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Analyzing and shaping human attentional networks[☆]

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Abstract

In this paper we outline a conception of attentional networks arising from imaging studies as connections between activated brain areas carrying out localized mental operations. We consider both the areas of functional activation (nodes) and the structural (DTI) and functional connections (DCM) between them in real time (EEG, frequency analysis) as important tools in analyzing the network. The efficiency of network function involves the time course of activation of nodes and their connectivity to other areas of the network. We outline landmarks in the development of brain networks underlying executive attention from infancy and childhood. We use individual differences in network efficiency to examine genetic alleles that are related to performance. We consider how animal studies might be used to determine the genes that influence network development. Finally we indicate how training may aid in enhancing attentional networks. Our goal is to show the wide range of methods that can be used to suggest and analyze models of network function in the study of attention.
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The goal of this paper is to inform people interested in neural network models about efforts to analyze the networks of neural areas revealed in imaging studies and to understand how genes and experience shape their development. To do this we first discuss attention networks as defined by anatomical areas active in functional imaging studies, and then examine physical and functional connections between these areas. Next we consider how these networks develop during infancy and early childhood and finally what is known about how genes and experience shape the network.

1. Networks of attention

What do we mean by an attentional network? In cellular physiology the idea of a network involves identified neurons that connect to one another by synapses and through other means of communication (Bullock et al., 2005). Connectionist models, inspired by neural networks, have considered units at particular levels that influence each other by direct or reciprocal connections (O'Reilly & Munakata, 2000). Imaging of human task performance has identified another level of network function, which is clearly related to both the models and the underlying cellular structure by showing that a number of quite separate brain areas must be orchestrated in even the simplest task. Each of these areas may be performing a different computation, which taken together allow performance of the task. We regard the set of activations and their connections as the network that underlies task performance.

It is often believed that attention is a general property of the whole brain, but neuroimaging studies have shown specific networks of neural areas are involved in functions related to attention (see Fig. 1). Attentional networks are special in that their primary purpose is to influence the operation of other brain networks. As illustrated in Fig. 1 three attentional functions for which brain networks have been imaged are: alerting which is involved in acquiring and maintaining the alert state; orienting to sensory stimuli and executive control involved in the resolution of conflict between neural systems and regulating thoughts and feelings (Fan, McCandliss, Fossella, Flombaum,
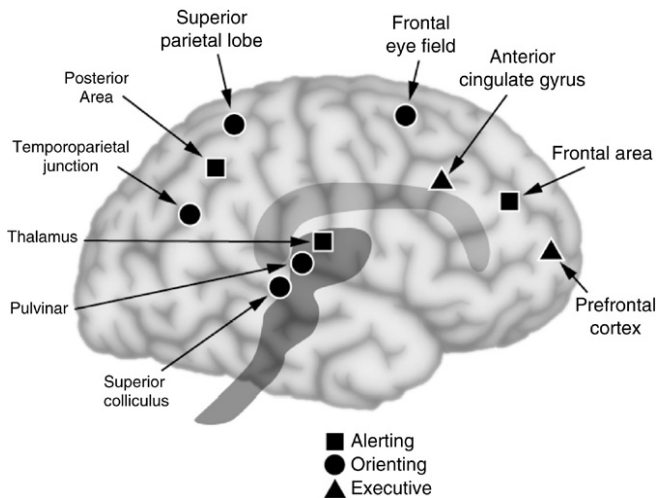
Fig. 1. This figure illustrates cortical areas involved in three attention networks. The alerting network (squares) includes thalamic and cortical sites related to the brain's norepinephrine system. The orienting network (circles) is centered on parietal sites (discussed below) and the executive network (triangles) includes the anterior cingulate and other frontal areas.

& Posner, 2005). Although the sites at which attention influence can be demonstrated involve most any brain area including primary sensory, limbic and motor cortex, as shown in Fig. 1 the sources of these activations are much more limited.

Orienting to sensory events has been the more studied of these networks both with imaging (Corbetta & Shulman, 2002) and cellular (Reynolds, 2004) methods. The convergence on the set of brain areas serving as the source of the amplification of sensory signals has been impressive (see Hillyard, Di Russo, and Martinez (2004), for a recent review). It is widely agreed that the frontal eye fields work in conjunction with superior and inferior parietal areas as the cortical nodes of the orienting network. In addition, studies have implicated some subcortical areas including the pulvinar of the thalamus and the superior colliculus. Most of the studies of this network have involved visual stimuli, but the sources of the attention influences in orienting to other modalities are much the same. Of course the site of amplification of the sensory message is quite different for each of the modalities.

Evidence to date suggests that both maintained alertness during task performance (tonic) and phasic changes induced by a warning signal involve a subcortical structure, the locus coeruleus that is the source of the brain's norepinephrine. A great deal of evidence (summarized in Posner and Petersen (1990)) indicates that the tonic state depends upon an intact right cerebral hemisphere. Lesions in this hemisphere can produce profound difficulty in responding to unexpected targets. Warning signals, however, may have their influence more strongly on the left cerebral hemisphere (Coull, Frith, Buchel, & Nobre, 2000; Fan et al., 2005). This distinction may reflect a more general division between the hemispheres where rapidly acting events are left lateralized while more slowly changing states involve right hemisphere activity.

Tasks that involve conflict between stimulus dimensions competing for control of the output often provide activation in the anterior cingulate gyrus and lateral prefrontal areas.

It is thought that the conflict, induced by a stimulus, is representative of situations where different neural networks compete for control of consciousness or output. Because of this we have termed this the executive attention network because it regulates the activity in other brain networks involved in thought and emotion (Crottaz-Herbtte & Mennon, 2006; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). This network shows a strong development in childhood and its maturation is related to what in developmental psychology has been called self-regulation.

Individual differences are invariably found in cognitive tasks involving attention. The Attention Network Test (ANT) was developed to examine individual differences in the efficiency of the brain networks of alerting, orienting and executive attention discussed above (Fan, McCandliss, Sommer, Raz, & Posner, 2002; Rueda, Fan, et al., 2004). The ANT uses differences in reaction time (RT) between conditions to measure the efficiency of each network. Each trial begins with a cue (or a blank interval, in the no-cue condition) that informs the participant either that a target will be occurring soon, or where it will occur or both. The target always occurs either above or below fixation and consists of a central arrow, surrounded by flanking arrows that can either point in the same direction (congruent) or in the opposite direction (incongruent). Subtracting RTs for congruent from incongruent target trials provides a measure of conflict resolution and assesses the efficiency of the executive attention network. Subtracting RTs obtained in the double-cue condition from RT in the no-cue condition gives a measure of alerting due to the presence of a warning signal. Subtracting RTs to targets at the cued location (spatial cue condition) from trials using a central cue gives a measure of orienting, since the spatial cue, but not the central cue, provides valid information on where a target will occur.

2. Network connectivity

Neural areas found active in studies of functional anatomy must be orchestrated in carrying out any real task. One approach to studying this connectivity uses fMRI to study the time course of activity and the correlations between active areas. Because of the relatively long delays between input and peak BOLD fMRI signal, small time differences may be hard to detect. Another approach to the examination of temporal connections between brain areas is based on electrical or magnetic signals since these signals can give higher temporal resolution, and can be combined with MRI to improve the spatial localization. A third approach to the measurement of connectivity involves the measurement of fiber tracts that connect neural areas by use of diffusion tensor imaging (DTI) that traces white matter tracts. Below we illustrate these methods by primarily considering the connectivity of the dorsal anterior cingulate during performance of the Attention Network Test.

The organization of anatomical areas in alerting and orienting is not fully known, but some promising beginnings have taken place. In alerting the source of the attention appears in the locus coeruleus (lc). Cells in the lc have two modes of processing. One mode is sustained and is perhaps related
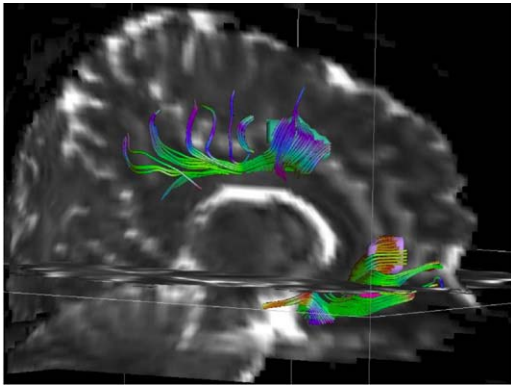
Fig. 2. The results of the Diffusion Tensor Imaging study of the structural connectivity of the dorsal and ventral anterior cingulate. The colors indicate the orientation of the fibers red = left–right, green = anterior–posterior, and blue = inferior–superior. DTI images were acquired from a single subject on a 3.0 T Siemens Allegra MRI scanner. Diffusion weighting was performed using $b = 700$ s mm^{-3} along 60 independent orientations (Jones et al., 1999). MR acquisition parameters were: TE/TR = 110 ms/10.9 s; matrix = 128×128 on a 256 mm FOV, slice thickness = 2 mm with no gap; 60 transverse slices covering entire brain. DTI data were analyzed on a Siemens Leonardo TM workstation NUMARIS 4 satellite console using MGH's *DTI Task Card* 1.69 software written by R.P. Wang (http://www.nmr.mhg.harvard.edu/˜rpwang/siemens/dti_taskcard/new). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to the tonic level of alertness over long time intervals. This function is known to involve the right cerebral hemisphere more strongly than the left (Coull et al., 2000; Sturm & Willmess, 2001). Alertness is influenced by sensory events and by the diurnal rhythm. However, its voluntary maintenance during task performance may be orchestrated from the anterior cingulate (Mottaghy et al., 2006). More phasic shifts of alerting can result from presenting any environmental signal. However, if the signal is likely to warn about an impending target this shift results in a characteristic suppression of the intrinsic brain rhythms (e.g. alpha) within a few tens of milliseconds and a strong negative wave (contingent negative variation) recorded from surface electrodes and that moves from a frontal generator toward the sensory areas of the hemisphere opposite the expected target.

According to Bush, Luu, and Posner (2000) an analysis of a number of conflict tasks shows that the more dorsal part of the anterior cingulate is involved in the regulation of cognitive tasks, while the more ventral part of the cingulate is involved in regulation of emotion. One way to examine this issue is to image the structural connections of different parts of the cingulate using diffusion tensor imaging. This form of imaging uses the diffusion of water molecules in particular directions due to the presence of myelinated fibers (Conturo et al., 1999). Thus it provides a way of examining the physical connections present in the brains of people. Fig. 2 shows the result of a DTI analysis of one subject run in our experiments. Note that the dorsal part of the ACC shows connections to cortical areas of the parietal and frontal lobes, while the ventral part of the ACC has strong connections to subcortical limbic areas (Abdullaev, in preparation).
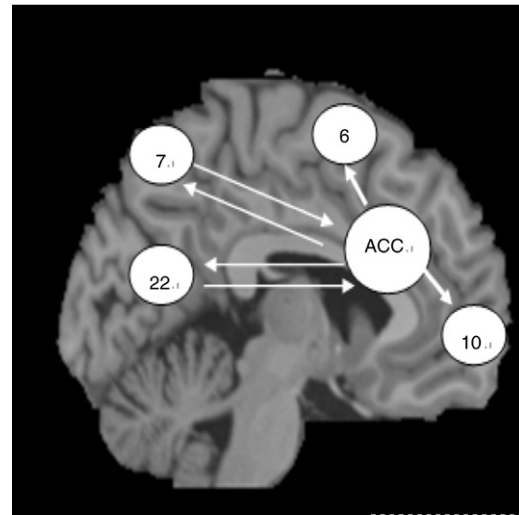

Fig. 3. The results of an fMRI connectivity analysis based on the correlations between the dorsal anterior cingulate and other cortical brain areas. Dynamic causal modeling (DCM) was used to infer the direction of influence. Each circle contains the Brodmann area involved. All influences among regions shown by lines are significant in the direction of the arrow.

Another step is to examine networks of neural areas related to the ACC during task performance. To illustrate this approach we consider a recent fMRI study, in which we ran 12 young adults in the ANT. The data were first analyzed by statistical parameter mapping (SPM2) (http://www.fil.ion.ucl.ac.uk/spm) to produce the functional anatomy of different attentional circuits shown in Fig. 1. For illustrative purposes we examined the cortical connectivity (Horwitz, Rumsey, & Donohue, 1998; Tang et al., 2006) to and from the dorsal anterior cingulate during performance of the conflict subtraction in the ANT (incongruent–congruent). As expected we found strong connectivity to parietal and frontal brain areas.

We then applied the Dynamic Casual Modeling (DCM) method for region of interest (ROI)-based effective connectivity analyses in the conflict task (Friston, Harrison, & Penny, 2003; Penny, Stephan, Mechelli, & Friston, 2004). Fig. 3 shows the results (numbers indicate Brodmann areas). Our findings showed interregional coupling (effective connectivity) for the conflict subtraction among the nodes of the attention system including the dorsal ACC, the lateral ventral prefrontal lobe (BA6, BA10), superior parietal gyrus (BA7) and temporal parietal junction (BA22). The ACC is likely to be the core mediation for the other brain regions in the conflict task. At the same time, BA7 and BA22 also modulate ACC. The interaction of the orienting and conflict network arises because following some cues (e.g. central) a shift of orienting must take place after the target occurs.

Another way to examine network activity during the ANT is to use scalp EEG electrodes to record neural activity synchronized in different frequency bands. This method can be used to separate rapid temporal events, for example, it can separate the cue effects from the target effects in the ANT. In one study using the ANT (Fan et al., in preparation), a spatial cue indicating the location of the target produced increased high frequency gamma activity (above 30 Hz) about 200 ms after the

cue presentation. When the cue brought attention to the target location, gamma activity was found following the cue, but not following the target. When the cue indicated the center location so that a shift of attention was needed following the target, the gamma activity was present following the target. These data suggest that gamma activity is associated with orienting of attention. It may occur 200 ms after the cue or only after the target depending upon when attention shifts. Taken together the fMRI, EEG and DTI methods can provide a detailed account of the orchestration of neural networks related to attention.

3. Development of attentional networks

The goal of understanding networks is to illuminate their role in actual human behavior. Efforts have been made to examine how the development of attentional networks influences infant and child behavior. Such landmarks of development are crucial for links between genetic differences and actual behavior. The alerting and orienting systems begin development in early infancy and allow the infant to stay alert and to be in contact with sensory information. However, in this paper we concentrate on the executive network, which has been more difficult to demonstrate even in a rudimentary form during infancy. One effort involves anticipatory looking paradigms such as the Visual Expectation Paradigm (Haith, Hazan, & Goodman, 1988). In this method a repeating predictable sequence of visual stimuli is shown to infants. Infant eye movements are recorded and coded for evidence of reactive looks, which occur in response to the presentation of stimuli, and anticipatory looks, which occur in advance of the presentation of stimuli. Reactive looks are thought to reflect exogenous control of attention in that looks to stimuli are in response to the stimuli itself and only require attentional processes associated with alerting and orienting. In contrast, anticipatory looks involve internal control of attention and may reflect the early functioning of the executive attention network.

Anticipatory looking to more complex, ambiguous sequences of visual stimuli may present a method for examining more sophisticated forms of executive attention in infancy. Working with adults, Curran and Keele (1993) showed that while stimuli appearing in an unambiguous sequence of locations (e.g., 123123) could be learned in the absence of attention, learning context-dependent sequences (e.g., 12131213) was dependent upon higher-order attentional processes. Clohessy, Posner, and Rothbart (2001) proposed that higher-order attentional processes may be required when anticipating a stimulus following Location 1 in a context-dependent sequence because there is a conflict that must be resolved between shifting attention to Location 2 and Location 3. They examined anticipatory looking to both unambiguous and context-dependent sequences of visual stimuli in infancy and found anticipatory looking during unambiguous sequences as early as 4 months. However, anticipatory looking during context-dependent sequences was not seen consistently until at least 18 months of age. These data suggest the possibility that rudimentary executive attention capacities may emerge during the first year of life but that more advanced conflict resolution capacities are not present until 2 years of age.

We are currently examining how executive attention as assessed through anticipatory looking is related to emotional and behavioral regulation in 7–9 month old infants. Preliminary analyses suggest that infants showing higher levels of anticipatory looking are also more likely to regulate approach tendencies when presented with novel toys and are also more likely to show self-soothing behaviors when presented with frightening stimuli. These results are consistent with findings from childhood that show higher levels of executive attention are broadly related to behavioral and emotional regulation (see Rothbart and Sheese (in press), for a review).

Another approach to examining executive attention in infancy involves the ability to detect errors (Berger, Tzur, & Posner, 2006) examined error detection capacities in seven-month-old infants. Using a method developed by Wynn (1992), infants were presented with simple addition problems using a visual display of cartoon-like characters that were either correct ($1 + 1 = 2$) or incorrect ($1 + 1 = 1$). As in previous studies the infants looked longer at problems with incorrect answers. EEG analysis showed an increased frontal negativity for the incorrect problems that closely resembled that found in adults and is known to arise in the anterior cingulate. This finding suggests that executive attention in infancy arises in the same anatomy as found in adults.

Two-year-olds have sufficient verbal and motor skills that have developed to allow for laboratory tests of executive attention that more closely resemble adult assessments. A spatial conflict task using a touch-sensitive screen for responding has been used to examine conflict resolution with children as young as 2 years of age. The spatial conflict task developed by Gerardi-Caulton (2000) places an object's identity and spatial location in conflict. At 24 months, children are generally unable to resolve this conflict and show high levels of incorrect responding. By 30 months children show much higher levels of correct responding but still show delays in reaction time on incongruent trials similar to what is found in adults. Children with better conflict resolution in the spatial-conflict task had higher levels of anticipatory looking and also higher parent-ratings of effortful control (Rothbart, Ellis, Rueda, & Posner, 2003). These results show the methodologically distinct measures of conflict resolution do reflect a common process that can be observed by parents in daily life.

The Child Attention Network Test (ANT-C) is a modified version of the adult ANT for use with children as young as 4 years of age. Using the ANT-C we (Rueda, Fan, et al., 2004) examined executive attention in children between 6 and 10 years of age and compared their performance with adults. Results suggest that executive attention continues to develop throughout childhood but may stabilize at near-adult levels of performance by about eight years of age.

There is considerable evidence that the executive attention network is of great importance in the acquisition of school subjects such as literacy (McCandliss, Beck, Sandak, & Perfetti, 2003), numeracy and in a wide variety of other subjects (Posner & Rothbart, 2007).

The impact of individual differences in executive attention can be seen in different areas of social development. We have proposed that individual differences in effortful control reflect differences in the functioning of the executive attention network (Posner & Rothbart, 1998; Rothbart, Derryberry, & Posner, 1994). Consistent with this hypothesis, we have found evidence that effortful control is related to executive attention measures throughout childhood (Gerardi-Caulton, 2000; Rothbart et al., 2003). Effortful control, in turn, has been related to a broad range of outcomes relevant to social development including empathy, the regulation of negative affect, conscience development, and theory of mind (Rothbart & Bates, 2006).

Emotion, thought, and behavior form a cluster of temporally associated processes in specific situations as experienced by the child. Single and repeated life experiences will thus shape connections between elicited emotion, conceptual understanding of events, and use of coping strategies to deal with these events. Several theorists have made contributions to this approach (e.g., Epstein (1998) and Mischel and Ayduk (2004)), but the overall framework is in keeping with the idea of Hebbian learning through network activation. Mischel and his colleagues have recently developed a cognitive affective personality (CAP) theory, making use of Cognitive Affective Units (CAUs) seen to operate within a connectionist network (Mischel & Ayduk, 2004). In their model, CAUs are variables encoding the features of situations, which include environmental effects as well as self-initiated thoughts.

4. Genes and experience build networks

As more is known about the developmental progression of executive attention as discussed above, there is an increased possibility of accounting for both the general development of the network and individual differences by examining how genes and experience interact to shape the executive attention network. Some progress made in that direction is discussed below.

To determine genes that might be related to building an attentional network we used the Attention Network Test (ANT) to examine individual differences in the efficiency of executive attention. We first used the ANT to assess attention in monozygotic and dizygotic same-sex twins (Fan, Wu, Fossella, & Posner, 2001). We found strong heritability of the executive network. These data supported a search for genes in executive attention.

We then used the association of the executive network with the neuromodulator dopamine as a way of searching for candidate genes that might relate to the efficiency of the network (Fossella et al., 2002). To do this, 200 persons performed the ANT and were genotyped to examine frequent polymorphisms in genes related to dopamine. We found significant association of two genes, the *dopamine D4 receptor* (DRD4) gene and *monoamine oxidase a* (MAOA) gene, with executive attention. We then conducted a neuroimaging experiment in which persons with different alleles of these two genes were compared while they performed the ANT (Fan, Fossella, Sommer, & Posner, 2003). Groups with different alleles of these genes showed differences in the ability to resolve conflict as measured by the ANT and also produced significantly different activations in the anterior cingulate, a major node of the executive attention network.

Recent studies have extended these observations. In two different studies employing conflict related tasks other than the ANT, alleles of the *catechol-o-methyl transferase* (COMT) gene were related to the ability to resolve conflict (Blasi et al., 2005; Diamond, Briand, Fossella, & Gehlbach, 2004). A study using the child ANT showed a significant relation between the dopamine transporter (DAT1) and executive attention as measured by the ANT (Rueda, Rothbart, McCandliss, Saccamanno, & Posner, 2005). In addition, research has suggested that genes related to serotonin transmission also influence executive attention (Canli et al., 2005; Reuter, Ott, Vaidl, & Henning, in press).

The relation of genetic factors to the functioning of the executive attention system does not mean that the system cannot be influenced by experience. Several training-oriented programs have been successful in improving attention in patients suffering from different pathologies. For example, the use of Attention Process Training (APT) has led to specific improvements in executive attention in patients with specific brain injury (Sohlberg, McLaughlin, Pavese, Heidrich, & Posner, 2000) as well as in children with Attention Deficit Hyperactivity Disorder (ADHD) (Kerns, Esso, & Thompson, 1999). Work with ADHD children has also shown that working memory training can improve attention (Klingberg, Forssberg, & Westerberg, 2002; Olesen, Westerberg, & Klingberg, 2004). With normal adults, training with video-games produced better performance on a range of visual attention tasks (Green & Bavelier, 2003).

To examine the role of experience on the executive attention network we have developed and tested a five-day training intervention that uses computerized exercises. We tested the effect of training during the period of major development of executive attention, which takes place between 4 and 7 years of age according to our previous results (Rueda, Fan, et al., 2004). We hoped to observe an improvement in conflict resolution as measured by the ANT in trained children, along with changes in the underlying network and generalization to other aspects of cognition. EEG data showed clear evidence of improvement in network efficiency in resolving conflict following training (Rueda et al., 2005). The N2 component of the scalp recorded ERP has been shown to arise in the anterior cingulate and is related to the resolution of conflict (Rueda, Posner, et al., 2004; van Veen & Carter, 2002). We found N2 differences between congruent and incongruent trials of the ANT in trained six-year-olds, that resembled differences found in adults. In the four-year-olds training seemed to influence more anterior electrodes related to emotional control areas of the cingulate (Bush et al., 2000). These data suggest that training altered the network for the resolution of conflict in the direction of being more like what is found in adults.

We also found a significantly greater improvement in intelligence in the trained group compared to the control

children. This finding suggested that training effects had generalized to a measure of cognitive processing that is far removed from the training exercises. We did not observe changes in temperament over the course of the training, but this was expected, due to the short time elapsing between assessment sessions.

Not all children need or benefit from attention training. This may be why variability is so high in children's performance. In some of our studies, children with the most initial difficulty in resolving conflict showed the greatest overall improvement due to training. Our research has also suggested a genetic marker of initial differences in attention among the children. We were able to genotype most of the 6-year-old children participating in our training study. Children were divided into two groups according to their particular form of a genetic polymorphism in the 3′ untranslated region of the *dopamine transporter* (DAT1); those carrying the pure long form and those carrying the mixed short/long form of the gene. Since our sample was small, we combined 6-year-olds who had attention training with those in the control condition. Although there were only seven children in the pure long allele group and eight in the mixed long/short group, we found a significantly greater efficiency in conflict scores for the pure long allele group.

Several features of our data supported the relation between the DAT1 polymorphism and individual differences in the efficiency of executive attention. Children in the two groups differed in their conflict scores on the ANT as well as in the effortful control scores obtained from the Children's Behavior Questionnaire (Rothbart, Ahadi, Hershey, & Fisher, 2001). In particular, the short/long mixed group showed higher conflict scores and lower effortful control than those in the pure long group. The two groups also differed in their EEG data. In the first session, children with the pure long allele showed the effect of flankers in the expected direction (larger N2 for incongruent trials), whereas children in the mixed alleles group did not show this effect. The larger N2 for incongruent trials was also found for trained children of 6 years of age and adults. Thus the presence of the pure long allele is associated with more mature executive attention. The DAT1 gene has also been associated with attention deficit hyperactivity disorder (ADHD). However, the exact relation between executive attention efficiency in normals and the presence of attention deficits in ADHD is not clear (Swanson et al., 2000).

Our findings are preliminary, because of the small number of children involved. We are currently examining a larger cohort of children in a longitudinal study from 7 months to 4 years of age. We hope to replicate our current results and explore other genes that might influence the development of attentional networks. We also hope to explore the origin in infancy of the executive attention network that we have measured in childhood.

Given the wide range of individual differences in the efficiency of attention, it is expected that attention training could be especially beneficial for those children with poorer initial efficiency. These could be children with pathologies that involve attentional networks, children with genetic backgrounds associated with poorer attentional performance, or children raised in different degrees of deprivation.

Genes do not directly produce attention. What they do is code for different proteins that influence the efficiency with which modulators such as dopamine are produced and/or bind to their receptors. These modulators are in turn related to individual difference in the efficiency of the attention networks. There is a great deal in common among humans in the anatomy of high level networks, and this must have a basis within the human genome. The same genes that are related to individual differences in attention are also likely to be important in the development of the attentional networks that are common to all humans. Some of these networks are also common to non-human animals. By examining these networks in animals it should be possible to understand the role of genes in shaping networks.

Can animals perform the same tasks we have developed for humans? The answer is clearly yes. Monkeys have been trained to shift attention to cues and to carry out conflict tasks like those in the ANT. More recently rodents have also been trained in attention shifting tasks (Beane & Marrocco, 2004). These tasks make it possible to examine the role that genes play in carrying out the same attentional operations as have been studied in humans. It has also been reported that areas of the frontal midline corresponding to the anterior cingulate are activated in the mouse during trace but not delayed conditioning (Han, O'Tuathaigh, & Koch, 2004). Since trace and delayed conditioning are both very simple tasks and the two are quite similar they could be used to assay operation of rodent brain areas that may be related to executive attention in humans.

An important need in this effort is the development of methods to manipulate relevant genes in specific anatomical locations that are important nodes of a particular network. Usually genes are expressed at multiple locations, so that changes (e.g. knock out studies) are not specific to one brain area. However, using subtractive genomics, a method currently being developed (Dumas et al., 2005), it should become possible to determine the specific operations performed by genes at particular places in different attentional networks. We believe that this kind of genetic analysis of network development will create a productive link between genes and both normal and pathological psychological function.

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