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Control Networks and Neuromodulators of Early Development¹

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Abstract

In adults most cognitive and emotional self-regulation is carried out by a network of brain regions, including the anterior cingulate, insula and areas of the basal ganglia, related to executive attention. We propose that during infancy control systems depend primarily upon a brain network involved in orienting to sensory events that includes areas of the parietal lobe and frontal eye fields. Studies of human adults and alert monkeys show that the brain network involved in orienting to sensory events is moderated primarily by the nicotinic cholinergic system arising in the nucleus basalis. The executive attention network is primarily moderated by dopaminergic input from the ventral tegmental area. A change from cholinergic to dopaminergic modulation would be a consequence of this switch of control networks and may be important in understanding early development. We trace the attentional, emotional and behavioral changes in early development related to this developmental change in regulative networks and their modulators.

Observations of parents and multiple experimental studies have revealed large behavioral changes in attention and self-regulation between infants, older children and adults (Posner & Rothbart, 2007; Rothbart, 2011). During infancy, regulation is often a function of the intervention of the caregiver. However, the infant does exhibit approach and withdrawal tendencies that provide a basis for self-regulation and, over the early years of life, children come to regulate their own emotions and behaviors more completely. This change in behavior is readily observed by all. However, the dramatic changes in brain function that lie behind the behavioral changes are only now becoming clear, based on studies of behavior and functional imaging.

In this paper, we propose that a brain network including frontal and parietal areas related to attentional orienting provides the chief means of self-regulation in infancy, but that by 3 to 4 years the executive attention system, including the anterior cingulate and basal ganglia, increasingly controls cognition and emotion through its connections to remote brain areas. In older children and adults, executive attention can be measured by behavior in cognitive tasks involving the resolution of conflict or by the higher-order factor of Effortful Control (EC) assessed through parent or self-report temperament questionnaires (Posner & Rothbart, 2007; Rothbart & Rueda, 2005).

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This paper is divided into three major sections: An introductory review, an empirical section in which we provide a new analysis of longitudinal data and an overall discussion. The introductory review begins with neural networks related to attention that serve to provide control in adult studies. The networks have different neuromodulators, as found in anatomic and pharmacological studies. The networks show an interesting time course, with long connections developing over the first years of life. There is also development of increasing independence between the orienting and executive networks. We consider genetic polymorphisms related to individual differences in efficiency of these networks in adults. In the second section we present a longitudinal study of how these various levels contribute to behavioral control in infancy and childhood. In the final discussion section, we examine how our results inform our understanding of attention and self-regulation during early development.

Brain Networks of Cognitive and Emotional Regulation

Studies of adults have revealed three brain networks involved in attention. The alerting network is related to the functions of obtaining and maintaining the alert state. The orienting network is involved in the selection of sensory events. The executive network is involved in resolving conflict among response tendencies (Posner & Petersen, 1990; Posner & Fan, 2008). These networks are distinct in that they serve different functions, have different neural anatomies, and involve different neuromodulators (Posner & Fan, 2008; Rueda, Posner, & Rothbart, 2011).

The alerting network is modulated by the brain's norepinephrine system arising in the midbrain and making contact with frontal and parietal areas. The orienting network involves areas of the inferior and superior parietal lobe and the frontal eye fields. Cholinergic systems arising in the basal forebrain play a critical role in modulating the orienting network. Lesions of the basal forebrain in monkeys interfere with orienting of attention (Voytko, Olton, Richardson, Gorman, Tobin et al., 1994). It appears, however, that the site of this effect is not in the basal forebrain, but instead involves the superior parietal lobe. Davidson & Marrocco (2000) made injections of scopolamine, a cholinergic antagonist, directly into the lateral intra-parietal area of monkeys and found that these injections blocked orienting. The lateral intra-parietal area of the monkey corresponds to the human superior parietal lobe and contains cells influenced by cues about spatial location. In human imaging studies the superior parietal lobe has been shown to become active when people are instructed to voluntarily switch attention to a location (Corbetta & Shulman, 2002).

The orienting network also involves two other major cortical areas: the temporal parietal junction and the frontal eye fields. When systemic, rather than localized injections of scopolamine were used, they also influenced orienting, but had a smaller effect than local injections into the parietal area. Cholinergic drugs do not affect the ability of a warning signal to improve alerting. Pharmacological studies (Beane & Marrocco, 2004) show that noradrenergic antagonists block the warning effect, but do not influence orienting. Thus, there appears to be a double dissociation, with norepinephrine (NE) involved mainly in the alerting network, and acetylcholine (ACh) relating to the orienting network. These observations in the monkey have been confirmed by similar studies in the rat (Everitt & Robbins, 1997). It is of special significance in the rat studies involving comparisons of cholinergic and dopaminergic mechanisms have shown that only cholinergic mechanisms influence the orienting response (Everitt & Robbins, 1997; Stewart, Burke & Marrocco, 2001). Hasselmo and Sarter (2011) review some of mechanisms by which cholinergic modulation of cognitive processes occurs and argue "that changes in cholinergic modulation on a timescale of seconds is triggered by sensory input cues and serves to facilitate cue detection and attentional performance" (p. 52).

The executive network involves the anterior cingulate gyrus, anterior insula, basal ganglia and parts of the prefrontal cortex (Posner & Fan, 2008). These areas are rich in dopamine and their function is modulated by dopamine from the ventral tegmental areas (da Silva Alves, Schmitz, Figue, Abeling, Hasler, et al., 2011; Williams & Goldman-Rakic, 1998). Attention tasks requiring the resolution of conflict, such as the Attention Network Test (ANT) have been shown to activate this area (Fan et al., 2003a), and individual differences in the extent of this activation have been shown to involve dopamine related genes (Fan et al., 2003b).

Imaging Functional Connectivity During Early Development

A major breakthrough in the neuroimaging of development arose in studies which examine the connectivity of various brain networks during rest. Functional connectivity is measured in terms of correlations in time dynamics of the BOLD (blood-oxygen-level dependent) fMRI signal measured from two distinct brain areas. These correlations suggest that the two areas are working together and thus in communication. The study of functional connectivity at rest allows comparison across ages without the need to adapt special tasks to infants and children at different ages. Recent imaging studies have examined the brain activity of infants and young children at rest using fMRI (Fair et al., 2009, 2011; Fransson, Skiold, Horsch, Nordell, Blennow, et al., 2007; Gao, Zhu, Giovanello, Smith, Shen et al., 2009). The Fair and colleagues' (2009, 2011) work involves children of 9 years of age, adolescents and teenagers while the Gao and colleagues' (2009) work includes newborns and infants up to a year.

These studies have examined two attention networks related to control systems (Fair et al., 2011). The fronto-parietal network was proposed to be important for rapidly adaptive control and to work on a shorter timescale. This network involves the same brain areas discussed above in connection with the orienting network. The cingulo-opercular network was thought to be important for more stable set-maintenance, operating on a longer timescale. This network shares similar brain areas to those discussed above as the executive network. During early development the two networks are closely integrated, while in adulthood the cingulo-opercular network becomes quite separate from the fronto-parietal network.

These resting MRI studies have also shown sparse connectivity between brain structures during infancy and a strong increase in connectivity at 2 years (Gao et al., 2009) and later (Fair et al., 2009; 2011). In neonates, the parietal areas, prominent in the orienting attention network, showed strong connectivity to lateral and medial frontal areas, areas that would later be connected to executive attention. By age 2, the anterior cingulate, which has been implicated in executive attention, showed stronger connections to frontal areas and to lateral parietal areas.

The fMRI connectivity findings suggest that control structures related to executive attention, including structures on the medial aspect of the frontal (anterior cingulate) and parietal (operculum) lobes, are present in infancy but do not exercise their full control over other networks until later. In accordance with this view, we have reported that error detection activates the anterior cingulate area at 7 months (Berger, Tzur & Posner, 2006), although the ability of the infant to take action based on errors seems not to be present until 3–4 years of age (Jones, Rothbart & Posner, 2003).

The remarkable similarity of the brain networks arising from studies of attention (e.g., Posner & Fan, 2008) and from developmental studies of resting fMRI connectivity (e.g., Fair et al., 2009; 2011) require a more careful examination of the behavioral landmarks related to the development of attention in infants and young children. The hope is to use

these behavioral landmarks to better understand the consequences of the changes in connectivity found in development.

Genes and Early Regulation

We have argued for a transition between two attentional control networks during the early years of a child's development (Rothbart, Sheese, Rueda & Posner, 2011). According to this view, during infancy, control is principally exercised by the orienting network but by 3 to 4 years of age this control shifts primarily to the executive network. Given that the orienting network is primarily modulated by cholinergic system and the executive by the dopaminergic system, the change in dominant control networks also means a change in dominant neuromodulators. Neuromodulatory systems are associated with different transporters and receptors. For both cholinergic and dopaminergic systems, there are substantial individual differences in genes related to some of these mechanisms. Below we review how genes and parenting interact to determine the efficiency of the executive control network.

How is the development of the executive control system related to research on genes and environment? Research by Bernier, Carlson & Whipple (2010) shows that maternal sensitivity, mindfulness and autonomy-support at 15 months are related to children's later executive functions at 18 to 20 months, suggesting a role for social environment in the development of self-regulatory capacities.

The connection between executive attention and dopamine modulation was mentioned above. Consistent with this link, research with young children has shown that parental quality interacts with the 7-repeat allele of the dopamine D4 receptor gene (DRD4) to influence temperament dimensions related to self-regulation (Bakersman-Krannenberg & van Ijzendoorn, 2006; Sheese, Voelker, Rothbart, & Posner, 2007). For example, we found that parenting made a strong difference in sensation seeking for children with the 7-repeat allele. Those with poorer quality parenting were more impulsive and sensation seeking than those with high quality parenting. Parenting quality made no difference for children without the 7-repeat allele.

At 3 to 4 years we measured a higher order factor in parental reports called Effortful Control. Effortful Control has been related both to executive attention and to a number of important landmarks in early child development (Rothbart, 2011; Rothbart & Rueda, 2005). At 4 years of age the DRD4 gene in interaction with parenting was related to children's Effortful Control. Higher quality parenting was related to greater effortful control for children with the 7-repeat allele, but not for those without the 7-repeat allele of the DRD4 gene (Sheese, Voelker, Rothbart & Posner, submitted). Another study has found that only those children with the 7-repeat of the DRD4 showed the influence of a parent training intervention (Bakersman-Krannenberg, van Ijzendoorn, Pijlman, Mesman, & Juffer, 2008), suggesting that at least some of the genetic effects are directly influenced by parenting practices.

The COMT gene, is involved in the degradation of dopamine at the synapse, particularly in frontal areas. In our research the more frequently studied val met SNIP was compared with a haplotype involving three polymorphisms in the gene. This haplotype had been reported to be more related to perceived pain than the val met SNIP (Diatchenko et al, 2005). Both haplotype and genotype interacted with parenting to influence attention as measured by anticipatory looks at 18–20 months (Voelker, Sheese, Rothbart, & Posner, 2009). Those children with high quality parenting and one form of the COMT gene showed more anticipations than any other group. The genotype and the haplotype showed similar gene by

environment interactions but the haplotype effects were larger. Later in childhood and in adulthood COMT has shown a strong influence on aspects of executive attention (Blassi et al., 2005; Diamond, Briand, Fossella & Gelbach, 2004), suggesting that aspects of parenting observed at ages 1–2 years are contributing to the developing child's attention networks and behavior. Although the findings indicate that the effect of parenting is dependent on individual differences in genetic variation, they also show that parents can play a role in shaping the child's behavior.

Both DRD4 and COMT are primarily related to dopamine function and both show strong gene by environment interactions during development. We have also examined the CHRNA4 gene. This gene is more related to cholinergic modulation but has an indirect influence on dopamine as well. At 18–20 months CHRNA4 was significantly related to Effortful Control (Sheese, Voelker, Posner, & Rothbart, 2009). In adults it relates more clearly to performance in tasks involving orienting (Parasuraman & Greenwood, 2004). These findings may be related to the integration of the orienting and executive network in early development and their separation in adult studies.

The imaging, behavioral and genetic data reviewed in this paper provides at least an indirect argument for a change in control systems from early infancy to later childhood. Changes in behavior are likely to relate to changes in the connectivity of the neurosystems modulated. The large scale connectivity between the executive attention network and areas of the frontal, parietal cortex and limbic system may depend upon the maturation of the large projection cells unique to the cingulate and anterior insula. The greater connectivity found between the orienting and executive network in infancy may allow the orienting network to dominate because of the strong influence of external input on its operation. The later development of cingulate connectivity may be driven by both genetically controlled maturation and environmental influences such as the presentation of novel objects.

Adult and animal data show that the modulators involved in the early developing orienting system and later developing executive system differ. However, evidence summarized by Benes (2000) on the development of the cholinergic and dopaminergic modulatory systems suggests that both are likely to start their development before birth and to develop gradually into adulthood. A more fine grain analysis relating modulators to their function may provide a more complete picture. Rothbart (1989) has pointed out that in rats cholinergic inhibitory mechanisms develop at about 15–20 days, but dopaminergic systems involved in motor inhibition develop later in development. In this paper we argue for a similar developmental progression in humans, such that early controls on behavior are a function of cholinergic systems but later, dopamine systems also become involved. This time course provides possible support for the network development discussed in this paper on the basis of human imaging and behavioral studies. To determine if the dominant modulator for control of emotion and behavior changes from infancy to childhood, it would be useful to develop animal models that would allow for demonstrations of this change, for example, by using drugs to temporarily reduce each network at different ages during early development. This kind of study could further illuminate the links between development, brain networks and neuro-modulators.

Behavior

Experimental studies of behavior of infants and young children have already begun to reveal some important properties of the development of attentional control networks on distress and soothing. In one study (Harman, Rothbart & Posner, 1997), 3 and 6 month old infants became distressed by presentation of sound and light stimuli. Many of the infants exhibited

crying and facial distress following offset of the sounds. They were temporarily soothed by the presentation of novel toy stimuli, and during orienting to the stimuli, their distress was greatly reduced. Subsequent to each toy presentation, however, distress returned to the same level present before the novel stimulus. We hypothesized that the amygdala might serve as a “distress keeper”, but that the expression of distress was controlled by the orienting of the infant. Recent adult fMRI data has shown more directly that distraction leads to a strong reduction in activity within the amygdala (Kanske, Heissler, Schonfelder, Bongers & Wessa, 2011). The control of distress by orienting is thus present from 3 months to adulthood. However, experimental studies in which adults are asked to use strategies to reduce distress to pictorial stimuli show increased functional connectivity between the anterior cingulate (executive attention network) and the amygdala under this instruction (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). Thus, in adults, reducing the amygdala response from an instruction involves both brain areas involved in orienting and those related to the executive network.

Previous Reports and The Current Study

We now describe a study investigating behavioral links to orienting and Effortful Control, and the prediction of later control from early orienting. In our work to date we have examined behavioral changes related to attentional control between infancy and early childhood. Children were observed longitudinally beginning at 6 to 7 months of age. In previous reports we have discussed our behavioral findings in infancy (Sheese, Rothbart, Posner, White, & Fraundorf, 2008). We also examined individual differences in infant and child temperament in relation to genetic variation among the children in our study (Sheese et al., 2007; 2009; Voelker et al., 2009). Finally, we reviewed findings linking temperament to behavior and emotional control (Rothbart, et al., 2011). At the time of our previous empirical papers we had not yet run the children at age 3 to 4 when they were tested on the Attention Network Test. In this paper we report the data for the first time linking time 1 results (6 to 7 months) with time 3 performance on the Attention Network Test (ANT) at 3 to 4 years of age.

In this paper, we focus on longitudinal links between early behavioral markers of self-regulation and later assessments of attention network efficiency. We began our longitudinal study with the idea that during infancy we could use the frequency of anticipatory looking to a sequence of fixed visual locations as a measure of the executive network, while reactive looks once the stimulus was presented would be related to the orienting network (Sheese et al., 2008). By examining the correlations between looking at 6–7 months of age and performance on the orienting and executive network scores of the Attention Network Test (ANT) at 3 to 4 years, we could test that assumption. However, we found that the frequency of both reactive and anticipatory looks was more closely related to the orienting network as measured at 3 to 4 years than to the executive network (Rothbart et al., 2011). In the current paper we ask if the percentage of correct anticipations might serve as a better measure of executive attention. When the infant correctly anticipates a location, we can be more certain that their response represents control rather than impulsivity.

We examined the following hypotheses: First, is there evidence for the use of orienting as a control system in infancy? Second, does the executive system begin to exercise control during early childhood? Finally, in light of our previous findings of control of emotional expression by orienting, we hypothesized that there would be earlier evidence of control of emotion than of cognition.

Method

In a longitudinal study, we have analyzed behavioral changes through questionnaire, observational and experimental techniques at ages 6 to 7 months (Time 1), 18 to 20 months (Time 2), and 3 to 4 years (Time 3). We provide a brief overview of the participants and assessments from three phases of our longitudinal project here. More detailed information about methods can be found in previous publications (Sheese et al., 2007; Sheese et al., 2008; Voelker et al., 2009).

Participants

Table 1 presents a summary of the ages, number of participants and assessments from Times 1, 2, and 3.

Fifty families were recruited at Time 1 through birth announcements or fliers distributed to day care centers and parenting programs in Eugene, Oregon and surrounding communities. These flyers informed families of the longitudinal nature of the study and parents were told that our focus would be on the development of attention, emotion and behavior. Families were predominantly white and non-Hispanic. Twenty of the infants were female; 30 were male.

Of the original 50 Time 1 families, 37 families returned at Time 2. Additional families were recruited through birth announcements or fliers to supplement the sample to include 70 total families (30 females).

At Time 3, 76 total families participated. Of these, 68 were families returning from at least one of the earlier assessments.

Measures/Procedure

Anticipatory looking procedures—The presentation of visual stimuli in a repeating pattern of locations was used to examine reactive and anticipatory looking at Times 1, 2 and 3. In brief, the child was shown a repeating sequence of stimuli at three positions on a screen. Each trial began with the child looking at a central fixation stimulus. After one second a stimulus was presented at one of the three positions. After the infant oriented to that event, a new position was used for the target, again with a 1-second delay, and this was repeated for the third location. If the child moved to a target before it was presented, it was called an anticipation; if the child oriented only after the stimulus was presented, it was seen as a reactive move. The outcome we focus on here is the percentage of correct anticipations at each age.

The Time 1 procedure is described in detail in Sheese and colleagues (2008). Details of the Time 2 and Time 3 Anticipatory Looking Procedure are reported in Voelker and colleagues (2009). The procedure used at Time 3 was nearly identical to the procedure used at Time 1, but replaced geometric figures with cartoon animals.

Behavioral responses to novel and threatening stimuli—The presentation of novel toys at Time 1 and animal masks at Times 1 and 2 were used to assess aspects of reactivity and regulation. In the toy segment, a series of toys was individually presented on a high-chair table and the child was videotaped while interacting with each toy. The child's response was coded for a variety of behaviors including fixating on the toy without touching the toy and time spent looking away from the toy. In the mask segment, a series of somewhat frightening masks was presented one at a time in front of the child. The child's coded reactions included looking away and intensity of distress.

Additional details of the Time 1 Toy and Mask Presentations are reported in Sheese and colleagues (2008). Measures examined here from the Toy measure at Time 1 include average time of visually fixating on the toy without moving toward the toy - a measure of caution -, and looking away from the toy. For the animal masks, we examined average time of distress face and time of looking away at Time 1. At Time 2, we examined the peak level of distress in response to the masks.

Temperament questionnaires—The Infant Behavior Questionnaire Revised (IBQ-R; Gartstein & Rothbart, 2003) and the Early Childhood Behavior Questionnaire (ECBQ; Putnam, Gartstein & Rothbart, 2006) were used to examine parent-reports of child temperament at Time 1 and Time 2, respectively. Detailed descriptions of the IBQ and ECBQ are reported in Sheese et al. (2008) and Rothbart (2011). The Children's Behavior Questionnaire (CBQ; Rothbart, Ahadi, Hershey & Fisher, 2001) was used to examine parent-reported temperament at Time 3. In this study we used factor scores for Orienting, Surgency/Positive Affect and Negative Affect at Time 1, and at both Time 2 and Time 3 we used factor scores for Effortful Control, Surgency/Positive Affect and Negative Affect.

Planning and error detection—The Nesting Cup procedure developed by DeLoache, Sugarman, & Brown (1985) was used to examine correct moves, error detection and correction at Time 2 as an assay of executive attention. In this procedure children are videotaped performing three successively more difficult cup stacking trials. Successful completion of these later trials required the children to recognize which cup structures should be left intact and which (if any) should be disassembled. Videos were coded for each move (cup combination) the child made, as well as error correction strategies and attempts at forcing together non-fitting cups. We used measures of correct moves and error detection as surrogates for executive attention at Time 2.

Attention networks—The Child Attention Network Test (ANT; Rueda, Fan, McCandliss, Halparin, Gruber et al., 2004) was used to assess the efficiency of executive, orienting and alerting attention at Time 3. The Child ANT presents five fish in a horizontal row that appear above or below a fixation point. Children press a key to indicate the direction of pointing of a central fish (left or right) while ignoring congruent or incongruent (pointing in the same or opposite direction) flanker fish. Completion of the task allowed calculation of three scores related to the efficiency of attentional networks. The alerting score involves subtracting the central cue RT from the no cue RT. The orienting score involves subtracting RTs from the correct spatial cue at the target location from RTs to a central cue. The executive attention score is obtained by subtracting congruent flanker RT from incongruent flanker RT indexing efficiency in resolving conflict. Each child participated in extensive practice and then most completed 2 blocks of 72 trials each.

Results and Discussion

Table 2 presents the means and standard deviations for our measures and the correlations between them for each individual time. Table 3 provides correlations between the behavioral tests during infancy and at Time 3 when the ANT was used.

The use of percentage of correct anticipations as a measure did not change our previous conclusion that performance on the visual sequence task was not closely related to executive attention as measured by the ANT. There was no evidence that the percent correct anticipations at Time 1 and executive network efficiency as measured by the ANT at Time 3 were significantly associated ($r = .16$, *n.s.*) The only significant correlation between Time 1 scores and the executive score of the ANT was for frequency of look aways from the mask ($r = .54$; $p < .05$).

Evidence congruent with the importance of orienting as a control system at Time 1 comes from parent reports of their child's temperament. At Time 1 IBQ Orienting showing a significant relation to IBQ Surgency/Positive Affect ($r = .46, p < .01$) and to IBQ Negative Affect ($r = -.30, p < .05$) (see Table 2). In addition, the orienting score of the ANT at Time 3 was related to behavioral measures of orienting. Looking away from toys at Time 1 was correlated with the ANT Orienting scores at Time 3 ($r = .90, p < .01$). Looking away from masks at Time 1 was also related to ANT Orienting score at Time 3 ($r = .92, p < .05$). Finally, the percentage of correct anticipations at Time 1 was correlated with ANT Orienting scores at Time 3 but this correlation was not significant ($r = -.43, n.s.$).

If correct anticipatory looks during infancy mainly reflect control by the orienting network, we must reinterpret two earlier findings that we previously reported (Sheese et al., 2008). This conclusion remains tentative due to the small number of subjects at time 1 who successfully completed orienting trials at time 3. However, there is not much evidence that time 1 relates to the executive network scores at time 3. In our previous work, we found that a cautious reach toward toys (e.g. long fixation before reaching) was related to the frequency of anticipatory looks. Rather than seeing this as early executive control, we now see it as more likely due to the effect of orienting on the response to the novel toy. Second, we found that look aways from the masks were also related to correct anticipatory looks. This provides evidence on the role of orienting as a control system over emotion.

At Time 2, parents begin to report control by their children of their own behavior in the Effortful Control measure derived from questionnaires. We found Effortful Control at Time 2 to be significantly related to Effortful Control at Time 3 ($r = .38, p < .01$). Moreover, Time 2 Effortful Control is negatively related to Time 3 Surgency/Positive Affect ($r = -.29, p < .05$) but unrelated to Time 3 Negative Affect ($r = .04, n.s.$). A negative relation between effortful control and negative affect has been found at later ages, including in adults (Rothbart & Rueda, 2005). Thus the switch to the executive network may not have been complete at Time 3 testing.

In general these new data confirm our previous findings relating anticipatory looking to the orienting network and support our first hypothesis that during infancy orienting serves as the primary control system while later in childhood effortful control becomes dominant.

We also hypothesized that control during infancy would be mainly in relation to emotion and only later related to cognition. In fact most of the significant correlations at Time 1 are with parent reported emotion or emotional regulation in the laboratory like look aways from frightening masks. The one exception was the cautious reach toward novel toys which could either reflect cognitive control or might be related to the control of fear. At Time 2 and 3 there is more evidence that Effortful Control is related to aspects of problem solving found in the nesting cup task. At Times 2 Effortful Control is significantly related to nesting cup correct moves ($r = .37, p < .01$) and to error detection ($r = .35, p < .01$). Time 3 Effortful Control is also significantly related to error detection in the nesting cup task ($r = .28, p < .05$). In later childhood and adulthood there is clear evidence that cognitive tasks such as IQ (Rueda, Posner, & Rothbart, 2011) and school grades (Checa, Rodríguez-Bailón, & Rueda, 2008) are related to Effortful Control. Since most of our measures in infancy are related to emotion, the data in support of hypothesis 2 remains ambiguous, but worthy of further study.

Conclusion

Integrating Levels

The ability to specify the neural networks involved in various functions of attention provides a means of integrating levels of analysis from genes to behavior. Since each network

involves somewhat different neural modulators, it is possible to examine the genes that produce the transporters and receptors involved in that modulation. In work with adults, the integration has also involved behavior because, for example, each network has been related to performance on the Attention Network Test. In our longitudinal study we have sought to discover connections between early infant behavior and underlying networks. We discovered strong evidence for control networks present as early as 6–7 months using looking behavior to a sequence of spatial locations. The infant's ability to anticipate the location of a stimulus is related both to controlled reaching and to regulation of emotion. Parent reported orienting provides evidence of control over both positive and negative emotion. These findings show the importance of orienting as a control system in early development.

Since the orienting network is modulated in animals and humans by the cholinergic system, these findings may suggest links between early infant behavior and modulatory functions of the cholinergic system. Genes regulating nicotinic and muscarinic cholinergic function have been shown to influence orienting behavior in adults (Greenwood, Lin, Sundararajan, Fryxell, & Parasuraman, 2009). Although dopaminergic modulation of the ACC is presumably present during infancy its effectiveness in the control of behavior must await the development of long connections between the ACC and other brain systems. This developing connectivity is accompanied by increasing independence between the executive and orienting brain networks and greater control of behavior by systems involving dopaminergic modulation. Future studies may be able to tie these underlying modulators more directly to behavior through the use of animal models (Haselmo & Sarter, 2011).

Sequencing Development

If dominant control changes from the orienting to the executive system during the period studied, how might this change take place? At three months, infants can be soothed by orienting to novel stimuli (Harman, et al., 1997). The novel stimulus blocks the expression of distress but the distress is likely held in the amygdala and the child's expression of distress returns to the same level when orienting ends. Parents use orienting to novelty in this way to soothe their infants starting at about 3 months. This possibility is supported by a study of adults (Shulman, Astafiev, Franke, Pope, Snyder et al., 2009) in which the presentation of a novel object recruits the executive network (cingulo-opercular network in their terms) to supplement the orienting network (ventral parietal frontal network in their terms), thus showing that orienting can be involved in recruiting the executive network. If this mechanism is present in infancy, it could mean that caregivers provide impetus for the development of self-regulation and exercise executive systems through the presentation of novel stimuli, which could be objects or other people. Reading to the child may be another source of this kind of stimulation.

Cultures where observation is the chief activity of the infant may also prepare the executive attention network through infants' orienting to novel stimuli. Individual and cultural differences in these activities may be important in understanding different types of socialization. The cingulate system is already on line at 7-months for the detection of error (Berger, Tzur & Posner, 2007). However, during subsequent years there is strong evidence from gene X environment interactions that experience is important in shaping the development of the networks involved (Sheese et al., 2007; Voelker et al., 2009). Moreover, recent research shows that training can increase the efficiency of white matter connections, even in adulthood (Tang, Lu, Geng, Stein, Yang et al., 2010). So if novelty works similarly in infants as in adults, it will activate the cingulate and help build the connections that have been found in later development (Fair et al., 2009, 2011; Gao et al., 2009).

It may be that the activation of the executive attention system via novel stimuli is also important for the evidence found in our longitudinal study that from Time 2 to Time 3, aspects of cognition are regulated by the executive system. For example, errors in the nesting cups are related to Effortful Control at Time 2 and Time 3. Thus executive control of cognition is beginning by 2 years. It was shown previously that children age 2–3 years showed some development of the ability to resolve conflict (Gerardi-Caulton, 2000) but that slowing following an error developed between 36 and 40 months of age (Jones, Rothbart & Posner, 2003). Thus, although the executive system can detect errors as early as 7 months, the first evidence of control of conflict and error is delayed to at least 18 to 20 months. We believe in this period the orienting system is frequently in control and the executive system is becoming connected in the control of behavior.

Our results provide a possible explanation for the changes that occur in control systems between infancy and later childhood. The development of behavioral methods for measuring control by neural network provides a means of integrating behavior changes with underlying brain networks, their modulators and the genes involved in constructing their components.

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Table 1

Participants and Major Procedures Conducted at Times 1, 2, and 3

Participants	Time 1	Time 2	Time 3
N (total)	50	70	76
N (returning)	--	37	68
Age of child	6–7 months	18–20 months	4 years
Procedures			
Parent-Reported Temperament	IBQ	ECBQ	CBQ
Anticipatory and Reactive Looking	Visual Sequence (Static Images)	Visual Sequence (Video)	Visual Sequence (Static Images)
Attention			ANT
Response to Novel Objects	Toys		
Response to Threatening Objects	Masks	Masks	
Planning and Error Detection		Nesting Cups	

Table 2

Descriptive Statistics and Intercorrelations

<u>Time</u> <u>1</u>	<u>M</u>	<u>SD</u>	<u>1.</u>	<u>2.</u>	<u>3.</u>	<u>4.</u>	<u>5.</u>	<u>6.</u>	<u>7.</u>	<u>8.</u>
1. IBQ - Surgency/PA	4.85	0.60	1.0							
2. IBQ - Negative Affectivity	3.09	0.67	.05	1.0						
3. IBQ - Orienting	4.99	0.56	.46*	.30*	1.0					
4. Toys - Fixation	2.07	3.02	.38*	.01	-.18	1.0				
5. Toys - Look Away	14.08	5.01	.21	.49*	.00	-.20	1.0			
6. Masks - Distress Face	3.75	5.06	.32*	.16	-.18	.27	-.08	1.0		
7. Masks - Look Away	28.64	8.44	.01	.11	-.11	-.20	.10	-.24	1.0	
8. Sequence - % Correct Antic.	0.05	0.05	-.26	-.11	-.16	.21	-.09	.26	-.41*	1.0

<u>Time</u> <u>2</u>	<u>M</u>	<u>SD</u>	<u>9.</u>	<u>10.</u>	<u>11.</u>	<u>12.</u>	<u>13.</u>	<u>14.</u>	<u>15.</u>
9. ECBQ - Surgency/PA	4.32	0.38	1.0						
10. ECBQ - Effortful Control	4.46	0.46	-.04	1.0					
11. ECBQ - Negative Affect	2.62	0.59	.12	-.06	1.0				
12. Masks - Peak Distress	0.80	0.85	.01	.09	.07	1.0			
13. Nesting Cups - Correct Moves	6.02	6.17	-.26	.37*	-.22	-.11	1.0		
14. Nesting Cups - Errors Detected	10.26	10.94	-.21	.35*	-.09	.04	.80	1.0	
15. Sequence - % Correct Antic.	0.09	0.06	-.10	-.08	.10	-.24	-.06	-.05	1.0

Time		M	SD	16.	17.	18.	19.	20.	21.	22.
3										
16.	CBQ - Surgency/PA	4.93	0.67	1.0 0						
17.	CBQ - Effortful Control	4.37	0.88	- .59*	1.0 0					
18.	CBQ - Negative Affect	3.87	0.84	- .28*	.04	1.0 0				
19.	ANT - Executive	125.1 4	81.98	-.07	.26	.15	1.0 0			
20.	ANT - Alerting	219.7 9	245.0 0	.00	-.03	-.04	.16	1.0 0		
21.	ANT - Orienting	181.8 6	180.5 0	.02	.04	.07	-.12	.72 *	1.0 0	
22.	Sequence - % Correct Antic.	0.08	0.05	.10	-.04	.12	.10	-.31	-.06	1.0 0

Table 3

Longitudinal Correlations - Time 1 and Time 3 Behavioral Measures

	Time 3			
	ANT			Vis. Sequence
	<u>Executive</u>	<u>Alerting</u>	<u>Orienting</u>	<u>% Correct Antic.</u>
	-	-	-	-
<u>Time 1</u>				
Toys - Fixation	-.39	.17	-.39	.17
Toys - Look Away	.01	-.38	.90 [*]	-.13
Masks - Distress Face	-.13	.11	-.36	-.36
Masks - Look Away	.54 [*]	.04	.92 [*]	.06
Sequence - % Correct Antic.	.16	.34	-.43	.13
N for each correlation	19	13	10	30

^{*} denotes the number of participants at T1 and T3 with complete data for each assessment. Participants were excluded from T3 ANT correlations if they missed more than 50% of the trials and/or they had negative network scores.