualitatively over development, such that children at each stage express more or less different phenotypes, each adapted specifically for that period (Bjorklund 1997; Bjorklund et al. 2009; Thompson-Schill et al. 2009). Examples would include private speech, pretend play, and a lack of cognitive control, all of which have been postulated as traits specific to early childhood that promote social and cultural learning (Bjorklund et al. 2009; Thompson-Schill et al. 2009).

The primary hypothesis that we address is that autism involves, in part, simply delay or non-completion of typical neurodevelopmental and psychological trajectories. By contrast, schizophrenia, and to some extent related psychotic-affective conditions such as bipolar disorder and depression, involve the opposite: acceleration, early differentiation, and maladaptive 'over'-development. This hypothesis can be addressed by comparing phenotypes characteristic of autism and schizophrenia with phenotypes of younger versus older typically-developing individuals (Crespi 2013b), and by extrapolating the trajectories of typical development beyond their usual bounds.

Progressive, sequentially developing, and increasingly complex human phenotypes include, most notably, theory of mind, conception and coherence of self, linguistic abilities, abstract thought, imagination including mental time travel and hypothetical scenario-building, controlled and long-term goal-seeking, social emotionality including pride, guilt, embarrassment and shame, and, most generally, what we can call mentalistic cognition (e. g., Badcock 2004; Crespi and Badcock 2008). As noted above, each of these phenotypes shows evidence of under-development in autism spectrum conditions, whereby typical trajectories are not completed (Crespi and Badcock 2008; Badcock 2009). Woodard and Van Reet (2011) characterize such psychological trajectories as involving a series of four stages in 'object identification', which can be defined as assimilation of external stimuli into the maturing structure of the internal, developing self:

'*(1) Part-object/inanimate object identification;*

(2) Part-object/initial or emerging human as part-object identification;

(3) Non-complete or non-integrated whole-object human identification;

(4) Whole-object, complete human identification' (the endpoint for typical development).

This conceptualization of stage-specific typical development is of particular interest because the intermediate stages so strikingly characterize several major, otherwise-disparate aspects of autism, including fascination with parts of objects, perceptions

focused on local more than global and integrated features of the environment, treating people as inanimate 'things', a reduced concept of self and self-agency (Crespi and Badcock 2008; Gray et al. 2011; Uddin 2011), and lower levels of empathy towards other humans. In the developmental heterochronic lexicon, autism may thus involve some combination of a slower rate (leading to so-called neoteny), and an earlier endpoint (referred to as progenesis). Comparable stage-specific analyses can be derived based on developmental-psychological theory from Vygotsky (Fernyhough 1996), or based on ideas from metarepresentation and theory of mind (Lombardo and Baron-Cohen 2011).

What phenotypes do we expect if such sequences of development are accelerated, or continue for a longer than usual time ('hypermorphosis'), along the psychological dimensions described above? As depicted in Figure 2, hyper-developed theory of mind descends into paranoia and delusions of persecution; over-developed sense of self extends to delusions of grandeur; linguistic abilities chaotically expand and fracture in thought disorder; imagination runs amok in hallucinations and delusions that manifest elaborate psychotic scenarios with no basis in reality (Nettle 2001); uncontrolled, risky goal seeking manifests as manic episodes; and social emotions, especially guilt, shame and embarrassment, hyper-express in depression (e. g., Zane-Wexler et al. 2006, 2008). With regard to object identification, we continue in psychotic-affective conditions to a novel step (5): ascribing animacy, agency and human attributes to non-human objects (Gray et al. 2011), and sometimes (6) identification with the spiritual external world as a whole, in association with magical ideation, paranormal experiences (Leonhard and Brügger 1998), hyper-developed empathy in exaggerated mirror neuron system activation (McCormick et al. 2012), hyper-agency in megalomania, and neurological alterations including temporal lobe epilepsy underlining hyper-religiosity and symptoms of psychosis (Trimble 2007).

These considerations indicate how even apparently-bizarre and inexplicable manifestations of psychotic-affective conditions can be understood as extremes of typical cognitive phenomena. From our neurodevelopmental perspective, proximate causes of such phenotypes can be considered to include loss of negative regulation of

social, linguistic, and emotional phenotypes, and loss of homeostatic control over positively and negatively valenced emotional and behavioral feedbacks, in schizoaffective disorder, bipolar disorder and major depression. In each case, the alterations result from certain forms of change to brain structure and neurochemistry, as described in more detail below. By contrast, ultimate causes of such symptoms derive from the recent human evolutionary trajectory towards increasingly elaborated social, emotional and linguistically based perception, cognition and behavior. This framework can be evaluated empirically by determining the degree to which the genes and alleles underlying psychotic-affective conditions, and their subclinical psychological manifestations in diverse aspects of human personality, have undergone adaptive molecular-evolutionary change along the human and great ape lineages (e. g. Crespi et al. 2007; Torri et al. 2012). Such tests can indeed determine the degree to which risk of schizophrenia (and the psychotic-affective spectrum more generally) represents a direct, pleiotropic byproduct of human evolution.

Above, we have discussed 'deferred adaptations', which involve developmental ratcheting of better and better skills in some specific domain as development proceeds. 'Ontogenetic adaptations', by contrast, entail qualitative differences between younger and older children, which allows direct tests of our developmental-heterochronic model. Thus, to the degree that the model is correct, perceptual, cognitive and behavioral differences between younger and older typically-developing individuals should reflect the differences between individuals with autism, typically-developing individuals, and individuals with schizophrenia.

Crespi (2013b) reviews data across four major research areas involving ontogenetic adaptations: (1) restricted interests and repetitive behavior (in autism), (2) local and parts-focused compared to global and gestalt processing of visual information, (3) absolute compared to relative pitch processing for auditory information, and (4) relatively short-range compared to long range neural connectivity. For each of these four domains, evidence from a broad swath of literature supported the idea that autism involves retention of phenotypes typical of relatively-early childhood: high levels of restricted interests and repetitive behavior, a local bias to visual processing, auditory

processing that differentially involves absolute pitch, and relatively short-range connectivity (Crespi 2013b). These inferences are, moreover, concordant with two of the most influential theories for understanding autistic traits, weak central coherence (Happé 1994) and enhanced perceptual functioning (Mottron et al. 2006).

For visual and auditory processing phenotypes, and neural connectivity, schizophrenia shows evidence of patterns opposite to those for autism, although direct comparisons of schizophrenia with autism and typical development, based on the same psychological or neurophysiological tests, are seldom available (Crespi 2013b). The most telling comparison, though, is the best-documented: lower relatively long-range neural connectivity in autism (and higher short-range connectivity than in typical individuals), but lower relatively short-range connectivity in schizophrenia, due in part to high rates of synaptic and neuronal loss that differentially affects short-range connections. In principle, this connectivity difference may explain many of the diametric perceptual, cognitive, and behavioral differences between autism and schizophrenia, including such well-documented patterns as: (1) larger versus smaller head size, (2) superior visual and auditory perception and processing in autism but degraded sensory functions in schizophrenia, which apparently contribute to hallucinations (Waters et al. 2012; Pynn and Desouza 2013); (3) the local versus global visual-processing biases discussed above, and (4) absent, highly-literal, or hyperlexic language skills in autism but, in schizophrenia, dyslexic reading profiles, auditory hallucinations, loose associations in speech, chaotic and metaphorical language use including neologisms (coining of new words) and clanging (focus on rhyming sounds of words), and, among poets, high levels of schizotypal cognition (Nettle 2001; Crespi 2008b; Crespi and Badcock 2008; Poirel et al. 2011). Most notably, typically-developing individuals undergo a trajectory of neuronal, synaptic, and dendritic pruning that starts in early childhood and continues through early adulthood and beyond (e. g., Shaw et al. 2006; Paus et al. 2008). In schizophrenia, this process apparently accelerates, or continues for a relatively long time, indicating that heterochronic alterations - failures of neoteny, as it were (Brüne 2000; Burns 2004) - underpin a substantial component of neurodevelopmental changes in schizophrenia. Diametric variation in neural

connectivity patterns may also provide, at least in part, a simple basis for the cognitive tradeoffs described above between social and non-social psychological functions.

Postulating and testing diametric variation in developmentally-based connectivity patterns in autism compared to schizophrenia is well and good - but not evolutionary *per se*, and so not evo-neuro-devo. In principle, brain connectivity has evolved along the human lineage, in the general direction of psychotic-affective (mentalistic) cognition, and also towards increases in both mechanistic and mentalistic cognitive abilities with tradeoffs between them. A simple scenario of such a possible evolutionary trajectory is shown in Figure 6, in the context of variation in brain connectivity among extant humans, and in autism and schizophrenia. But what empirical data can be, or has been, collected to evaluate such hypotheses, or other hypotheses that seek to connect evolution with human neurodevelopment?

[Figure 6]

The origin of modern human neurodevelopment

A voluminous literature has accumulated on the so-called 'genes that make us human', which are inferred from studies of molecular evolution driven by statistically-inferred natural selection. Such studies have produced large lists of ranked genes, about which we know virtually nothing substantial about function in body and brain, or roles in human evolution (Hughes 2007), except in a few aforementioned cases involving microcephaly and speech. This unfortunate situation has arisen because deciphering molecular-developmental functions for particular amino acids or haplotypes is challenging, and because research in human molecular-evolutionary genetics proceeds largely independently from research on human neurodevelopment and its disorders.

Three simple and feasible methods can, however, be deployed to close the loops between human evolution, neurodevelopment, and neurodevelopmental conditions such as autism and schizophrenia.

First, studies of the 'genes that make us human' can be complemented by studies that systematically determine what cognitive and psychological phenotypic variation can

be ascribed to ancestral versus derived amino acids, haplotypes, or other genetic polymorphisms. Such analyses simply require genotyping large sets of non-clinical individuals (to determine if each individual has the derived or ancestral allele, for a given site inferred from previous work to be subject to positive selection), and phenotyping them for a broad set of cognitive and psychological traits (to determine what traits, if any, differ between individuals with derived and ancestral alleles). Cognitive and psychological traits can, of course, be chosen based on previous knowledge of what particular genes appear to do, where they are expressed, and if they are known to be associated with particular phenotypic domains or diseases. In one of the few examples of this approach, Wong et al. (2012) found that having more derived alleles at a specific amino acid site in the ASPM gene was associated with better performance in perception of auditory tone. The primary limitation of this approach is that it can be used only for analyzing polymorphic genetic variation, not alleles that have gone to fixation along the human lineage. Its primary advantage is that, given data from enough genes and phenotypes, we should be able to infer the trajectories of ongoing evolution of human cognition and neurodevelopment.

Second, DNA sequencing of recent human fossils, from the last tens of thousands of years (i. e., along the recent human lineage), can be used to directly determine what series of genetic changes has taken place in conjunction with the origin of modern humans. Such studies are technologically feasible (Meyer et al. 2012), though they would require ancient DNA samples from at least several tens of humans for robust inferences to be drawn. Such analyses could be complemented by phylogenetic analyses of DNA from extant humans (to infer ancestral states and time frames), and they would also dovetail nicely with the first method described above.

Third, the cognitive correlates of well-validated risk alleles for autism and for schizophrenia can be analyzed in non-clinical populations, to determine just what these alleles actually 'do' in normal neurodevelopment and neurological-psychological function. How many such alleles mediate tradeoffs between social and non-social cognition, or between other sets of domains? How do they do so, in terms of brain function? Studies such as these are especially useful because they will generate

insights into both the cognitive architecture of typically-developing individuals, and the causes of psychiatric conditions, with novel implications for therapy.

For each of the three approaches above, relevance of the alleles to neurodevelopment *per se*, and to short range compared to long range connectivity patterns, can be evaluated using brain imaging studies of typically-developing individuals that differ in genotype, studies of individuals with psychiatric conditions, and studies of mice engineered to express human alleles such as the human-derived allele of FOXP2 (Enard et al. 2009). Convergence of results from independent evolutionary, neurological, developmental, and genetic approaches should lead to robust insights into human evo-neuro-devo, and bring this nascent field fully to life.

Conclusions

In this article we have constructed a rudimentary scaffold for the field of evo-neuro-devo, an emerging discipline that focuses on how human neurodevelopment, and risk for psychiatric conditions mediated by neurodevelopment, have evolved together. The field is challenging due to the complexity of human brain development and the paucity of hard evidence regarding the evolutionary history of human neurological and cognitive traits. However, the connections of genetic data to both human neurodevelopment and evolution can be used to leverage robust, empirically-based inferences, given the causal primacy of genes in neurodevelopment and their evolutionary encoding of population-genetic forces past.

The primary pillars of our scaffold are twofold. First, the major features of autism and psychotic-affective spectrum conditions can be derived by hypo-development, or hyper-development, of human-unique or human-elaborated phenotypes (Figure 2). This explanatory framework explicitly connects human evolution with psychiatric conditions that involve variation in human social and non-social brain systems, indicating that both can be analyzed together, most notably in the context of genetically-based cognitive tradeoffs. Second, we have presented evidence that developmental heterochrony characterizes, at least to some degree, the neurological bases of autism and schizophrenia (Figure 5), such that simple shifts in the rates and timing of

neurodevelopmental processes can help to explain a broad suite of diverse phenotypes that characterize the two sets of conditions. The question then becomes, both for therapy and for understanding human brain evolution, what processes orchestrate temporal sequences and shifts in how the brain changes through childhood, adolescence, and beyond. Answers to this question should raise evo-neuro-devo to maturity, and, eventually, into the forefront of evolutionary biology, anthropology, neuroscience, and psychology.

Acknowledgements

We thank NSERC for financial support, and S. Read for technical assistance.

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Figure Legends

Figure 1. The 'microcephaly paradigm' posits that human-derived and human-elaborated developmentally-based phenotypes, such as brain size, evolve through a series of small, positively-selected changes, and can be reduced or lost (or, in some cases, increased) due to large scale mutational or environmental alterations. This paradigm connects human evolution with human development, in the contexts of their joint genetic underpinnings and risks of particular forms of disease.

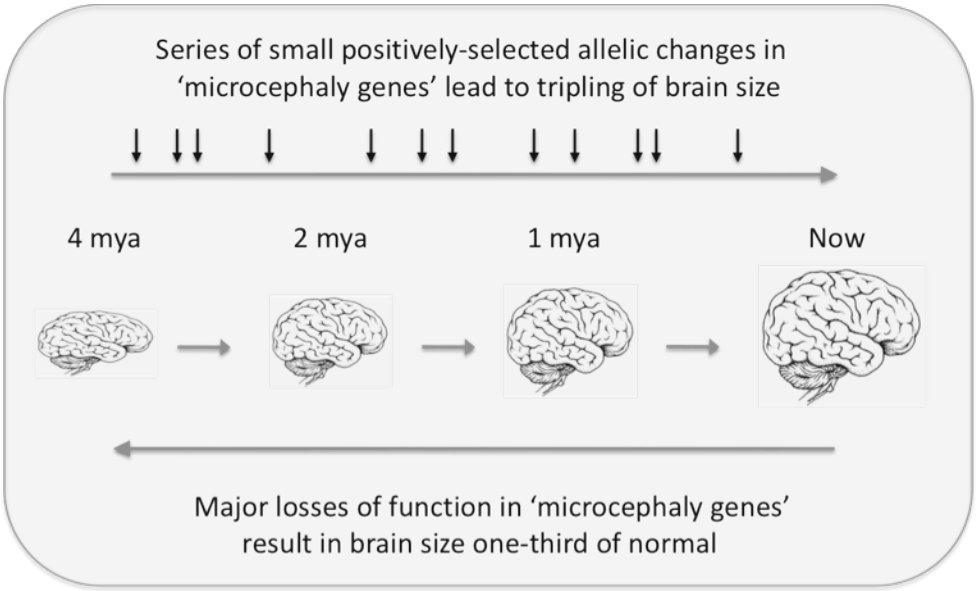

Figure 1

Figure 2. The diametric brain hypothesis represents an application of the microcephaly paradigm to human perceptual, cognitive and affective architecture. By this hypothesis, humans have a suite of social brain adaptations, and a suite of non-social brain adaptations, which tend to exhibit tradeoffs with one another with or without statistical adjustment for general intelligence. Psychotic-affective conditions involve maladaptively over-developed social-brain phenotypes in conjunction, to some degree, with maladaptive under-development of non-social brain phenotypes, and autism spectrum conditions involve the converse. For evidence regarding these alterations, in psychiatric conditions, see Kravariti et al. (2006); Mottron et al. (2006); Crespi and Badcock (2008); Soulières et al. (2009, 2011); Baron-Cohen (2010, 2012); Crespi (2011b); Johnson et al. 2012).

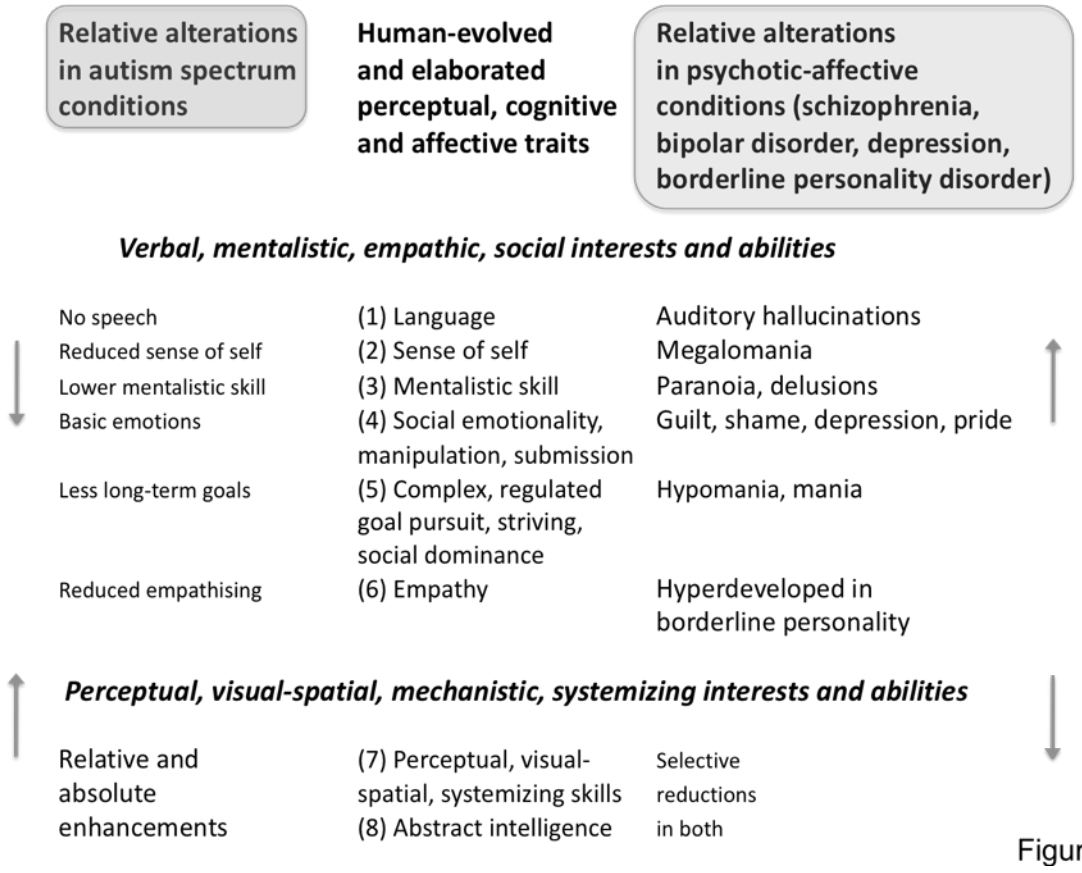

Figure 2

Figure 3. In a non-clinical population of males, having more schizophrenia risk alleles for the single nucleotide polymorphism rs3916971, in the gene DAOA (D-amino acid oxidase activator) is associated with better vocabulary skills, but worse mental rotation skills ($p < 0.05$ for each, t-tests, SEs shown on plot; data from Leach et al. 2013). This locus thus provides evidence of a genetically-based tradeoff between verbal skills and visual-spatial skills.

Figure 3

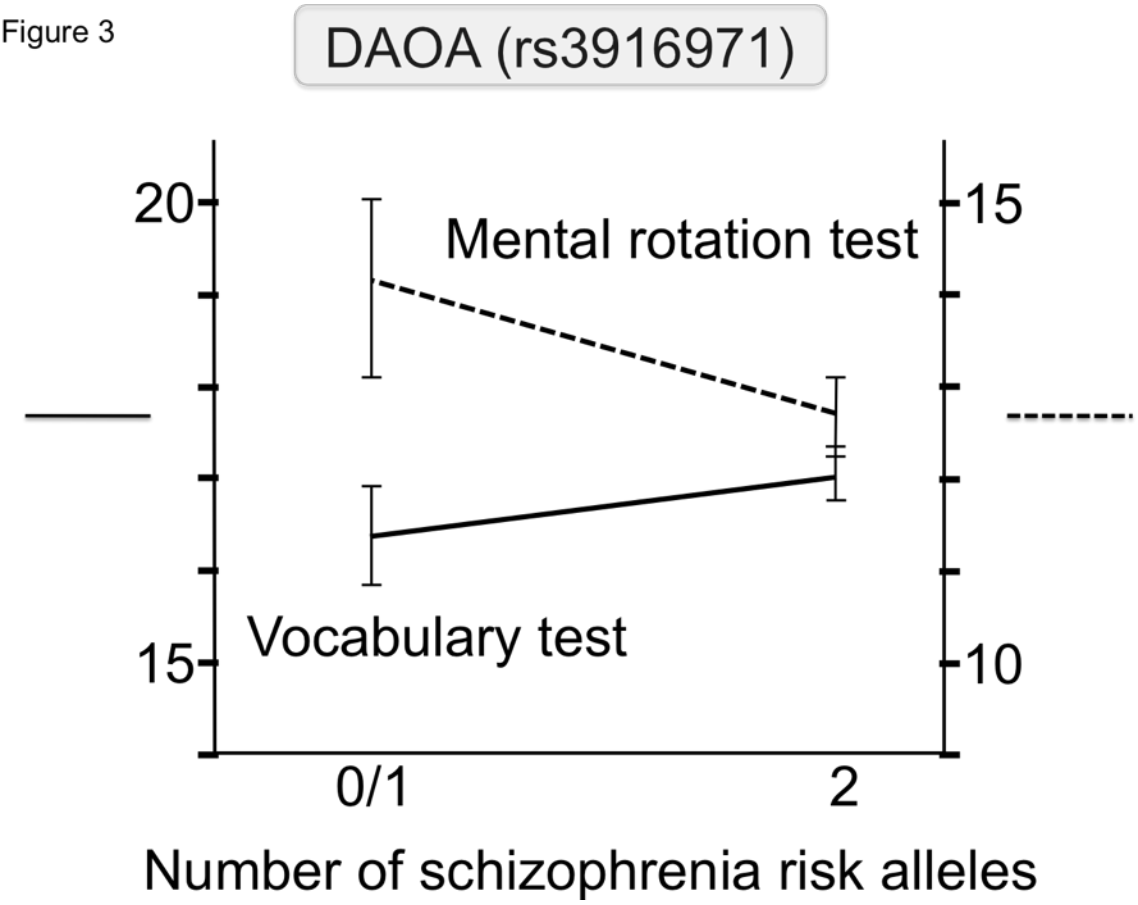

Figure 4. Autism spectrum and psychotic-affective spectrum conditions, both of which are strongly modulated by neurodevelopment, may be conceptualized as representing extremes of joint variation in social (and mentalistic), relative to non-social (and mechanistic), interests and abilities. Under this framework, alleles 'for' either set of conditions represent arrows, of variable magnitude, that point towards the conditions. These alleles result in either adaptively-increased interests and abilities in one domain (nearer the diagonal balance line) with moderate decreases in the other domain, or maladaptively over-developed interests and abilities in one domain, and maladaptively reduced interest and abilities in the other domain (near the upper left, or lower right, corners). Intensities of shading represents degrees of expression of perceptual, cognitive and affective phenotypes characteristic of the autism spectrum, and psychotic-affective spectrum.

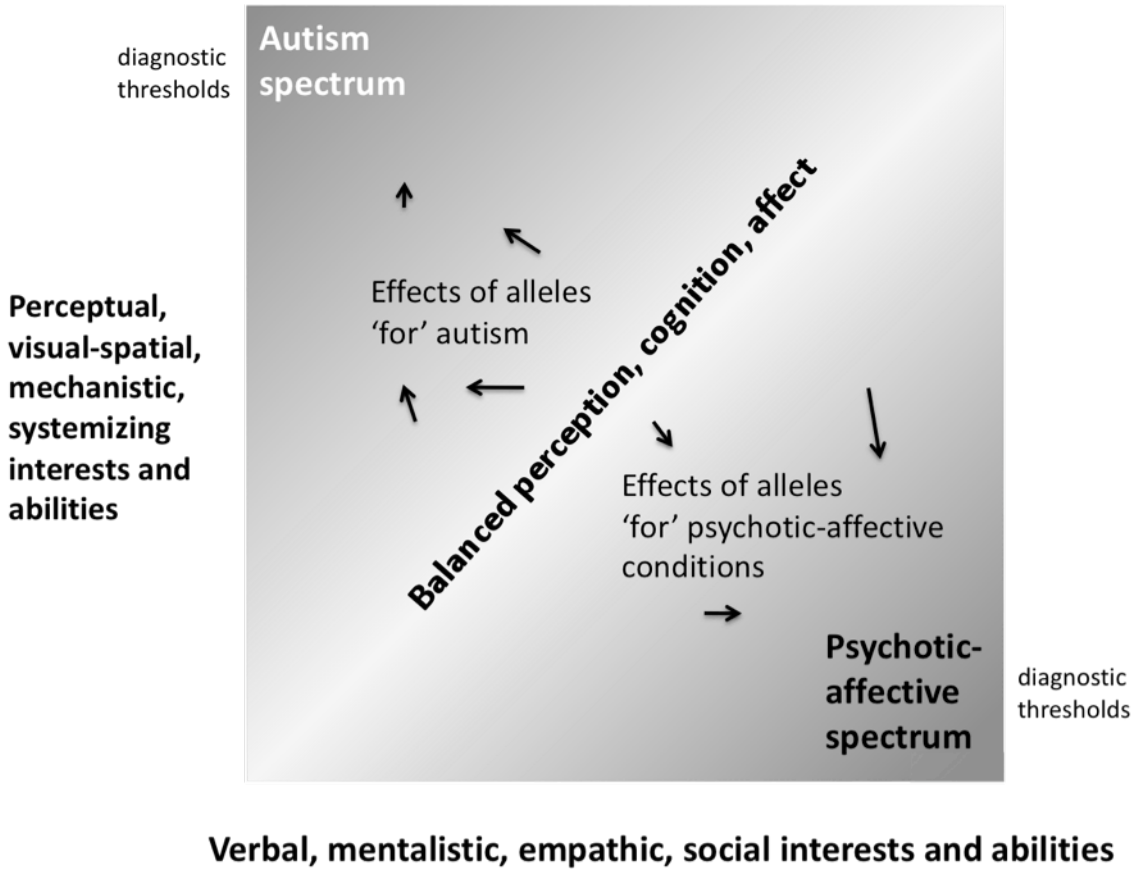

Figure 4

Figure 5. Three forms of genomic and epigenetic alteration can result in large alterations to gene expression in two opposite directions, towards increases or decreases from the typical range (which is circled, in each case). Copy number variants may include one to dozens of genes with higher or lower expression, imprinted genes involve losses or gains of expression due to losses or gains of epigenetic marks, and X chromosome aneuploidies involve partial or complete loss of an X in females, or gain of an X in males or females. To the extent that these alterations change expression of genes that mediate social and non-social brain development, they provide tests of the diametric brain hypothesis, as described in Table 2.

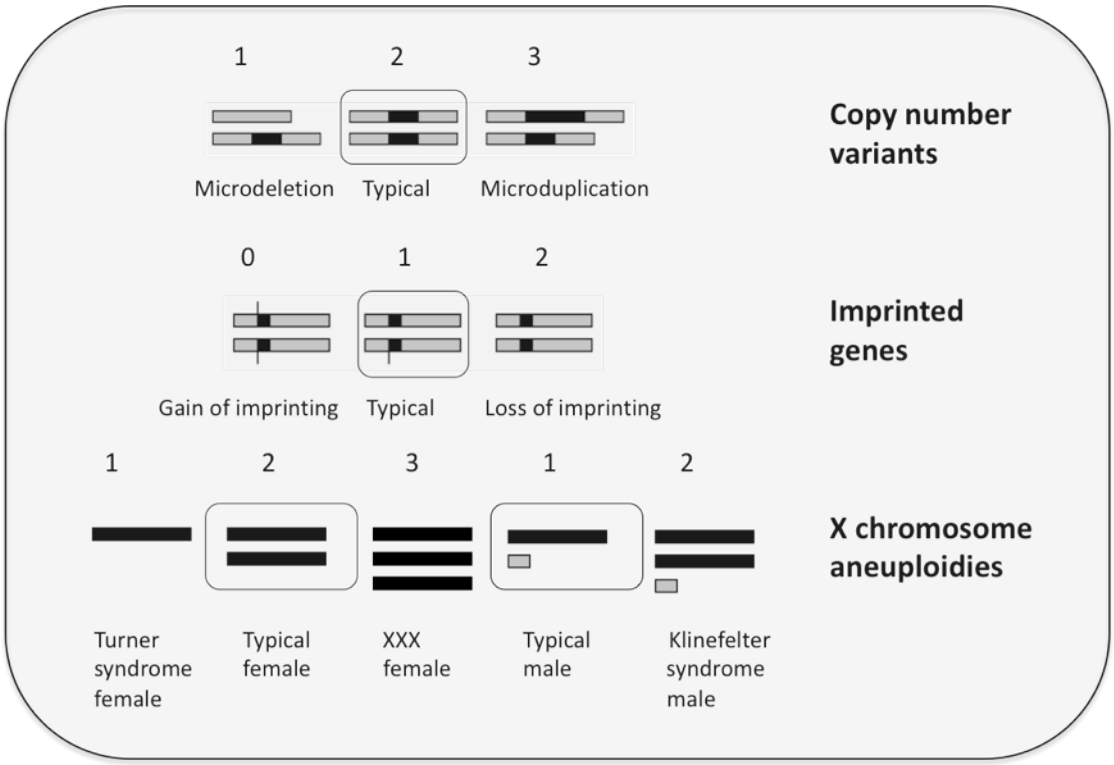

Figure 5

Figure 6. A highly simplified 'evo-neuro-devo' model for how human local and global brain connectivity may have evolved, and how their development is altered in autism and in schizophrenia. Two connected brain regions are shown, with each region showing 'small-world' connectivity patterns with highly-connected hubs, and decreased connectivity with age due to (primarily short-range) synaptic and neuronal pruning. By this model, increases in brain size along the human lineage involved strong selection to maintain and increase long-range connectivity, which otherwise decreases with absolute size. Examples of brain structures manifesting such increases in connectivity along the human lineage include the arcuate fasciculus (connecting Broca's area with Wernicke's area)(Rilling et al. 2008), and the corpus callosum itself (connecting the left and right hemispheres) (Rilling and Insel 1999). Among modern humans, autism involves reduced long-range connectivity and reduced pruning, both of which lead to more-local connectivity. By contrast, schizophrenia involves increased pruning (and grey matter loss), which can lead differentially to less-local and more-global connectivity.

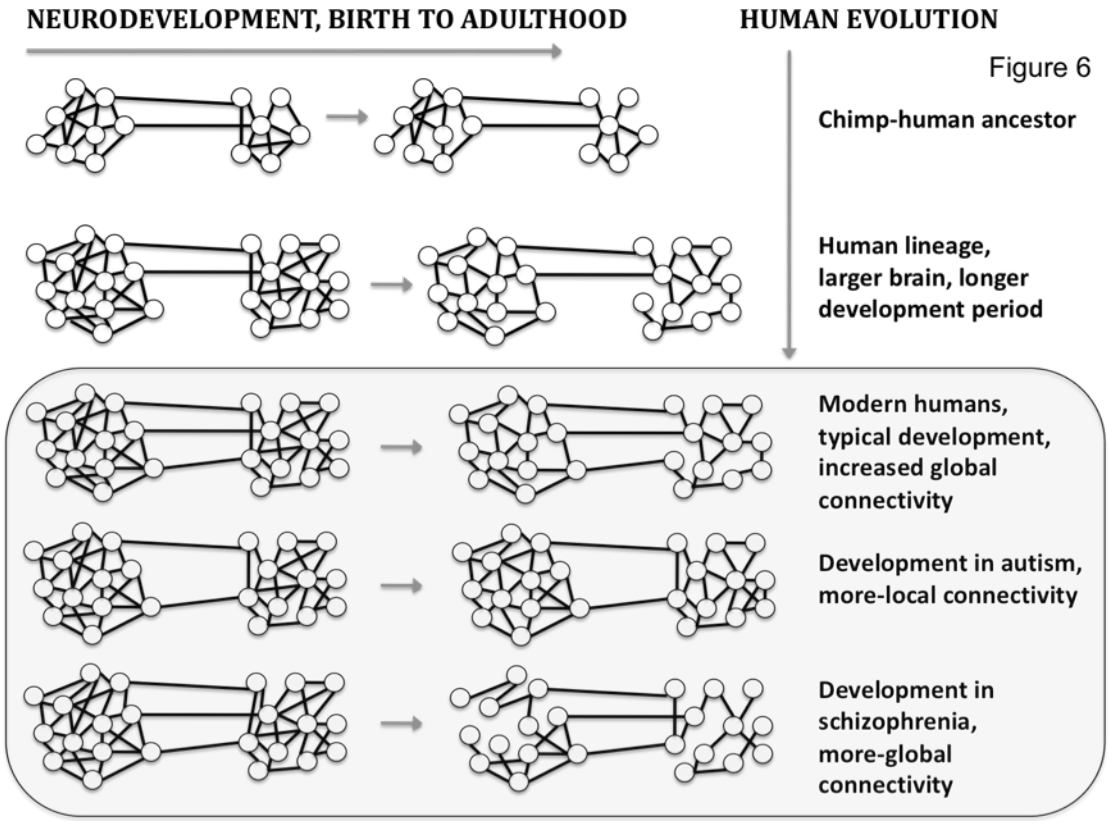

Table 1. Evidence of negative correlations between social skills and non-social skills, which are indicative of tradeoffs.

Social skill	Non-social skill	Citations
Verbal skills	Spatial-imagery	Johnson and Bouchard 2007
Empathizing	Systemizing	Nettle 2007
Empathizing	Mental rotation	Cook and Saucier 2010
Theory of mind	Embedded figures	Jarrold et al. 2000
Social skills	Embedded figures	Pellicano et al. 2006 Russell-Smith et al. 2012
Social skills	Raven's matrices	Fugard et al. 2011
Social skills	Visual search	Keehn et al. 2012 Joseph et al. 2002, 2009
Reading mind in the eyes	Embedded figures	Baron-Cohen and Hammer 1997 Baron-Cohen et al. 1997
Social interest	Mental rotation	Dinsdale et al. (unpublished)

Table 2. Effects of large diametric genomic or epigenetic alterations on risk of autism spectrum conditions versus psychotic-affective spectrum conditions.

Copy-number variants	Citations
At four loci, 1q21.1, 16p11.2, 22q11.2 and 22q13.3, deletions are associated with one set of conditions (autism or schizophrenia), and duplications are associated with the other	Crespi et al. 2010 Crespi and Crofts 2012
Imprinted-gene syndromes	**Citations**
Prader-Willi syndrome involves high risk of psychosis, Angelman syndrome involves high risk of autism	Crespi 2008a Crespi et al. 2009
X chromosome aneuploidies	**Citations**
Turner syndrome involves high risk of autism, XXX involves high risk of schizophrenia	Crespi 2008a,b Crespi et al. 2009
Klinefelter syndrome involves high levels of schizotypy, high risk of schizophrenia	Crespi 2008b Crespi et al. 2009