



# The State of Individual's Brain Circuits and Vulnerability to Nicotine Dependence

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Both genetic and environmental factors are known to influence smoking behavior, although the major factors linked to smoking behavior are genetics [1,2] and mental illnesses [3,4]. The process of finding an effective therapeutic agent for smoking involves 1) identification of relevant genes and 2) identifying the brain circuit(s) linking the "risk alleles" to smoking. A recent NIDA (National Institute of Drug Abuse) funded study recognized the key role played by a network of brain circuits in determining vulnerability to nicotine dependence. Gusnard et al. [5] and Gusnard and Raichle [6] at the Washington University School of Medicine in St. Louis did pioneering studies on resting-state circuits of brain and noted that some brain regions synchronize their activity when individuals are awake and alert but are not performing any specific task. Research on resting-state circuits of brain can provide insights into how the brain works at a basic level.

Hong et al. [7,8] at University of Maryland School of Medicine, Baltimore, studied the resting-state neural signatures for nicotine dependence and assessed the impact of nicotine replacement therapy on brain circuits. They studied the circuits in the cingulate cortex because activity in that part of the brain was found to be disturbed due to addiction behavior. Using a resting-state functional connectivity (rsFC) approach, Hong and his coworkers explored the entire cingulate region of the brain and showed that a dorsal

anterior cingulate (dACC)-ventral striatal circuit which expresses the  $\alpha 5$  subunit, is associated with nicotine addiction. The dACC is known to be associated with impulse and emotional control, which are impaired in addiction. It was found that participants with weaker communication in this circuit scored higher on the Fagerström Test for Nicotine Dependence. The most replicated functional marker linked to smoking is the  $\alpha 5$  subunit gene (CHRNA5) rs16969968 or Asp398Asn polymorphism that converts aspartic acid (Asp) to asparagine (Asn) [9-11].

Recently, Hong et al. [8] showed that  $\alpha 5$  gene variant Asp398Asn is associated with a dorsal anterior cingulate-ventral striatum/extended amygdala circuit, such that the presence of this "risk allele" decreases the functional connectivity strength in the brain circuit. The vulnerability to smoking among smokers is more strongly dependent upon brain circuits than gene variants. It was shown that weakening of signal strength in the dACC-striatum brain circuit accounted for 10 to 12% of the differences in nicotine dependence among smokers. In contrast, the contribution of genotype alone was only 1 to 4 percent. The resulting data indicated that the variant of  $\alpha 5$  gene interacts with other genes or environmental factors to weaken the brain circuit and increases vulnerability to smoking. In this particular study, there were 76 participants suffering from various mental disorders such as schizophrenia, substance dependence, and anxiety and depressive disorders. The individuals with mental disorders had weaker dACC-striatum circuit strength and higher smoking rates than individuals without mental disorders. The frequency of high-risk  $\alpha 5$  gene variant in people with mental disorders was less, indicating that other genes or factors might contribute to the relative weakness in their brain circuitry. Future research efforts should focus on these unidentified gene variants that predispose certain individuals to mental illness and disrupt the circuit. I am sure the "Journal of Addiction Research & Therapy" from OMICS Publishing Group will make a positive impact in this direction.

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