Journal Club

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# Impact of the Tri-Allelic Serotonin Transporter Polymorphism on the White-Matter Tract Connecting the Amygdala and the Prefrontal Cortex

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Review of Pacheco et al.

Imaging genetics integrates neuroimaging and molecular genetics to examine the structural and functional correlates of common genetic variation in the human brain *in vivo*. These brain endophenotypes, or intermediate phenotypes, are postulated to lie etiologically closer to the genes than more complex and heterogeneous behavioral and clinical phenotypes, and may therefore prove easier to link to the underlying genes. This knowledge may help us explain the neurobiological bases of individual differences in susceptibility and resilience to mental disorders such as depression.

One prominent line of research has focused on the effects of the serotonin transporter-linked polymorphic region (5-HTTLPR) in the promoter of the serotonin transporter gene on the function and structure of the amygdala-prefrontal cortex (PFC) system in humans. The serotonin transporter protein is a crucial regulator of serotonergic signaling: it terminates the synaptic action of serotonin via its reuptake into the presynaptic neuron. The 5-HTTLPR presents two common length variants that have functional consequences *in vitro*: a short (S) allele with low transcriptional efficiency, and a long (L) allele with high transcriptional efficiency (Heils et al., 1996). In addition, an A/G nucleotide substitution in the L allele (rs25531) renders the 5-HTTLPR tri-allelic, with $L_G$ allele functionally equivalent to the S allele *in vitro*, compared with the $L_A$ allele (Hu et al., 2006).

Since the amygdala-PFC system plays a central role in a variety of emotional processes such as response to threat and emotional memory, and the serotonin system modulates these processes via dense serotonergic innervations of both structures, researchers postulated that an individual's 5-HTTLPR genotype would affect the processing of emotional information. And indeed, a consistent association has been found between the S allele and increased amygdala reactivity to threat stimuli (e.g., angry or fearful faces) as measured with functional magnetic resonance imaging (fMRI) in healthy subjects (Hariri et al., 2002).

Despite such associations, complex processes such as response to threat likely occur at a system level and involve reciprocal interactions between multiple brain regions. Consequently, more recent imaging genetics research has examined the impact of the 5-HTTLPR genotype on measures of functional connectivity in the amygdala-PFC system. S allele carriers displayed increased functional coupling between the amygdala and the ventromedial PFC (Heinz et al., 2005) but decreased functional coupling between the amygdala and the perigenual anterior cingulate cortex (pACC) (Pezawas et al., 2005) compared with LL homozygotes. Decreased functional coupling between the amygdala and the ACC in S allele carriers may constitute a neural susceptibility marker, because a similar decrease has been reported in patients with unipolar and bipolar depression compared with healthy controls (Anand et al., 2009). Nevertheless, a question remains whether the genotype-specific differences in functional connectivity correspond to any genotype-specific differences in structural connectivity in the amygdala-PFC system. Pacheco et al. (2009) set out to answer this question using diffusion tensor imaging (DTI) in a sample of 37 healthy female subjects (age 13–28) genotyped for the tri-allelic 5-HTTLPR/rs25531.

DTI is a MRI technique that is used to examine white-matter tracts in the human brain *in vivo* based on the rate and direction of diffusion of water molecules in different regions of the brain. In axon tracts, diffusion of water molecules is restricted by cellular membranes. If axons are aligned in fibers, diffusion is limited to one principal direction (anisotropic diffusion), parallel to the predominant direction of the fibers. Outside of axonal bundles, water

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molecules diffuse randomly in all directions (isotropic diffusion). DTI data are used on a voxel-by-voxel basis to calculate the fractional anisotropy of diffusion, which is thought to reflect the degree to which axons are aligned. More precisely, variability in fractional anisotropy can reflect the number of axons forming a fiber, the degree of their myelination, and/or the presence of other fibers crossing in different directions. Fractional anisotropy is a nonspecific measure of the white-matter microstructure and other complementary methods are needed to explain the underlying processes.

Pacheco et al. (2009) focused on the bilateral uncinate fasciculi as their white-matter pathway of interest. The uncinate fasciculus is a hook-shaped association bundle that directly connects the anterior temporal lobe and the amygdala to the inferior portions of the frontal lobe, and is considered to be crucially involved in emotional processing, among other functions. Each uncinate fasciculus was further divided into the frontal and temporal regions for a more precise analysis.

Using linear regression with the number of the $S/L_G$ alleles as an independent variable, Pacheco et al. (2009) found a significant main effect of the 5-HTTLPR/rs25531 genotype on the microstructure of the left frontal uncinate fasciculus, such that as the number of the $S/L_G$ alleles increased, the fractional anisotropy in the left frontal uncinate fasciculus decreased ($p < 0.005$). The direction of the association appears to be consistent with the view that compromised connectivity between the amygdala and the prefrontal regions may underlie the heightened emotional reactivity and impaired cognitive regulation of emotion observed in depression (Mayberg, 1997). A recent study combining DTI and functional MRI in the same subjects found a significant positive association between the fractional anisotropy in the uncinate fasciculi and the functional coupling between the amygdala and the ACC (Wang et al., 2009).

Pacheco et al. (2009) also replicated a previously reported positive correlation between age and the fractional anisotropy in the bilateral frontal uncinate fasciculi. White-matter cohesion, as measured with fractional anisotropy, increases with age from early childhood through adolescence and into adulthood, and then begins to decrease from middle adulthood through old age (Salat et al., 2005; Snook et al., 2005). In Pacheco et al.'s report (2009), the fractional anisotropy of the frontal uncinate fasciculi increased with age in the whole sample. Age explained 39% of the variance in the fractional anisotropy in the left frontal uncinate fasciculus and 20% of the variance in the fractional anisotropy in the right frontal uncinate fasciulus. The significant effects of age point to the importance of considering the impact of genetic variation on brain structure and function in the neurodevelopmental framework: the genetic effects may play into dramatic maturational changes that are part of normal brain development but also constitute "windows of vulnerability" to environmental pathogens such as severe stressors (Andersen and Teicher, 2008). Because the number of the $S/L_G$ alleles simultaneously decreased the fractional anisotropy in the left frontal uncinate fasciculus, it is possible that the genetic vulnerabilities may slow down or perhaps even reverse the normal maturational trajectories. However, unless the age distribution was balanced across the genotype groups, the effects of age could potentially confound the effects of genotype.

Finally, gene-by-environment interaction research strongly suggests that genetic factors interact with environmental pathogens such as stressor exposure. In particular, the landmark study by Caspi et al. (2003) showed that the 5-HTTLPR genotype significantly moderates the impact of stressor exposure on depressive outcomes in young adults. Future prospective longitudinal studies could examine the effects of the 5-HTTLPR genotype, as well as the interaction of the 5-HTTLPR genotype and stressor exposure, on the uncinate fasciculus and other white-matter tracts at discrete developmental stages, to more fully map the impact of genetic variation on this aspect of brain development both in health and in disease.

The study by Pacheco et al. (2009) provides the first evidence that the 5-HTTLPR genotype has a significant impact on the microstructure of white-matter tracts connecting two brain regions crucially involved in emotional processing, the amygdala and the prefrontal cortex, in healthy subjects. However, the inherent nonspecificity of the measure used, the potentially confounding effects of age, and a relatively small sample size all warrant caution in interpreting the results before replication. Nonetheless, the approach used by Pacheco et al. (2009) constitutes the logical next step in the line of imaging genetics research focused on the impact of the 5-HTTLPR on the functional and structural correlates of emotional processing in the human brain.

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