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Environmental and genetic influences on neurocognitive development: the importance of
multiple methodologies and time-dependent intervention*

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Abstract

Genetic mutations and environmental factors dynamically influence gene expression and developmental trajectories at the neural, cognitive and behavioral levels. The examples in this article cover different periods of neurocognitive development - early childhood, adolescence and adulthood – and focus on studies using a variety of methodologies, which illustrate the early effects of socio-economic status and stress on brain function as well as how allelic differences explain why some individuals respond to intervention and others do not. Our studies highlight how similar behaviors can be driven by different underlying neural processes and show how a neurocomputational model of early development can account neurodevelopmental syndromes like autism spectrum disorders, with novel implications for intervention. Finally, our studies illustrate the importance of the timing of environmental and genetic factors on development, consistent with our view that phenotypes are emergent, not predetermined.

Introduction

It may seem a truism to state that development is dynamic, not static. Yet the literature continues to use the phenotypic end state of the mature adult brain as a rather static framework for understanding genotype/phenotype relations and as an explanatory model for neurodevelopmental disorders. Indeed, disorders are often explained in terms of intact or impaired modules (Clahsen & Temple, 2003), with genotype/phenotype relations frequently invoked as one-to-one mappings (Gopnik 1990; Pinker 2001), and plasticity used solely to explain a system's response to injury (Wexler, 1998). Yet, human development – whether typical or atypical – involves a dynamic, self-structuring system in which plasticity is the rule, not solely an exceptional response to injury. The infant brain self-structures over developmental time (Johnson, 2001) and is not predetermined by the genome. Rather, environmental influences play a crucial role in gene expression, e.g., epigenetics (Meaney, 2010), in brain function (Johnson, 2012; Malter Cohen et al., 2013) and overall in phenotypic outcomes (Karmiloff-Smith, 1998; Karmiloff-Smith et al., 2012). In early development, brain circuits interact dynamically across different regions prior to becoming progressively specialised. If the mature adult brain is specialised (albeit also open to plasticity), we argue that this is the result of a process of gradual specialisation over developmental time in which both genetic and environmental factors play a critical role as the human brain progressively structures itself (Johnson, 2001; Karmiloff-Smith, 1992, 1998). There is, indeed, a profound difference between the *developed* brain and the *developing* brain (Casey et al 2005; Durston et al 2006; Karmiloff-Smith, 2010).

Four approaches address the above issues in early childhood, adolescence and adulthood, using a variety of methodologies: behavioral, neuroimaging, electrophysiology, genetics, animal models and computational models. First, using electrophysiological measures of resting state

brain activity, we examine the impact of the environment on the infant brain, i.e., how differences in socio-economic status influence developing neural activity from a very young age (Tomalski et al., 2013). Using other methods such as human neuroimaging and mouse models of genetic risk and protective factors, we go on to explore the impact of stress and anxiety on the developing brain (Hartley & Casey, 2013). In doing so, we examine why some adolescents with anxiety disorders respond well to exposure-based cognitive behavioral therapy, whereas others (some 40-50%) do not, highlighting the importance of allelic differences as well as carefully identified intervention time-windows for the developing brain.

The next two approaches focus on autism spectrum disorders (ASD) in both adulthood and early childhood. Like the SES studies, the first uses electrophysiological methods, this time to differentiate between overt behavior and the underlying neural activity that supports recognition memory (Massand et al., 2013). Using the same method to measure neural activity, we next examine aspects of auditory recognition memory in infants at risk of ASD. The final example also focuses on neural processes at work in early childhood, building a neurocomputational model to test and explore the hypothesis that ASD may be caused by over-aggressive pruning early in development (Thomas, Knowland & Karmiloff-Smith, 2011). We conclude by examining a number of outstanding questions and future directions, arguing that multiple converging methodologies are critical for understanding both the typical and atypical case, and that neurocognitive theory and methodology must always be couched in the context of a dynamic developing system.

Using electrophysiology to examine the effects of SES on early neural activity

Family socio-economic status (SES) differs widely in every population, making it difficult for those at the lower SES end to access resources that are critical for health and wellbeing

(Bradley & Corwyn, 2002). SES is mediated by multiple factors, including *inter alia* prenatal health (e.g., exposure to toxins, stress hormones), nutrition, parental care, and cognitive stimulation. SES not only affects behavior but, importantly, impacts both structural and functional brain development (Hackman, Farah & Meaney, 2010). Recent data have revealed significant long-term influences of SES on both language and attention (e.g., Noble, McCandliss, & Farah, 2005; Stevens, Lauinger, & Neville, 2009; Fernald, Marchman, & Weisleder, 2013). Correspondingly, disparities in SES are strongly associated with differences in the volume of neural structures supporting these abilities (e.g., Noble, Korgaonkar, Grieve, & Brickman, 2013; Rao et al., 2010). But, does the impact of low SES build up slowly over developmental time, or can its effects on brain function already be demonstrated very early in life?

With this question in mind, and because studies of toddlers (16-30 month-olds) had already shown that frontal gamma power of EEG predicted language development at 4-5 years of age (Gou, Choudhury & Benasich, 2011), we targeted much younger infants (6-9 month-olds), living in East London UK, an area of high levels of socio-economic deprivation. Using electroencephalography, we measured spectral power of resting brain activity across the scalp in the awake state (Tomalski et al., 2013). Between-subject comparisons of infants from low- and high-SES families revealed significantly lower frontal gamma power in those from low-income homes. Similar power differences were also found when comparing infants according to maternal occupation, with the brains of infants from lower occupational status groups yielding lower power over frontal electrodes. Surprisingly, maternal/paternal education did not differentiate groups. This may be due to the fact that the low-SES infants came mainly from migrant families with reasonable levels of education gained in their countries of origin, but obliged to carry out menial jobs in the host country, i.e., mothers working significantly below their qualifications. This suggests that, in some circumstances, the negative effects of poverty

may override the positive effects of education. SES was clearly a contributor because our analyses revealed that these group differences were not explicable in terms of differences in age, sleep quality, monolingual vs multi-lingual language environment, breastfeeding, family history of dyslexia, or exposure to tobacco smoke.

Interestingly, the findings were scalp region-specific to the frontal areas, whereas occipital, left and right temporal channels yielded no differences across SES groups. Noteworthy also was the fact that there were no significant SES-related individual differences in other frequency bands (theta, alpha or beta). Thus, the differences that emerged were not only frontal region-specific, but also power-band specific to gamma oscillatory activity, which is thought to index regional synchronization of brain networks (Grice et al., 2001). This finding dovetails nicely with recent neuroimaging work showing that low-SES status of infants is associated with a delayed trajectory of brain development, especially in frontal and parietal areas (Hanson et al., 2013). In sum, our results indicate that the effects of differences in SES on brain activity can already be detected in the first months of life, highlighting a potential increase in the risk for subsequent atypical developmental trajectories, and the need to focus interventions on this very early period of infant development.

Using human imaging and mouse genetics to examine the effects of fear and anxiety on brain development

Understanding intervention was one of the direct targets of the next set of studies on anxiety disorders (e.g., social phobia, separation and generalized anxiety), which are the most common form of psychiatric disorders, with a lifetime prevalence of some 20-40% (Hartley & Casey 2013). Interestingly, diagnosis of anxiety disorders reveals a peak during the adolescent period of development. One of the most commonly used interventions to treat these disorders is

exposure-based cognitive behavioral therapy (CBT) that relies on basic principles of fear learning and fear extinction. And, indeed, a substantial portion of patients does improve with this intervention; yet some 40-50% do not. Why? To examine how fear-related processes differ across individuals and across developmental time, a series of empirical studies was run employing both human imaging and mouse genetics (Hartley & Casey, 2013). The aims of the studies were: 1) to understand changes in the brain during the transition into and out of adolescence; 2) to use this knowledge to inform the identification and/or treatment of anxiety disorders; and 3) ultimately to develop novel, evidenced-based interventions. The focus was specifically on adolescence, a period when the brain's emotional *reactivity* centers are developing prior to the brain's emotion *regulation* ones, with this imbalance affecting some adolescents more than others. What explains this difference?

Environmental factors, particularly early experience of institutionalization (e.g. orphanage), turned out to play a critical role in anxiety, even when children had been subsequently adopted into caring families offering stimulating environments. It was found that the brain regions of children adopted later in life, particularly in the amygdala, were activated differently to threat cues than those adopted sooner and with fewer symptoms of anxiety (Tottenham et al., 2011). A mouse model that controlled for differences in environmental and genetic backgrounds, an inherent confound of naturalistic human studies, showed that early life stress played a crucial role in this restructuring of the brain (Malter Cohen et al., 2013). Although environmental factors yielded strong effects, a knock-in mouse model (Chen et al., 2006) of the human allelic variant in Brain Derived Neurotrophic Factor (Val66Met) showed how, not just environmental factors like stress, but also individual genetic factors contributed to differences in individuals' ability to control fear and anxiety: altered fear extinction was shown to be a function of allelic differences in the murine BDNF genotype (Soliman, Glatt et al., 2010).

This extended to those humans whose genes express less neurotrophin and whose brains show *less emotion regulation* and *more emotion reactivity*. These allelic differences have profound implications for intervention, pointing to which individuals are likely to be the most responsive to CBT intervention that relies on basic principles of extinction learning.

Can such findings inform us not only about the efficacy of intervention for individuals, but also as to *when* treatment may be most effective? Further studies revealed that the period of adolescence was associated with less successful extinction of fear memories and diminished response for CBT exposure-based interventions compared to preadolescence or adulthood (Pattwell, Duhoux et al 2012, Drysdale et al 2013), pointing to a potentially key developmental time-window for the design of novel, evidence-based interventions. In sum, behavioral, genetic and brain imaging data offer not only insights as to who may be at greater risk for anxiety, but also for whom and when, during development, exposure-based CBT intervention may be most effective.

Using electrophysiology to understand aspects of the autistic profile across development

The next studies did not focus on intervention per se, but they are relevant to the design of intervention studies in that they demonstrate how ostensibly “normal” behavior may still require intervention because of the atypical brain processes that underlie the overt behavior. So, for instance, compared to healthy controls, high-functioning individuals with Autism Spectrum Disorder (ASD) present with no differences in recognition memory (Bowler et al., 2007) nor in immediate memory or cued recall (Boucher & Lewis, 1989; Boucher and Bowler, 2008). Indeed, their behavioral scores on a variety of memory tasks are comparable to typically developing individuals (Bowler Gardiner & Grice, 2000). Yet, hitherto it was unknown whether ASD memory processes relied on similar or qualitatively different *neural* mechanisms from the

typical case. Using electrophysiological activity in the brain, we measured recognition memory in individuals with ASD compared to age- and IQ-matched neurotypicals. Previous event-related potential (ERP) studies on healthy participants (Cycowicz et al., 2001) had shown that recognition of studied items is accompanied by enhanced positive potentials for those words that are correctly identified as ‘old’ from an earlier study phase, compared to items correctly rejected as ‘new’ (the so-called old/new ERP effect). The enhanced ERP positivity for old words is assumed to reflect the engagement of cognitive strategies to aid recognition memory (Rugg & Curran, 2007; Cycowicz et al., 2001).

Here, we used the same method to explore the neural activity underlying “normal” recognition memory in ASD (Massand et al., 2013). Replicating earlier research (Bowler et al., 2007), the behavioral data revealed no overall differences in recognition memory scores between the ASD and comparison groups. By contrast, electrophysiological data yielded diminished old/new ERP effects in the ASD group, mainly at the central and fronto-central scalp sites. The unusual ERP effect in individuals with ASD indicates that their cognitive strategies and neural responses differ from those of typically developing individuals, despite equivalent behavioral scores. The evidence further suggests that individuals with ASD may rely on a single, non-differentiated memory system, whereas in neurotypicals, two systems have emerged over developmental time. This distinct recognition memory profile at the neural level may turn out to be an endophenotype of ASD, this being the first study to reveal atypical ERP recognition memory effects in ASD, thereby demonstrating that normal behavior can result from a pattern of differing cognitive and neural processes.

The distinction between similar behavior but different underlying neural processes does not only hold for recognition memory in ASD. Face processing in another neurodevelopmental

disorder, Williams syndrome, has yielded a similar difference between scores in the normal range at the behavioral level, but atypical neural underpinnings (Karmiloff-Smith et al., 2004). This once again highlights the importance of neural measures to distinguish between atypical and typical profiles and their implications for decisions about intervention.

Another example of the importance of examining the neural level comes from sensitivity to foreign language contrasts. It had long been thought that the capacity to discriminate non-native phonemes disappears towards the end of the first year of life. Indeed, although 6-month-old infants can distinguish non-native contrasts, this ability becomes significantly diminished behaviorally around 9-10 months when infants fail to distinguish non-native contrasts as they come increasingly to specialise in the phonemic repertoire of their native tongue. But neuroimaging of adults, who show no behavioral signs of distinguishing the non-native contrasts, reveals that their brains are in fact still registering the foreign-language phonemic differences (Rivera-Gaxiola, Csibra, Johnson & Karmiloff-Smith, 2000). This once more highlights the importance of going beyond behavior and focusing on both the cognitive and neural levels of explanation, as well as pointing to the potential for successful foreign-language phonemic training even in the adult.

The study on memory processes in ASD described above focused on the brains of adults. But how can we understand the progressive specialization, or lack thereof, of memory processes at the other end of the developmental continuum? Can we derive EEG data from infants at risk of ASD, i.e., from families where older siblings already have an ASD diagnosis, to examine the early profile of the ASD developmental memory trajectory? In fact, it has already been shown that infants at risk of ASD fail to habituate and thus differentiate auditory tones (Guiraud et al., 2011). New studies in our lab have targeted cross-syndrome comparisons (D'Souza et al., 2013)

and used ERPs in infants with various neurodevelopmental disorders (Fragile X, Williams syndrome and Down syndrome), compared to those at risk of ASD (Elsabbagh & Johnson, 2010). These studies measured infant memory, not for words as in the adult studies, but for more simple auditory input like changes in speech sounds or pitch. Electrophysiological brain activity was measured while infants listened to a sequence of sounds, 70% of which were standard repeated sounds (/u/ low pitch), interspersed with 15% speech deviants (/i/ low pitch) and 15% pitch deviants (/u/ high pitch) (based on Lepisto, et al., 2005). The infant's brain should register simple sound encoding early on (at about 150 ms after stimulus onset), create for recognition memory a representation of the repeated standard sounds, and show different neural activation (mismatch negativity) to changes in speech sounds or changes in pitch compared to the standard. This was indeed the case for neurotypicals (Elsabbagh & Johnson, 2010), but not for infants with neurodevelopmental disorders, each revealing somewhat different patterns of neural activation (D'Souza et al., 2013). In general, electrophysiological measures can uncover neural differences in both adults and infants, which are not necessarily revealed in behavioral measures, and which could be important for the planning of intervention studies.

Using neurocomputational modelling to explore regression in ASD

Another interesting aspect of ASD in early development is the tendency of a subset of toddlers to regress, i.e., to lose rather suddenly during the second year of life various already established motor, social, cognitive or language skills. Hitherto, these regressive events have been noted in observational research, but attempts to explain regression have been rare. Neurocomputational models turn out to be crucial tools for addressing such issues by investigating the mechanistic causes of developmental deficits. This is because implemented

models force specification of the fine details of developmental processes and often lead to novel, testable predictions.

The profile of development and regressive loss, as well as the variability in outcome of ASD in early development, has hitherto proven very hard to explain but, because of the need to specify development in great detail, it lends itself particularly well to the neurocomputational approach (Thomas, Knowland & Karmiloff-Smith, 2011). We thus used a neurocomputational model to test the hypothesis that regression in autism is caused by early, overly aggressive pruning of brain connections, an exaggeration of a normal phase of brain development that occurs during early childhood (Thomas, Knowland & Karmiloff-Smith, 2011). If such pruning differentially impacts long-range connectivity, this would explain the ASD phenotype in terms of impairments in particular to those domains relying on integrative processing (Lewis & Elman, 2008).

The model has three main virtues. First, it can explain the source of variability observed in the severity and prognosis of regression, by specifying protective and risk factors for the pruning of network connectivity. For example, the model demonstrates that larger network size is a risk factor for suffering greater impairments to connectivity from aggressive pruning, which would explain why infants with ASD have been observed as a group to have larger brains (e.g., Schumann et al., 2010). Second, aggressive pruning may allow us to link the regressive subtype of autism to the broader ASD phenotype; that is, pruning may explain other developmental trajectories of autism, where regression is not observed because the underlying development is slower and/or because the aggressive pruning occurs earlier. Third, the hypothesis generates a number of novel predictions that are both unique and testable via emerging studies, mentioned above, that are following the development of infants at greater risk of autism because they are siblings of older children already diagnosed with ASD. Most notably, the over-pruning

hypothesis predicts that the earliest symptoms in the emergence of autism should be sensory and motor rather than social, despite a serious deficit in social skills characterizing the phenotypic end state of older children and adults (Thomas, et al., submitted). That the profile of strengths and weaknesses may change across a disorder illustrates the importance of placing the developmental process itself at the heart of accounts of developmental deficits (Karmiloff-Smith, 1998).

The over-pruning hypothesis of ASD, inspired by the neurocomputational model, differs from other accounts in that it does not propose a narrow primary deficit that causes secondary deficits across development (such as, e.g., attention problems causing later social deficits; Bryson et al., 2004). Instead, it proposes (like the model of adolescent anxiety discussed earlier) a time-varying, multi-system pathological process with wide impact. The challenges for this hypothesis are to specify atypical pruning mechanisms in sufficient detail that they are testable by neuroscience data, and to generate sufficiently precise predictions of the timing of the emergence of particular behavioral deficits that they are testable against psychological data and useable in the planning of intervention studies.

Future directions

The interdisciplinary, multi-method approach to neuroscience is still in its infancy, and yet it has already yielded many exciting advances for the field, with both theoretical and clinical implications. What are the challenges that scientists still need to address? What future directions surface from the studies described in this article? We address in this concluding section five general issues that must, in our view, be at the heart of future research: 1) the importance of using converging methodologies in the same study, 2) the critical nature of longitudinal research targeting individual differences, 3) consistency across multiple levels of

description, 4) intervention and the need for a greater focus on understanding not just risk factors but also protective factors in development, and 5) the general issue of emerging phenotypes.

1) The importance of converging methodologies

We illustrated our approach with five different methodologies: behavioral, EEG/ERP electrophysiology, structural/functional MRI, animal models, and neurocomputational models. Obviously, any single method will at best offer only a partial understanding of a neurocognitive disability. Far richer theoretical discussion and datasets stem from the convergent use of several methodologies. Future research needs, in our view, to use a combination of computational, animal, genetic and cellular models, as well as eye-tracking, brain imaging, behavioral and environmental measures, for the study of psychiatric and neurodevelopmental disorders in infancy, childhood, adolescence and adulthood.

It is in the area of functional brain imaging that we have witnessed huge advances in cognitive neuroscience in recent decades. However, while an attractive tool, brain imaging is no better than a pencil or a fishing trip if it is not hypothesis-driven. The developing brain is unlikely to involve a series of specific brain regions simply maturing and coming ‘on-line’. In fact, most regions in the infant brain are partially active from very early on; what develops is best captured at the level of the complexities of changing intra- and inter-regional networks (Johnson, 2001). So, suitable methods are critical for tracing the details of developmental change in brain function for infants, children, adolescents and adults. Moreover, a combination of methodologies is critical to capture the changes in both the temporal activity of the brain (e.g., high-density EEG) as well as their location (e.g., fMRI).

A compromise that may turn out to be particularly suitable for the thin skulls of infants is functional Near Infrared Spectroscopy (fNIRS), which is inexpensive and portable. The method can also tolerate a degree of movement, which is critical when testing awake infants sitting upright on their parent's lap. Also, fNIRS is even more suitable for infants than for older children because the optical geometry of the infant head renders biological tissue more transparent to light in the near infrared part of the spectrum (particularly in those with as yet no hair!). Moreover, fNIRS can acquire data at a rapid temporal rate (Huppert, Diamond & Boas, 2008), overcoming some of the intrinsic limitations of fMRI. Finally, fNIRS surpasses EEG in providing a better spatial resolution, thereby allowing more accurate localization of brain responses to specific cortical regions (for a review, see Lloyd-Fox et al., 2010). While fNIRS produces better spatial resolution than EEG and better temporal resolution than fMRI, its temporal resolution is lower than EEG and its spatial resolution not as good as fMRI. So, currently fNIRS sits between the advantages and limitations of the two other methods, but that also constitutes its major advantage and will, in our view, be increasingly used in future studies of the typical and atypical developing brain.

What will be required in future research is more simultaneous data acquisition using different methods in the same participants, which results in complementary, converging data about changes in the time course, the spatial location and connectivity of neural activity. This multi-method approach is starting to appear in studies of even very young infants (Telkemeyer et al., 2011) as well as of children (Casey, Soliman & Glatt, 2010; Grossman et al., 2008) and of adults (Huppert, Diamond & Boas, 2008; Steinbrink et al., 2006). Moreover, in future, a cleverly designed developmental study of neural change over a mere few days of intervention might tell us more about change in child brain plasticity than simply comparing child and adult brains measured at only one time point.

2) The need for longitudinal research targeting individual differences

In this paper, we covered three periods of development: infancy, adolescence and adulthood, in a number of cross-sectional and computational studies. Clearly, there is also a pressing need to focus on individual differences in longitudinal approaches which, although costly and labor-intensive, are critical if we are to understand the intricacies of development over time in the kind of detail required for neurocomputational models and intervention studies. Our earlier discussion of the neurocomputational model of regression in ASD is a case in point. The model led to exciting, novel hypotheses, but the kind of data that would be even more useful to further advance our understanding of this debilitating disorder has to involve longitudinal studies of brain connectivity change, and how variations in connectivity align with emerging individual differences in behavior. To understand and model the substrate of plasticity, much finer-level measures are required, and such details can best be garnered from the findings of longitudinal research.

A number of future questions also arise from our study of the effects of SES on infant brain development. Why is resting brain activity in early childhood such a sensitive measure of the effects of adverse environments and developmental risk, or such a good predictor of developmental disabilities? And why were only frontal regions on the gamma-band range implicated? Is that a mere reflection of structural changes in the brain that occur throughout this period, e.g. changes in connectivity? Or does it index processes vital for cross-domain learning? One important line of future research would therefore be to establish longitudinal relationships between structural brain development, activity of resting state neural networks and emerging cognitive and language skills in the first years of life.

3) The need for consistency across levels of description

Theoretically, scientists must generate mechanistic accounts that link between levels of description (gene, neuron, neural networks, brains, behavior, environment) to reconcile theories of mind at these different levels (so-called multi-scale models). Bringing together levels of description may continue to reshape our theories at each level to make them more consistent (for example, altering our theories of cognition to become more consistent with the computations that the brain is readily able to carry out). Neuroscientists need to consider development and individual differences within a common framework, as well as accepting that accounts of each may diverge in their locus of influence. For example, the process of species-universal development might be highly experience dependent, while individual differences in trajectories of development might be largely due to genetic differences. Studies that focus on individual differences (such as twin studies and association analyses) may therefore shed little light on the importance of experience for driving species-universal development.

4) Intervention and the importance of identifying protective factors in development

Timing turns out to be one of the most crucial factors involved in both neurotypical and atypical developmental change. The studies discussed in this paper highlight the fact that there is not a single time-window in development, such as infancy, when intervention must be done to be successful, nor can just any developmental period be targeted for intervention. All depends on the domain, the state of the developing brain, allelic differences in the organism's reaction to environmental inputs as well as time-sensitive effects of the environment. For example, it is likely that the effects of SES on cognitive outcomes, particularly on executive function, may be best be treated in early infancy before changes in prefrontal functioning become consolidated. Also, future research should examine not only the neural effects of SES at the group level, but

also at the level of individual differences that may point to specific allelic differences, explaining how and why infant brains respond differentially to poor environments. We already know at the behavioral level, for instance, that adopted children from the same very adverse initial circumstances either thrive or continue to suffer in new stimulating adoptive environments (Rutter, 2008; Tottenham et al., 2010). A major question remains: do the effects of poor SES on prefrontal areas of the infant brain differ as a function of allelic differences in infants' genome, as was shown above to be the case for adolescents' differing responses to intervention for stress and anxiety?

In this paper, we have placed a good deal of emphasis on risk and protective factors in genetics, but what about environmental influences? We are gradually gaining understanding of the negative consequences of SES disparities for various domains of cognitive development, but what about the strengths, compensation mechanisms and coping skills of families living in poverty? What are the *protective* factors in the environment that mitigate against the adverse effects of SES in early development? For instance, to what extent is the quality of early infant-mother interaction (in the first few months of life) a mediator/moderator of unfavorable SES effects? The study of protective factors in early infant environment, sensitive periods in their operation and underlying mechanisms, may tell us a great deal about early brain plasticity and the best targets for designing new interventions.

But infancy is not the only period when intervention can be targeted. The research on adolescence already made very clear that appropriate time-windows must be identified through consideration of multiple levels, including allelic differences that make some individuals more responsive to intervention than others. Indeed, adolescence is a life stage during which the differential developmental trajectories of regions of the brain that generate fear responses and those that regulate them are imbalanced. The timing of this imbalance, which contributes to

inefficient fear regulation that is adaptive to the behavioral demands of adolescence but can also contribute to anxiety disorders, turns out to be critical for successful intervention. These studies have clear implications for novel treatments for the developing brain because developmental and individual variation in fear responses is likely to inform the treatment of anxiety disorders. The only evidenced-based behavioral treatments for anxiety disorders currently build upon basic principles of extinction learning in the identification and desensitization of the individual to the cause of their anxiety. As such, the efficacy of this treatment will be associated with the ability to extinguish fear memories (Drysdale et al 2013). The combination of individual and developmental inefficiencies in extinction learning that predisposes to anxiety disorders in the first place means those most in need of desensitization therapies may actually benefit the least.

Studies of *adaptive* fear learning may provide a future way forward, with implications for novel evidence-based treatments that go beyond the current standard of care, opening up a number of crucial new questions for future research: 1. Does age impact the efficacy of cognitive behavioral therapy in youth with anxiety disorders? 2. How should current behavioral exposure therapies be modified or tailored for patients as a function of age? 3. How should current psychiatric treatments be modified or tailored for patients as a function of genetics? And, 4. As fear memories can undergo erasure in adults, can similar techniques be used to “erase” unwanted fear memories in developing individuals, particularly during adolescence, when fear memories are resistant to classic extinction training? Recent studies (Monfils et al., 2009; Schiller et al., 2010) have shown that a single, isolated presentation of a fear-associated cue opens a “reconsolidation window” during which extinction learning to that cue is enhanced. These studies were conducted on adults and, given the research discussed in this paper, they obviously must be tested on adolescents. However, they already suggest that informed modifications of standard behavioral therapies for anxiety disorders may improve the treatment

of these common and debilitating disorders. It is clear that such questions must continue to be addressed with both human studies and animal models of adolescent anxiety.

Future intervention targets also spring from our computational modeling. In terms of a specific prediction of the over-pruning account of autism, the hypothesis is that the cause is a multi-system, time-varying deficit. This contrasts with many current accounts which posit a narrow primary deficit (e.g., to social orienting or to attention) with many secondary deficits across development. The two theories predict that different types of intervention will be effective. The multi-system hypothesis predicts that interventions must be wide, separately addressing multiple domains of deficit, and that a narrow intervention will only improve the domain to which it is targeted (see discussion in Karmiloff-Smith et al., 2012). The primary deficit accounts predict that, if intervention occurs early enough, a narrow intervention will suffice to alleviate many or all of the wider secondary deficits. The extent to which early interventions to improve narrow skill sets in autism generalize to wider skill sets is therefore of central importance in distinguishing between these two accounts of the cause of autism (Thomas, et al., submitted).

5) Emergent phenotypes

Theoretically, it has become increasingly clear that phenotypes are emergent, not predetermined by genes or environment, and that there is a very complex interplay between allelic and environmental risk/protective factors, both of which must be understood in detail to advance the field. In our view, neuroscience will make significant future progress if we focus on individual differences at multiple levels – genetic, cellular, neural, cognitive, behavioral and environmental - rather than only on group data at a single level. This should also aid the planning of successful intervention. It is crucial to continue to forge the interface between our

growing theoretical understanding of neurodevelopmental disorders and the practical implications for understanding behavior and treating disorders. The challenges before the field are difficult, but necessary. There clearly remain more questions than answers. However, rather than attempting to simplify our approaches to neurocognitive disability, we argue that the field must embrace the complexity of a dynamic neurodevelopmental canvas that is constantly changing over time.

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