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REVIEW

ASSESSING THE MOLECULAR GENETICS OF THE DEVELOPMENT OF EXECUTIVE ATTENTION IN CHILDREN: FOCUS ON GENETIC PATHWAYS RELATED TO THE ANTERIOR CINGULATE CORTEX AND DOPAMINE

K. BROCKI,[a,b] S. M. CLERKIN,[a] K. G. GUISE,[a] JIN FAN[a] AND J. A. FOSSELLA[a]*

[a]*Department of Psychiatry, Box 1230, Mount Sinai School of Medicine, One Gustave Levy Place, New York, NY 10029, USA*

[b]*Department of Psychology, Uppsala University, Sweden*

Abstract—It is well known that children show gradual and protracted improvement in an array of behaviors involved in the conscious control of thought and emotion. Non-invasive neuroimaging in developing populations has revealed many neural correlates of behavior, particularly in the developing cingulate cortex and frontostriatal circuits. These brain regions, themselves, undergo protracted molecular and cellular change in the first two decades of human development and, as such, are ideal regions of interest for cognitive- and imaging-genetic studies that seek to link processes at the biochemical and synaptic levels to brain activity and behavior. We review our research to date that employs both adult and child-friendly versions of the attention network task (ANT) in an effort to begin to describe the role of specific genes in the assembly of a functional attention system. Presently, we constrain our predictions for genetic association studies by focusing on the role of the anterior cingulate cortex (ACC) and of dopamine in the development of executive attention.

Key words: genetic, brain, dopamine, child, development, cingulate.

Contents

The ability to use attention to control the processing of information from the environment is a central concept in developmental psychology and the study of psychopathology (Posner et al., 2007). The now widespread application of genetic and neuroimaging methods to the study of executive control makes it possible, in principle, to fathom how certain genes function in the development of neural networks that carry out executive attention. This is because individual differences can be observed in assessments of psychological processes or constructs, and then correlated to individual differences in brain structure, neural activity and genetic variation (reviewed in Green et al., 2008). For example, a variable number tandem repeat (VNTR) polymorphism in exon III of the *dopamine d4 receptor* (DRD4), a gene that is reliably associated with risk for the developmental disability ADHD, shows a correlation with cortical thinning in young children (Shaw et al., 2007) and interacts with parenting style to influence temperament (Sheese et al., 2007) suggesting a biological link between cortical development and cognitive development. Other developmental disabilities such as phenylketonuria, Angelman syndrome and fragile X mental retardation reveal the profound way in which single genes alter the normal trajectory of brain and cognitive development (Scerif and Karmiloff-Smith, 2005). Some genes may even function very early in embryogenesis, but only cause noticeable disruptions rather late in behavior. The *forkhead box a2* (FOXA2) gene, for example, regulates the earliest stages of the birth of dopamine (DA) neurons but contributes to a parkinsonian form of neural degeneration when the organism reaches late adulthood (Kittappa et al., 2007). Lastly, we know that genes act under the influence of the environment during development, as evidenced by the interaction of early childhood stress with the MAOA and 5HTT genes increasing the risk of aggressive behavior and depression later in life (Caspi et al., 2002, 2003). Furthermore, early maternal stress can lead to epigenetic modification of the fetal genome, as seen in promoter of the *glucocorticoid receptor* gene (Meaney and Szyf, 2005). Hence, it is of interest to specify the role of genetic variation in terms of its influence on structural and cognitive change during development.

CHOOSING APPROPRIATE PSYCHOLOGICAL CONSTRUCTS: CONVERGENCE ON ATTENTIONAL CONTROL

In previous studies on executive attention, we have reported that several genetic polymorphisms were related to variation in performance as well as to the activity of brain regions known to function as nodes in larger neural net-

*Corresponding author. Tel: +1-241-8030; fax: +1-646-417-6208.
E-mail address: John.Fossella@mssm.edu (J. A. Fossella).
Abbreviations: ACC, anterior cingulate cortex; ANT, attention network task; DA, dopamine; TAC1, *tachykinin, precursor 1*.

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works that carry out attention (Fan et al., 2003). Since these studies were conducted with adult participants, we are unable to discern whether the role of specific genes has been one limited to the maintenance of and/or homeostatic regulation of the mature networks, or perhaps a developmental role in the early assembly of the attention system. To begin to assess the possible developmental roles of genes associated with executive attention, we seek to utilize tasks that can measure the efficiency of the attention system at different age ranges, such as a child-friendly version of the attention network task (ANT). In choosing this strategy, we acknowledge a few of the many complexities in choosing suitable behavioral assessments for child populations. Firstly, it is important that the behavioral assessments be consistent with an established psychological model or framework. Practically speaking, it is also important to consider tasks that can be adapted to a neuroimaging environment and to consider tasks where performance can be compared across a wide range of ages by parametrically manipulating task difficulty. Substantial evidence points to a unified conceptual framework for the development of executive control where central attentional mechanisms are involved (Miyake et al., 2000; Rothbart and Posner, 2001; Davidson et al., 2006), as well as dissociable processes such as inhibition and working memory (Diamond, 2002). Therefore, we expect attention and, moreover, genes that contribute to the development of the attention system to play a central, but limited, role in the development of executive function.

A number of studies have already adapted the central construct of attention, upon which the ANT is built, to studies of attentional function in infants, toddlers and young children. Infants show a propensity to gaze longer during incorrect trials and show increased negative activity on measurements of event related potentials (Berger et al., 2006) while 2 to to 3-year-olds demonstrate correlation in their ability to resolve stimulus-response conflict and anticipatory eye movements (Rothbart et al., 2003). A few behavioral performance measures have been found to relate to aspects of temperament using scales that are appropriate for infants and children. In infants, the orienting of attention was found to relate to positive affect and function as a means to distract children from distress and reduce negative affect (Harman, Rothbart and Posner, 1997). In young children, effortful control was related to executive attention as measured by the child-friendly ANT (Rothbart and Rueda, 2005). By age 7, executive attention as measured by performance on the ANT appears stable (Rueda et al., 2004). However, performance on many traditional executive function tasks involving component functions such as working memory and inhibition (e.g., the Wisconsin Card Sorting, Tower of Hanoi and N-back) continues to improve in adolescence and into early adulthood.

Our use of the child version of the ANT is based on earlier work of Rueda et al. (2005) as well as the work of Konrad et al. (2005) who have reported functional activations in children who performed the ANT in the MRI scanner. Each trial begins with a cue (or a blank interval, as in the no-cue condition) that informs the child either that a target will appear soon, and/or where it will appear on the screen. The target always occurs either above or below fixation, and consists of a central arrow (in the shape of a smiling fish), surrounded by flanking arrows (smiling fish). The flankers point either in the same direction as the target arrow (congruent) or in the opposite direction (incongruent) and a subtraction of RTs of congruent from incongruent target trials provides a measure of conflict resolution that assesses the efficiency of the executive attention network. The data presented in Fig. 1, were obtained from a collection of 110 healthy children somewhat evenly distributed in gender and ages 5–13 years old who performed the task while under adult supervision. A view of both the distribution of raw and of normalized (conflict RT/overall RT) shows that children experience a reaction time cost of

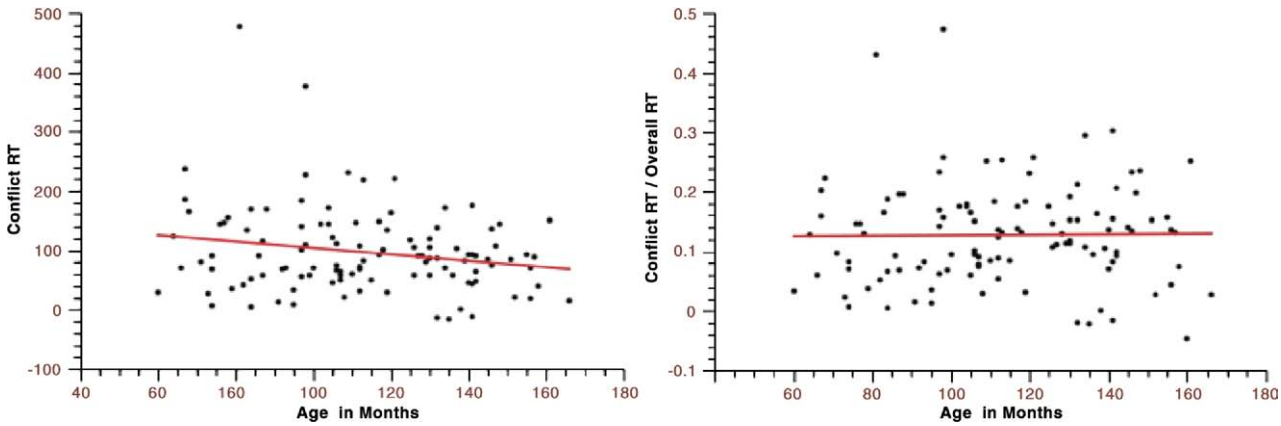

Fig. 1. Executive attention scores of children 5–13 years of age. Healthy participants (n=110, 53% male) residing in the vicinity of New York City were recruited to perform the task on a Dell PC desktop computer (Round Rock, Texas, USA). Children sat at the desk and used the two-button computer mouse to perform the task in a similar manner as described in (Rueda et al., 2004). Each child was individually supervised by Dr. Brocki during the task and who provided feedback during the practice block and encouragement to the subjects. Children were awarded small stickers and a child science book as a prize for completing the study. The conflict score was calculated by using the child's median RT for either incongruent or congruent flanker conditions (across cue conditions) and then the congruent score was subtracted from the incongruent score. The left panel shows the raw scores (Y-axis) for each child whose age is plotted in months (X-axis). The right panel shows the scores when normalized by dividing by overall reaction time. In both panels, a linear least squares fit is provided in red.

about 90 ms related to the resolution of stimulus-response conflict and that there is little change in the efficiency of conflict resolution as children mature beyond this age range. This is largely in agreement with previous reports (Mezzacappa, 2004; Rueda et al., 2004) and suggests that genetic correlates of performance on the child-friendly ANT may relate to developmental processes that occur before the age of 5.

CHOOSING APPROPRIATE NEURAL CORRELATES: CONVERGENCE ON DA AND THE ANTERIOR CINGULATE CORTEX (ACC)

The next step in our research strategy has been to choose appropriate candidate genes, and variants within those genes, suitable for behavioral and imaging genetic association studies in mixed populations of healthy volunteers. Since there are several million common genetic variants in the human genome and thousands of voxels in both white and gray matter in the human brain, we seek to avoid inherent type I statistical limitations by crafting hypotheses that are as specific as possible. Within the scope of our interest in the development of executive attention, the robust and reliable brain activity observed in the cingulate cortex of healthy children suggests that the ACC may be an ideal region of interest (Bush et al., 2005). For example, event related potential recordings in infants as young as 6–9 months of age show increased negativity in response to conflict that is spectrally very similar to the error-related negativity seen in adults, a neural process that has been localized to the ACC (Berger et al., 2006). In a population of children ages 7–11, Casey et al. (1997) reported that the blood-oxygen-level-dependent (BOLD) response in the ACC varied as a function of increased number of errors on a go–no-go task and demonstrated that activity in ventral prefrontal regions was correlated with accuracy. This type of error-related activity in the ACC is suggested to inhibit dopaminergic function via projections to the striatum which, in turn, supports learning of the no-go response (Frank et al., 2007). Like the prefrontal cortex, the cingulate cortex, however, does show evidence for a somewhat prolonged time course of development (Ridderinkhof et al., 1997; Sowell et al., 2004; Guo et al., 2007). A recent functional connectivity study in children showed that correlated activity among voxels across the ACC was found to be weaker than in other areas of the brain (Kelly et al., 2008). Therefore, in the ongoing construction of specific hypotheses for our cognitive and imaging genetic studies, we constrain the scope of the research by limiting our focus to the development of the ACC.

Another strategy to focus and constrain the scope of our gene association studies, is to consider the role of DA in the development of executive attention. In the seminal work of Diamond (1991), infants show marked improvement in tasks that require them to both inhibit a pre-potent response, and also hold in mind the location of a target and performance on these measures was shown to be dependent on the frontal cortex in monkeys (Diamond and Goldman-Rakic, 1985). Animal models of phenylketonuria show that cognitive disruptions associated with PKU were dependent on reductions of DA in the prefrontal cortex (Diamond et al., 1994) which is consistent with Goldman-Rakic and colleagues who, using a primate model, found that the reduction of DA was as effective in diminishing executive function as lesions to the frontal cortex (Brozoski et al., 1979). In primate models, age-related improvement on executive control tasks is paralleled by postnatal increase in DA levels (Goldman-Rakic, 1981) and an increase in DA receptor gene expression (Lidow et al., 1991). Within the developing brain, DA participates in cellular changes such as myelination, synaptogenesis and pruning (Shen et al., 2007; Fasano et al., 2008; Feng, 2008) but may mainly subserve executive function as a modulator of excitability of recurrent synaptic inputs (Surmeier et al., 2007). The time course of these processes may be quite variable and outside the range of our present study population (5–13 years old) however, as, for example, synaptogenesis and myelination in the ACC may peak before age 5, while pruning may continue well after age 13 (Sowell et al., 2004).

CONSTRUCTING HYPOTHESES CENTERED ON SPECIFIC GENES: PATHWAYS FOR ACC DEVELOPMENT

In the design of cognitive and imaging genetic associations studies, hypotheses should be generated that specify a particular allele of a candidate gene and its relation to brain and/or behavior. The choice of candidate *gene* then, should stem from converging evidence that implicates that gene in the development or function of targeted neural correlates (the ACC and DA in our case). The choice of *allele* is a more practical consideration of its frequency in human populations across ethnic backgrounds and whether there is some functional change in the encoded protein or in the abundance of the gene product that is conferred by the polymorphism. In mammals, a number of genetic pathways are known to regulate the development of the frontal midline. The most well-studied are genes that lead to holoprosencephaly, a genetic disorder where the ACC fails to develop due to poor division of the double lobes of the embryonic forebrain (Takahashi et al., 2003). Mutations in *Sonic hedgehog* (SHH) and several downstream factors including *7-dehydrocholesterol reductase* (DHCR7), *patched* (PTCH), *zic family member 2* (ZIC2), *Kruppel family member gli2* (GLI2) all give rise to midline deformities in humans (reviewed; Cohen, 2003). Gene expression profiles for three types of interneurons and two types of projection neurons (layer 5 and layer 6) in the ACC show enriched expression of *secreted frizzled-related protein 2* (SFRP2) natriuretic peptide precursor C (NPPC), *endothelin converting enzyme-like 1* (ECEL1), *tachykinin, precursor 1* (TAC1) and *neurexophilin 3* (NXPH3) among other genes (Sugino et al., 2006). TAC1 is of particular interest since it shows associations with depressive illness in humans and depression- and anxiety-related behaviors in mice (Bilkei-Gorzo et al., 2002). Lastly, the development of the dopaminergic system in the frontal cortex is regu-

lated by a number of members in the FGF family of proteins. For example, mice with a conditional inactivation of *fgf2* as well as a null *cnp1* background display no obvious anatomical abnormalities, but display hyperactivity that can be suppressed by dopaminergic antagonists (Kaga et al., 2006), while the growth factor *fgf20*, which promotes dopaminergic cell survival, has been implicated in psychiatric illness (Murase and McKay, 2006). Frontal identity has been shown to be imparted by *fibroblast growth factor-8* (FGF8) (Fukuchi-Shimogori and Grove, 2001).

In principle, each of these genetic factors would be ideal for future cognitive and imaging genetic experiments where measurements of executive attention and measurements of ACC activity and structure were obtained. While ongoing work in the laboratory proceeds in this direction, presently, however, no converging evidence exists in the cognitive or imaging genetic literature. We therefore begin our analysis of candidate genetic data by comparing our findings to existing converging evidence. The *dopamine transporter* gene (DAT1 or SLC6A3), which encodes a protein that is the molecular target of methylphenidate, a therapeutic used to treat ADHD and hyperactivity (Dresel et al., 2000) contains a 40-bp repeat polymorphism in the 3′ untranslated region. The 10-repeat allele of this polymorphism, has been associated with ADHD (Faraone et al., 2005) and structural aspects of the striatum (Durston et al., 2005), which is the same area to which methylphenidate is known to bind. Also, Rueda et al. (2005) reported that children who were homozygous for the long (10/10) genotype showed lower scores on the child ANT. When this evidence is tested using our population, the data shown in Fig. 2 also reveal this trend where children ages 5–7 who carry the long/long (10-repeat homozygotes) genotype are somewhat more efficient at resolving conflict ($P=0.05$). The shifting trend in the data among 10-repeat homozygotes toward higher scores with age is also consistent with previous findings that (10/10) adults are less efficient in the resolution of incongruent trials during the ANT (Fossella et al., 2002). The shift from more to less efficient conflict resolution with age may be connected to age-dependent changes in DAT1 levels (Volkow et al., 2001) that could alter the organism's sensitivity to the inverted-U-shaped dose/response dependency for DA. Also, the paucity of DAT1 in the frontal cortex and ACC suggest that the relationship between performance on the ANT and ACC function could be indirectly mediated through *dopamine d1 receptor* (DRD1) which are stimulated by extrasynaptic DA in the cortex (Sesack et al., 1998; Bilder et al., 2004).

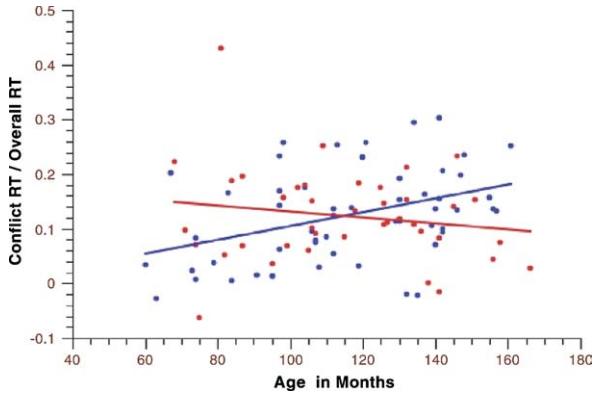

Fig. 2. Relationship of DAT1 3′ UTR polymorphism to executive attention scores in children 5–13 years of age. Genomic DNA was collected using the Oragene DNA Self-Collection Kit (Ottawa, Canada) by each child providing a saliva sample of approximately 2 ml. From this sample, approximately 100 μg of genomic DNA was extracted and used for genotyping. To measure variation at a 40 bp repeat polymorphism in the DAT1 gene (Daly et al., 1999), PCR was performed using forward: 5′-TGTGGTGTAGGGAACGGCCTGAG-3′ and reverse 5′-CTTCCTGGAGGTCACGGCTCAAGG-3′ primers in standard buffer conditions along with the addition of 10% (final v:v) DMSO in a "touchdown" PCR regimen using a PTC-100 Programmable Thermal Controller (Bio-Rad). Gel electrophoresis in either Metaphor agarose followed by staining in ethidium bromide was used to resolve and visualize DNA fragments. The Y-axis shows the normalized executive attention scores (conflict scores/overall RT) and the X-axis shows the age in months. The data were subdivided and best fit using linear least squares method so as to visualize the differences between children with the long/long (10/10-repeat) genotype (blue) vs. long/short (10/9-repeat) and short/short (9/9) genotypes (red).

CONCLUSION

We have noted that it is important to understand the function of genetic variation in the context of brain and cognitive development. We describe a strategy for the design of hypothesis-driven cognitive and imaging genetic studies in developing populations. To overcome the expense and statistical limitations faced in exploratory studies, we have adopted a hypothesis-driven investigative approach where gene- and allele-specific predictions are rooted in evidence obtained from structural and functional studies in humans, mice, and cell-based systems. We are focused on the developmental biology of executive attention networks and, most recently, on the role of the ACC and dopaminergic modulation within the ACC. In presenting our strategy, we are also mindful of several limitations. Firstly, there is a wide range of genetic factors that are expressed in circuits that carry out attention and executive control, and, in principle, any type of genetic variant, such as a single-nucleotide polymorphism (snp) a variable number tandem repeat (vntr) or a large deletion of genetic material could impact brain development at *any* stage of fetal, neonatal or child development. We also acknowledge that we are probing a specific node (ACC) in a wider set of complex neural networks whose functional connectivity is organizing and re-organizing during development. Within this node, many of the biological changes that we seek to measure vis-a-vis genetic markers that index dopaminergic modulation, synaptogenesis, myelination and/or pruning may have largely occurred by age 5, or perhaps occur later than age 13. Lastly, we acknowledge that children may use a mix of alternate networks to carry out task demands, which therefore may confound the interpretations of the cognitive and imaging genetic assessments.

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