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Cognitive Control, the Anterior Cingulate, and Nicotinic Receptors: A Case of Heterozygote Advantage

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Review of Sadaghiani et al.

The cholinergic neurotransmitter system, via diffuse projections emanating from the basal forebrain and synapsing onto numerous cortical targets, modulates several neurocognitive functions, including attention, working memory, and cognitive control (Picciotto et al., 2012). Concordantly, loss-of-function in this system is associated with cognitive impairment in numerous psychiatric and neurological disorders such as Alzheimer's disease (Francis et al., 1999), epilepsy (Ghasemi and Hadipour-Niktarash, 2015), and schizophrenia (Sarter et al., 2012; Smucny and Tregellas, 2013), making it an attractive target for therapeutic intervention.

The most abundantly expressed cholinergic receptor in the mammalian brain is the ionotropic nicotinic $\alpha_4\beta_2$ receptor. Interestingly, behavioral phenotypes may be modulated at the level of single-nucleotide polymorphisms (SNPs) of $\alpha_4\beta_2$ receptor-encoding genes. A striking example of this phenomenon is demonstrated by the rs1044396 SNP of the α_4 subunit encoding gene *CHRNA4*, which influences neurocognitive processes such as attention (Parasuraman et al., 2005; Reinvang et al., 2009; Espeseth et al., 2010) as well as nicotine addiction (Breitling et al., 2009; Rocha Santos et al., 2015). The relationships between its allelic combinations (T/T, T/C, and C/C) and cognition, however, are unclear. Some studies have demonstrated an advantage (e.g., increased attentional load capacity) with the T allele (Greenwood et al., 2005, 2012; Espeseth et al., 2010) and others an advantage (e.g., decreased reaction times) with the C allele (Parasuraman et al., 2005; Reinvang et al., 2009). Heterozygotes, furthermore, have not been well characterized.

To clarify the effects of these alleles, Sadaghiani et al. (2017) recently examined functional activation (using fMRI) and performance during cognitive control-associated tasks in healthy young adults with the T/T, T/C, or C/C rs1044396 genotype. The authors focused on activation of the cingulo-opercular network because of its demonstrated importance in cognitive control-associated functions (Lesh et al., 2011; Sheffield et al., 2015) and robust nicotinic receptor expression (Paterson and Nordberg, 2000).

To maximize statistical power, Sadaghiani et al. (2017) used large datasets from two publicly available databases: the IMAGEN dataset (Schumann et al., 2010; $n_{\text{fMRI}} = 1358$) and the Philadelphia Neurodevelopmental Cohort (PNC; Satterthwaite et al., 2014; $n_{\text{fMRI}} = 228$). For the IMAGEN dataset, brain network activity was analyzed during a Stop-Signal task. In this task, subjects were asked to respond to left or right-pointing arrows with a left or right button press (respectively), but were told to withhold the response when the arrow was followed by a "stop" signal (up arrow). Cognitive control-associated activity was defined as brain activity during all "stop" trials and during errors on "go" trials. Activity during "stop" trials measures the response inhibition aspect of control, and activity during errors-only "go" trials measures the response conflict-driven, task adjustment aspect of control (Verbruggen and Logan, 2008). For the PNC dataset, network activity was analyzed during a visual *n*-back working memory task. For this task, subjects were asked to determine whether an abstract geometric image matched a target image (0-back condition), the image shown previously (1-back condition), or the image shown two trials previously (2-back condition). Cognitive control-associated activity was defined as brain activity across all conditions.

Under this framework, Sadaghiani et al. (2017) found that heterozygotes (T/C subjects) showed greater task-associated activity in the cingulo-opercular network than either T/T or C/C homozygotes. This effect was specific to the cingulo-opercular network: group differences were not observed in the default, dorsal attention, or frontoparietal networks. Heterozygotes also showed greater accuracy during other visual continuous performance tasks relative

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to homozygotes. These results suggest that heterozygotes show both increased activation of neuronal circuits during cognitive control-related tasks as well as improved overall performance relative to either homozygous genotype.

To further understand the mechanism underlying this difference, Sadaghiani et al. (2017) analyzed gene expression data from the Genotype-Tissue expression project database (GTEx Consortium, 2015). They found that T/T homozygotes had the greatest CHRNA4 expression levels, with T/C heterozygotes showing intermediate levels and C/C homozygotes the lowest levels. This finding suggests that the rs1044396 SNP may affect cognition by affecting α_4 subunit expression.

These results have important implications for our understanding of the relationships between receptor expression and neurotransmitter signaling by suggesting that intermediate expression of the CHRNA4 gene may confer an optimal level of nicotinic signaling for cognitive control. Why might such an "inverted U" shaped effect occur? One possibility may lie in how the nicotinic system influences the balance between excitation and inhibition (i.e., E/I balance) in the brain. Healthy brain function depends upon homeostatic control of cortical excitability allowing for dynamic control of plasticity and information transfer to optimize efficiency according to task demands (Krause et al., 2013). Over-inhibition may prevent the appropriate neural circuits from being activated, whereas prolonged hyperexcitation may induce neurotoxicity (Krause et al., 2013). Improper E/I balance may also reduce the dynamic range over which neuronal circuits may be perturbed, inducing floor or ceiling effects preventing performance optimization. Given that one of the primary functions of the nicotinic $\alpha_4\beta_2$ receptor is to enable ion influx and neuronal depolarization, it follows that rs1044396 T/C heterozygotes (which show intermediate levels of receptor expression) may have improved E/I balance relative to either homozygous genotype. Indeed, previous studies have shown that knock-out of the *lynx1* gene, which acts as a "brake" on nicotinic receptor signaling, not only enhances receptor activation but also induces vacuolation and neurodegeneration (Miwa et al., 2006). Differences in basal nicotinic signaling may also affect E/I balance by inducing downstream alterations in glutamatergic (Mansvelder et al., 2002) and GABAergic (Maloku et al., 2011) signaling. Interestingly, it is possible that the inverted U-shaped dose–response curves observed in other neurotransmitter systems, such as dopamine (Cools and D'Esposito, 2011) and serotonin (Cano-Colino et al., 2014), are also due to the influence of these systems on E/I balance.

Regardless of the mechanism, the results of Sadaghiani et al. (2017) have important implications for the understanding and treatment of diseases with nicotinic associations. Schizophrenia, for example, is associated with high rates of nicotine dependence that have been hypothesized to be a form of self-medication to normalize deficient levels of nicotinic signaling (Winterer, 2010). Supporting this view, previous neuroimaging studies have observed reduced expression of nicotinic receptors in schizophrenia (Freedman et al., 1995; D'Souza et al., 2012). Tying this result to the Sadaghiani et al. (2017) paper, schizophrenia patients also show behavioral and functional deficits in cognitive control (including reduced anterior cingulate activation; Lesh et al., 2011, 2013; Culbreth et al., 2016; Smucny et al., 2017). Although no known relationship exists between risk for schizophrenia and the rs1044396 SNP, it is possible that the rs1044396 SNP may influence endophenotypic traits associated with the illness, e.g., deficits in cognitive control. Indeed, it has been suggested that the effects of single gene mutations may be better isolated in polygenic disorders such as schizophrenia on an endophenotypic level (as demonstrated by the nicotinic α7 receptor-encoding the *CHRNA7* gene and impaired P50 gating; Leonard et al., 2002; Sinkus et al., 2015) due to the fact that large numbers of genes influence schizophrenia risk (Leonard et al., 2002). In regard to treatment, although the nicotinic receptor has received considerable attention as a potential drug target for schizophrenia (Freedman, 2014; Featherstone and Siegel, 2015), results from these trials have thus far been mixed. Several trials have failed, and no drug is yet FDA approved to treat any symptom (Freedman et al., 2008; Shim et al., 2012; Velligan et al., 2012; Walling et al., 2016; Kem et al., 2017). One possible explanation for the slow progress of these drugs is genetic heterogeneity. Some patients, for example, may have SNPs in *CHRNA4* and other nicotinic receptor genes that affect receptor affinity and expression (Greenwood et al., 2012). Different drug doses might consequently be required to elicit maximum benefit depending on haplotype, and comparison of nicotinic drug effects between rs1044396 (and other) alleles could help optimize doses. Related to this point, a previous neuroimaging study using an α_7 nicotinic receptor partial agonist found differential effects depending on CHRNA7 (the α_7 nicotinic receptor gene) genotype (Tregellas et al., 2011).

By demonstrating heterozygote advantage in human nicotinic receptor SNPs, the work by Sadaghiani et al. (2017) makes an important contribution to our understanding of how genes can shape the neuronal mechanisms of cognition. This study is also one of the first neuroimaging genetics studies to take advantage of large public databases. To this point, reproducibility has been an issue in neuroimaging genetics studies due to low power associated with small sample sizes (Carter et al., 2017). This challenge has been difficult to overcome because of the high costs ($500–1000 per MRI scan; Paulus and Stein, 2007) and long study durations necessary to conduct large-scale functional imaging studies. Publicly available databases such as IMAGEN and the PNC will help overcome this hurdle by freely enabling neuroscience researchers to analyze data collected in parallel across numerous sites, exponentially increasing overall efficiency and reproducibility in the search for genetic mechanisms that underlie dysfunctional neurocognitive processes in neurological and psychiatric disease.

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