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The influence of *CHRNA4*, *COMT*, and maternal sensitivity on orienting and executive attention in 6-month-old infants

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ABSTRACT

Despite claims concerning biological mechanisms sub-serving infant attention, little experimental work examines its underpinnings. This study examines how candidate polymorphisms from the cholinergic (*CHRNA4* rs1044396) and dopaminergic (*COMT* rs4680) systems, respectively indicative of parietal and prefrontal/anterior cingulate involvement, are related to 6-month-olds' (n = 217) performance during a visual expectation eye-tracking paradigm. As previous studies suggest that both cholinergic and dopaminergic genes may influence susceptibility to the influence of other genetic and environmental factors, we further examined whether these candidate genes interact with one another and/or with early caregiving experience in predicting infants' visual attention. We detected an interaction between *CHRNA4* genotype and observed maternal sensitivity upon infants' orienting to random stimuli and a *CHRNA4-COMT* interaction effect upon infants' orienting to patterned stimuli. Consistent with adult research, we observed a direct effect of *COMT* genotype on anticipatory looking to patterned stimuli. Findings suggest that *CHRNA4* genotype may influence susceptibility to other attention-related factors in infancy. These interactions may account for the inability to establish a link between *CHRNA4* and orienting in infant research to date, despite developmental theorizing suggesting otherwise. Moreover, findings suggest that by 6 months, dopamine, and relatedly, the prefrontal cortex/anterior cingulate, may be important to infant attention.

1. Introduction

Early attention is associated with executive functioning development (Cuevas & Bell, 2013) and the ability to regulate the self and emotions (Rothbart, Sheese, Rueda, & Posner, 2011). These abilities are, in turn, predictors of well-being across the lifespan (e.g., psychopathology, academic performance; Graziano, Reavis, Keane, & Calkins, 2010; Pennington & Ozonoff, 1996).

In adults, the fully developed attention system may be comprised of multiple neural and neuromodulatory networks (Petersen & Posner, 2012; Posner & Petersen, 1990). For example, the orienting attention network is theorized to underlie more reflexive and/or automatic aspects of attention, and to facilitate shifts in attention towards the locations of environmental stimuli. In contrast, the executive attention network may control behavioral responses in the presence of conflicting environmental cues and is theorized to underlie more voluntary and/or endogenously controlled attention (Petersen & Posner, 2012; Posner & Petersen, 1990). Indeed, attentional control, which includes selective attention and self-monitoring, is in itself sometimes considered an aspect of executive functioning (EF), which can influence a variety of EF abilities including cognitive flexibility, goal setting, information processing, and the abilty to complete tasks in a required order (Anderson, 2002). Likewise, as eye movements that occur in anticipation of an outcome require goal-directed control, anticipatory

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looking may be considered reflective of executive attention (Voelker, Sheese, Rothbart, & Posner, 2009). Still, despite its importance, the neural underpinnings of attention, both orienting ("exogenous") and "anticipation" ("endogenous"/"executive attention") in early development remain unclear.

1.1. Development of the human attention system

Infant research suggests gradual progression in attentional processing sub-systems, with exogenously driven attention emerging earlier in development, and more complex aspects coming on-line later. As reviewed by Colombo (2001), some have argued that reactive shifts in gaze to external stimuli occur as early as the neonatal stage, with more complex aspects of attentional orienting becoming apparent at 6 months. Furthermore, research utilizing the visual expectation (VE) paradigm, in which objects appear in a spatial pattern and gaze behavior is observed, tentatively suggest that anticipation, which is frequently considered indicative of "endogenous attention," may be observed in the first few months, but is notably enhanced in later infancy (Reznick, Chawarska, & Betts, 2000; Teubert et al., 2012).

Despite many behavioral studies, the neural underpinnings of these processes in infancy remain unclear. This is in contrast to adult research, in which imaging studies indicate that orienting is tied to the frontal eye fields as well as more posterior cortical regions such as the intra-parietal sulcus and temporo-parietal junction and is modulated by acetylcholine. In contrast, executive attention is more closely tied to later-developing regions and is modulated by dopamine (see Petersen & Posner, 2012 and Posner, Rothbart, Sheese, & Voelker, 2012 for a review, but see Lundwall, Guo, & Dannemiller, 2012 for conflicting results). With regards to executive attention, early theory suggested that it was sub-served by only one network (see Petersen & Posner, 2012), but recent imaging work suggests attentional control is sub-served by both a frontoparietal network, which includes the dorsolateral prefrontal (PFC) cortex, intraparietal sulcus, and inferior parietal lobule, and a cingulo-opercular network, which includes the anterior cingulate (ACC; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008).

Whether these same structures respectively underlie orienting and executive attention in infancy is unclear, in part due to the lack of adult-like differentiation between neural networks early in development (Fair et al., 2009). Indeed, Posner and colleagues (Posner et al., 2012; Rothbart et al., 2011; Sheese, Voelker, Posner, & Rothbart, 2009) have suggested that the orienting network may be the predominant regulatory system from birth until early childhood, with both orienting and seemingly executive-like attention behaviors modulated by cholinergic functioning early in life, and executive behaviors gradually coming under the influence of dopaminergic functioning. Still, despite prolonged ACC and PFC development, other research suggests that the PFC may be involved in attention, even during the first year of life (Richards, Reynolds, & Courage, 2010). For example, in their study of 4.5–7.5 month olds, using source localization techniques, Reynolds and Richards (2005), observed that an electrophysiological marker of attention (i.e., the Event Related Potential component, Nc, which was greatest to novel and infrequent, rather than familiar and infrequent or familiar and frequent, stimuli, had its neural underpinnings in the medial/inferior frontal and anterior cingulate cortices. Yet, the results from an additional source electrophysiological source localization study by Xie and Richards (2017) may suggest that the posterior occipital, ventral temporal, lateral inferior occipital, middle temporal, and superior temporal regions are important to 3.5–4.5 month olds' attention during a spatial cueing paradigm, as these regions show less activity to trial stimuli that were invalidly spatially cued trials than to trial stumuli that had been validly and/or neutrally cued.

In addition to electrophysiological techniques, another non-invasive window into the neural substrates of infant attention is through candidate genetic association studies, focused on genes related to particular neurotransmitters, which are differentially associated with theoretically relevant neuroanatomy. Relevant to the current paper, the *CHRNA4* gene may be indicative of acetylcholine and parietal involvement, while the *COMT* gene may be indicative of dopaminergic and PFC/ACC involvement. Still, genetic association research, without consideration of environmental factors, may not yield consistent findings.

1.2. Parenting sensitivity and the development of attention

Parental sensitive care may be an important environmental influence. First, because sensitive caregiving includes the ability to perceive and appropriately respond to an infant's distress and attentional focus (Ainsworth, 1964; Ainsworth, 1967) sensitive parents will often help to orient infants' attention away from distressing events and, through correctly detecting subtle infant cues, towards objects or persons that the infants' behavior suggests are endogenously interesting. Thus, infants of sensitive caregivers may help their infants practice goal-directed attention, thereby facilitating the development of endogenous control in everyday life. Second, and in keeping with views expressed by Licata et al. (2013), infants of sensitive primary caregivers may also be "more free" to explore their cognitive environment, as they are likely to experience comparatively fewer demands on internal emotional regulation, a process that sensitive mothers facilitate during the infancy period. Third, at the biological level, maternal sensitivity is associated with stress hormones (Atkinson et al., 2013) that influence the PFC cortex (McKlveen, Myers, & Herman, 2015) and may shape PFC connectivity patterns (Rifkin-Graboi et al., 2015). As expected, then, sensitivity and the closely related construct of mother-infant attachment have been found to be related to attention and/or executive function (Bernier, Carlson, Deschenes, & Matte-Gagne, 2012; Fearon & Belsky, 2004; Kok et al., 2013), and there is some evidence that both cholinergic and dopaminergic genes may moderate these environmental influences (Grazioplene, DeYoung, Rogosch, & Cicchetti, 2012; Voelker et al., 2009). It is therefore important to consider potential effects of caregiver sensitivity in genetic association studies of early infant attention.

1.3. CHRNA4

The *CHRNA4* gene codes for a subunit of the neuronal nicotinic acetylcholine receptor (Steinlein et al., 1994), which is a ligand-gated ion-channel implicated in fast synaptic signaling (Alkondon, Pereira, Eisenberg, & Albuquerque, 2000). Past adult research indicates that variation at a particular location on the *CHRNA4* gene, at a synonymous single nucleotide polymorphism (SNP) site within coding exon 5 known as *CHRNA4* rs1044396 (C1545T), associates with visual orienting using spatial cuing paradigms (Parasuraman, Greenwood, Kumar, & Fossella, 2005). Specifically, individuals with two T alleles (i.e., T-homozygotes) exhibited the poorest (i.e., slowest) visual orienting performance compared to those with one or no T alleles. In addition, T/T carriers exhibit greater anterior cingulate, supplementary motor, and left parietal activity when performing a visual oddball task than do T/C and C/C carriers (Winterer et al., 2007), which may suggest both that nicotinergic acetylcholine is involved in the functioning of these regions and that recruitement of these regions is greatest amongst T/T carriers. Likewise, fMRI work performed in conjunction with a re-orienting task found that T/T carriers exhibited the greatest activity of the superior temporal cortex, which is a region linked to the bilateral superior temporal sulcus and left superior parietal sulcus, or, in other words, may be part of a system involved in spatial shifts and reorienting (Gießing et al., 2012). In sum, then, while work in adults suggests that CHRNA4 may affect a variety of brain regions, its variation may be especially important to the temporo-parietal junction.

Still, genetic association work with 6- to 7-month-old infants (Markant, Cicchetti, Hetzel, & Thomas, 2014; Sheese et al., 2009) has