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Review

The genetic epidemiology of substance use disorder: A review

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ABSTRACT

Background: Substance use disorder (SUD) remains a significant public health issue. A greater understanding of how genes and environment interact to regulate phenotypes comprising SUD will facilitate directed treatments and prevention.

Methods: The literature studying the neurobiological correlates of SUD with a focus on the genetic and environmental influences underlying these mechanisms was reviewed. Results from twin/family, human genetic association, gene-environment interaction, epigenetic literature, phenome-wide association studies are summarized for alcohol, nicotine, cannabinoids, cocaine, and opioids.

Results: There are substantial genetic influences on SUD that are expected to influence multiple neurotransmission pathways, and these influences are particularly important within the dopaminergic system. Genetic influences involved in other aspects of SUD etiology including drug processing and metabolism are also identified. Studies of gene-environment interaction emphasize the importance of environmental context in SUD. Epigenetic studies indicate drug-specific changes in gene expression as well as differences in gene expression related to the use of multiple substances. Further, gene expression is expected to differ by stage of SUD such as substance initiation versus chronic substance use. While a substantial literature has developed for alcohol and nicotine use disorders, there is comparatively less information for other commonly abused substances.

Conclusions: A better understanding of genetically-mediated mechanisms involved in the neurobiology of SUD provides increased opportunity to develop behavioral and biologically based treatment and prevention of SUD.

1. Introduction

The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) defines substance use disorder (SUD) as a constellation of behaviors involved in compulsive drug seeking including impaired control of substance use, impaired social interactions with others because of substance use, risky drug use (e.g., substance use in hazardous settings), and pharmacological changes (e.g., experiencing withdrawal symptoms). Further, the DSM-5 defines addiction as the most severe, chronic stage of the SUD diagnosis, which is characterized by subsantial loss of self-control, manifesting in compulsive drug-seeking behavior despite the desire to discontinue use (American Psychiatric Association, 2013; Volkow et al., 2016). SUD and addiction remain a significant global public health concern, resulting in substantial socioeconomic burden (Collins et al., 2006; Heslin et al., 2015; Whiteford et al., 2015). Globally, 52.3 million cases of alcohol and drug dependence/problem use were reported in 2004 (World Health Organization, 2008). In 2010, this number increased to 147.5 million cases (Whiteford et al., 2015), and SUD is expected to become more prevelant over time.

Genetic factors within multiple overlapping neurobiological systems have been consistently implicated in SUD etiology (Nestler, 2001). Here, we summarize the genetic epidemiology of SUD and focus on commonly abused substances including alcohol, nicotine, marijuana, cocaine, and opioids. Although results will be summarized across all substances, genetic epidemiological studies of alcohol and nicotine use currently out number cannabis, cocaine, and opoids. Further, we connect this knowledge with the neurobiology of SUD and provide suggestions for future research in this area.

2. Major SUD neural substrates

Although different drug classes act on distinct cellular substrates, initial drug reward/saliency appears to be primarily encoded by midbrain dopamine neurons projecting into the prefrontal cortex as well as

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the dorsal and ventral striatum (Volkow et al., 2009). Human imaging studies indicate the extent to which a drug increases striatal dopamine is proportional to self-reported euphoria (Drevets et al., 2001; Sharma and Brody, 2009; Volkow et al., 2009). Nonetheless, it is important to note that responding for rewarding stimuli is also encoded by other ascending monoamine fibers such as norepinephrine (Stein and Himwich, 1962) and other non-dopaminergic systems within the medial forebrain bundle (Crow, 1973).

2.1. Commonly abused substance usurp learning mechanismns

Dopamine also encodes salience or a teaching signal, which may contribute to the learned component of substance abuse. For example, dopamine neurons initially fire with reinforcer delivery, but with time dopamine neuron firing becomes time-locked with predictive conditioned stimuli that precede an expected reinforcer (the unconditioned stimulus) rather than the reinforcer, itself (Schultz, 1997). Similar findings have also been observed in detoxified cocaine abusers. Specifically, presentation of drug-associated cues increase dopamine levels in brain regions that participate in habit circuitry (Belin et al., 2009; Volkow et al., 2011, 2006) to a level greater than the drug itself (Volkow et al., 2011; Volkow et al., 2006). This dopamine signal is correlated with self-reported craving (Drevets et al., 2001; Heinz et al., 2004). After repeated or habitual use, previously neutral stimuli become imbued with the drug experience and eventually acquire the ability to increase dopamine in anticipation of reward. This dopamine signal can elicit strong motivation to pursue a drug of abuse (Owesson et al., 2009; Salamone et al., 2007). Thus, dopamine signaling in several brain regions including the nucleus accumbens, dorsal striatum, ventral pallidum, dorsolateral prefrontal cortex, anterior cingulate, and orbitofrontal cortex modulate the motivation to pursue abused substances (Salamone et al., 2007).

2.2. Compulsive drug-seeking behavior

Once addiction has developed, decreased ability to avoid drug craving and/or inhibit drug-seeking behavior commonly manifests despite decreased hedonic effects of the drug. These inhibitory 'top-down' deficits may emerge from a lack of executive control over circuits that parse reward/saliency, aversion avoidance/stress reactivity, interoception, and motivation (Koob and Le Moal, 2001; Volkow et al., 2003, 2011). Decreased hedonic drug effects may stem from a shift away from phasic and tonic midbrain dopamine firing patterns toward more tonic firing, which results in lower levels of dopamine release (Grace, 2000). Blunted dopamine release and decreased hedonic effects have been observed in cocaine-addicted individuals challenged with either methylphenidate (a cocaine-like compound) or amphetamine (Martinez et al., 2007; Volkow et al., 1997, 2011). These and other neural adaptations induced by the drug are thought to usurp normal learning and habit circuitry and increasingly recruit cortical glutamatergic signalling (Bowers et al., 2010; Kalivas, 2009; Kalivas and O'Brien, 2008; Koob and Volkow, 2010; Luscher and Malenka, 2011), which can manifest as compulsive drug-seeking behavior and relapse (Everitt and Wolf, 2002; Hyman et al., 2006).

3. Twin and family studies of substance use disorder

3.1. Genetic and environmental effects

Family studies report that children of parents with high-risk alcohol dependence, or that are from families where one member is diagnosed with an SUD, are at much greater risk for developing alcohol problems (Chassin et al., 1991). Consequently, family studies have demonstrated that SUD clusters within families, implicating a role for both genetic and environmental influences. In comparsion to family studies providing estimates of familial clustering, twin studies have estimated specific sources of variance in the etiology of SUD. Twin studies use monozygotic and dizygotic twin pair variances and covariances to estimate the proportion of total phenotypic variance of a trait due to additive genetic (additive genetic effects of alleles at every locus), shared environmental (environmental influences common to both twins), and unique environmental influences (environmental influences not shared by members of the twin pair; (Cherny, 2009). Twin studies of SUD consistently report that substance initiation is significantly influenced by genetic as well as shared and unique environmental factors. This is consistent across populations that initiate tobacco, alcohol, or cannabis use (Agrawal et al., 2010; Huizink et al., 2010). In contrast, additive genetic influences are greater for substance progression; often defined as regular use as well as dependence. There is no longer a significant influence of shared environmental factors for either regular use or dependence in adulthood, although shared environmental influences remain significant during adolescence (Maes et al., 2017; Rose et al., 2009; Bergen et al., 2007; Hopfer et al., 2003). Additive genetic influences remain significant for regular use and dependence even when adjusting for genetic influences specific to substance initiation (Maes et al., 2004; Sullivan et al., 2001). Measurement of progression and dependence varies and can reflect the amount of substance used within a specific time frame or symptoms related to SUD diagnosis.

3.2. Genetic and environmental influences on SUD across multiple substances

As a whole, SUD twin studies suggest a common set of genetic and environmental factors that are shared across drugs as well as genetic and environmental influences that are specific to a given substance. Studies of initiation report substantial shared environmental influences common to multiple substances (Fowler et al., 2007; Han et al., 1999; Koopmans et al., 1999). In contrast, studies of use and dependence reported significant additive genetic and unique environmental influences shared across SUD as well as genetic and environmental influences specific to a given drug (Agrawal and Lynskey, 2006; Baker et al., 2011; Palmer et al., 2012; Palmer et al., 2009; Xian et al., 2008; Young et al., 2006). Further, the influence of genetic and environmental factors shared between different forms of substance abuse are likely to remain significant across time (Palmer et al., 2009).

3.3. Neuroimaging in twins

Neuroimaging twin studies of SUD have begun to connect knowledge regarding the role of neural networks invovled in SUD with genetic and environmental influences on the disorder. For example, small, widespread negative associations were recently reported between cigarette pack-years and the volume and/or surface area of several cortical as well as subcortical brain structures (Prom-Wormley et al., 2015). Importantly, correlations were the result of shared genetic and unique environmental factors in brain structures involved in the processing of environmental influences related to smoking.

4. Genetic association studies

The goal of genetic association studies of SUD is to identify genetic markers that may have a role in the development or progression of addiction. Identifying these markers may aid in the treatment or prevention of SUD. There are two main catagories of genetic association studies. Candidate gene association studies (CGAS) test the association of previously identified markers with SUD phenotypes. Markers are selected for CGAS analysis due to demonstrated functional significance in prior animal, molecular genetic, and/or human SUD studies (Kwon and Goate, 2000; Rebbeck et al., 2004). Together, these studies can develop a strong case for the importance of a genetic variant or biological pathway in SUD etiology. In contrast, genome-wide association studies (GWAS) test for significant associations between a SUD

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