Published in final edited form as:
*Trends Cogn Sci*. 2014 April ; 18(4): 211–217. doi:10.1016/j.tics.2014.01.010.

# Personality Traits and Vulnerability or Resilience to Substance Use Disorders

**Annabelle M. Belcher**[1], **Nora D. Volkow**[2], **F. Gerard Moeller**[3], and **Sergi Ferré**[1]

[1]National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Baltimore, MD 21224, USA

[2]National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892, USA

[3]Departments of Psychiatry and Pharmacology and Toxicology, Virginia Commonwealth University School of Medicine, Richmond, VA 23219, USA

## Abstract

Clear evidence supports a genetic basis for Substance Use Disorders (SUD). Yet the search to identify individual gene contributions to SUD has been quite unsuccessful. Here we argue for the study of endophenotypes within the frame of individual differences, and identify three high-order personality traits that are tied to specific brain systems and genes, and that offer a tractable approach to studying SUD. These personality traits, and the genes that moderate them, interact dynamically with the environment and with the drugs themselves to ultimately determine an individual's vulnerability or resilience to developing SUD.

## Genes and Substance Use Disorders

Although most people in the general population are exposed to drugs and/or alcohol at some point in their lives, only a small fraction of these individuals develops an unremitting Substance Use Disorder (SUD) [1]. Informed estimates place lifetime risk of transitioning from drug use to dependence from 8.9%-67.5% [2] depending on the drug used. Strong evidence suggests an important genetic contribution to the vulnerability to SUD. Epidemiological family and twin studies provide heritability estimates of approximately 50% [3]. Some genetic variance could be specific to drug class (particularly for opiate and nicotine addiction), but in this review we only address the general, shared, heritable genetic variance that predisposes an individual to SUD irrespective of drug class [3].

Despite the clear demonstration that genetic factors contribute to SUD, traditional molecular genetics approaches have largely failed to identify specific SUD-associated genes (Box 1). It has been argued that molecular genetics will continue to be mostly unsuccessful in the search for genes associated with neuropsychiatric disorders for two reasons: 1) any observable direct genetic effects are subject to strong environmental influences, and 2) the causal link between the gene and the disease is likely too long and complex to be directly observable [4]. The introduction of the 'endophenotype' concept has provided an invaluable approach for the identification of genes that predispose or indemnify individuals from mental and psychiatric disorders. The endophenotype concept is understood as simpler clues

*Corresponding author:* Ferré, S. (sferre@intra.nida.nih.gov).

to genetic underpinnings than the disease syndrome itself, and involves the genetic analysis of any of a variety of biological markers (cognitive, neurophysiological, anatomical, biochemical, etc.) of the disease. The concept promotes the view that psychiatric diagnoses can be decomposed or deconstructed into more tractable genetic dissection by virtue of their assumed proximity to the genetic antecedents of disease [4-6]. Here we review the current evidence that demonstrates that personality traits can be used as endophenotypes of SUD, building the bridge between genes and SUD, allowing for a better understanding of which individual differences in specific brain circuits provide vulnerability or resilience to SUD.

## Positive emotionality/extraversion and SUD

The positive emotionality/extraversion (PEM/E) personality trait represents an underlying dimension of sensitivity to reward (Box 2). PEM/E is characterized by a state of positive affect, strong motivation, desire, wanting, as well as feelings of being excited, enthusiastic, active, and optimistic. The best candidate brain system involved in these affective states is the central dopaminergic system, which originates in the mesencephalon (substantia nigra and ventral tegmental area) and innervates the striatum, frontal cortex, amygdala and hippocampus (Fig. 1). This system is involved in the establishment and elicitation of reward-related behaviors, and its participation is well established in: 1) the provision of incentive motivation for reward (i.e., the degree of desire or willingness to exert effort to approach or work) [7,8], and 2) the establishment of new attractors (by conferring stimuli associated with rewards the ability to act as new, conditioned rewards) [7].

Depue and colleagues have been fundamental in making explicit the parallel between PEM/E and the central dopaminergic system [9-11]. First, they showed that the efficacy of a dopamine $D_2$ receptor agonist at increasing spontaneous eyeblink and decreasing serum prolactin levels correlates with PEM, but not with negative emotionality (NEM) or constraint (CON) [10]. Dopaminergic modulation of spontaneous eyeblink can be considered an index of activity of a portion of the central dopaminergic system originating in the substantia nigra [12], while dopaminergic modulation of serum prolactin depends on a separate hypothalamic-pituitary system [13]. These results strongly suggest that PEM/E depends on a general sensitivity to $D_2$ receptor agonists. In fact, significant correlations between PEM or E scores and striatal $D_2$ receptor availability (as measured by PET) have been found [14,15].

More recently, Depue and Fu [11] found that high (but not low) PEM individuals show a significant methylphenidate-induced conditioned contextual facilitation in three separate processes (motor velocity, positive affect and visuospatial working memory). These results could be explained by individual differences in $D_2$ receptor sensitivity (in this case, to endogenous dopamine), but individual differences at the presynaptic level (higher increases in extracellular levels of dopamine following methylphenidate administration) cannot be discarded. In fact, Treadway et al. [16] found a significant correlation between amphetamine-induced increases in forebrain extracellular dopamine levels and willingness to expend greater effort for rewards (a putative laboratory index of PEM/E). Thus, both pre- and postsynaptic mechanisms are most probably involved in the higher reactivity of the central dopaminergic system of high PEM/E individuals.

Drugs of abuse are strong rewards by themselves and their common biochemical effect is a powerful increase in central dopaminergic neurotransmission [17]. Thus, acute administration of psychostimulants, nicotine, alcohol and marijuana to humans elevate extracellular dopamine in the striatum [17], elevations which are correlated with subjective feelings of euphoria in SUD individuals [17]. Therefore, one common assumption in the field of individual differences and SUD has been that the PEM/E personality trait or other

theoretically related traits ('Novelty-Seeking', 'Sensation-Seeking') constitute vulnerability factors for SUD; the rationale being that a more sensitive reward-related (dopaminergic) brain system should be more sensitive to drugs of abuse. However, evidence is accumulating for precisely the opposite: that a high trait PEM/E constitutes a resilience factor, conferring protection against SUD.

Several studies have shown that PEM/E is a protective factor for SUD in adolescents [18,19]. Additionally, high PEM/E was found in non-drug-using family members of alcoholic subjects [14]. Expectably, those subjects also showed a significantly higher density of striatal $D_2$ receptors [14]. On the other hand, a consistent finding is that individuals with SUD, including alcoholic subjects, have low striatal $D_2$ receptor availability [17,20], which is associated with diminished OFC/ACC metabolism [17]. The low OFC/ACC metabolism is likely secondary to striatal postsynaptic $D_2$ receptor hypofunction (Box 3). In fact, studies in psychostimulant- and alcohol-addicted subjects have shown a correlation between striatal $D_2$ receptor availability and OFC/ACC metabolism [17,20,21]. Furthermore, we have found PEM/E to associate with both increased striatal $D_2$ receptor density, and high OFC/ACC metabolism [14,22], which might play an important protective role for SUD, as these are key brain areas involved in decision-making, dysfunctions of which lead to 'impulsive choice' (Box 3).

In addition to the striatal postsynaptic $D_2$ receptor hypofunction, there is also evidence for a blunted presynaptic dopaminergic response in SUD individuals, with striatal increases in extracellular dopamine induced by intravenous methylphenidate or amphetamine being at least 50% lower than in control subjects [23,24]. Additionally, cocaine users have reduced spontaneous eye blinking (as discussed above, another laboratory measure of dopaminergic function) [25]. Overall, these studies demonstrate that SUD individuals have a less sensitive central dopaminergic system. Indeed, a core, defining characteristic of SUD is that of little interest for rewards other than the drug. When not engaged in drug-related behavior, they show low disposition toward positive emotions and a very low degree of incentive motivation.

The $D_2$ receptor gene could moderate PEM/E and low PEM/E could constitute an endophenotype of SUD (Fig. 2). The minor A1 allele of the Taq1A polymorphism of the gene cluster *ANKK1/DRD2* is associated with low striatal $D_2$ receptor density [26,27]. Several studies have linked the A1 allele with low extraversion (as measured by scales other than MPQ or NEO-PI-R) [28,29] and with a low magnitude of neural reward responses (as measured by fMRI experiments) [30]. It has been suggested that the presence of the A1 allele confers vulnerability to SUD and, although conflicting results have been reported, a recent large-scale meta-analysis strongly suggests an association with alcohol dependence [31], which would be related to the associated low striatal $D_2$ receptor density and low PEM/E.

As highlighted above, evidence for high striatal $D_2$ receptor density and high PEM/E was found in unaffected members of alcoholic families [14]. This would suggest those family members do not share the vulnerable endophenotype or that not only genetic factors play and important role in the final expression of striatal $D_2$ receptor density and concomitant PEM/E. In fact, striatal $D_2$ receptor density is strongly moderated by environmental factors [32], as well as by the drug itself [32,33]. In experimental animals, repeated psychostimulant exposure is associated with very significant decreases in striatal $D_2$ receptor density [32,33], and with the expected OFC dysfunction [33,34], strongly suggesting that a less sensitive central dopaminergic system (and related low trait PEM/E) is not only a premorbid vulnerability factor, but a drug-induced phenomenon. Thus, chronic drug use increases

vulnerability to SUD by decreasing striatal $D_2$ receptor density and consequently OFC/ACC metabolism and PEM/E, further dispensing the likelihood of SUD.

## Negative emotionality/neuroticism and SUD

The NEM/N personality trait represents an underlying dimension of sensitivity to signals of punishment (Box 2). Individuals with high NEM/N are more likely to experience such feelings as anxiety, anger, envy, guilt, and depressed mood. They respond more poorly to stressors, being more likely to interpret ordinary situations as threatening and minor frustrations as hopelessly difficult. The bidirectional connections between prefrontal cortex, particularly rostral anterior cingulate cortex (rACC) and ventromedial prefrontal cortex (vmPFC), and the amygdala and insula play a key role in the expression (non-volitional control) of these negative affective states [35,36]. FMRI studies have provided clear evidence for individual differences in the functional and structural connectivity between prefrontal cortex and amygdala, with a negative correlation between prefrontal cortex-amygdala connectivity and scores of N (or trait anxiety measured by scales other than MPQ or NEO-PI-R) [37,38]. Individuals with high NEM/N would display diminished automatic control of the expression of negative emotions because of diminished rACC/vmPFC control over amygdala function (Fig. 1).

SUD and the other two most common mental heath disorders, depressive and anxiety disorders, are associated with high NEM/N [39,40]; in fact, there is a high rate of comorbidity between them (Box 2). Individuals with SUD and their non-addicted biological siblings score higher than controls in measures of stress sensitivity, strongly suggesting that NEM/N could constitute an endophenotype of SUD [41]. A variable number of tandem repeats (VNTR) in the 5′-promoter region of the human serotonin transporter (5-HTT) gene influences the transcriptional activity and subsequent availability of 5-HTT, and individuals carrying one or two copies of the low-expressing 5-HTT short allele (S allele) exhibit high NEM/N [41,42]. This polymorphism has become the most investigated genetic variant in neuroscience because (among other reasons) it has provided a clear example of a gene-by-environment interaction. Thus, a significant number of S-allele carriers develop depression after experiencing stressful life events and childhood maltreatment [43]. Neuroimaging studies have shown that S-allele carriers exhibit elevated amygdala reactivity to those stimuli [44]. Also, the S allele is associated with reduced gray matter in the rACC/vmPFC and amygdala, and reduced morphological and functional connectivity between both structures [45].

Interestingly, although by definition, NEM/N constitutes an endophenotype for SUD moderated by 5-HTT (Fig. 2), there are no clear studies indicating an association between 5-HTT gene polymorphisms and SUD. This underscores one of the main tenets of this review: the lack of utility of directly connecting genes and clinical phenotypes. It is also tempting to speculate that the decreased metabolism in ACC secondary to drug use could also increase vulnerability to SUD by decreasing prefrontal-amygdala function, thereby increasing NEM/N.

## Constraint-disinhibition and SUD

The higher order dimension of constraint (CON) encompasses tendencies toward behavioral restraint *versus* impulsiveness (Box 2) or more properly, impulsive action, to distinguish it from impulsive choice (Box 3). CON implies intentional, volitional motor control, which can be operationally measured by laboratory tests of response inhibition and task switching [46]. Neuropsychological studies after brain lesions and imaging studies are providing a clear picture of the prefrontal-basal ganglia network involved in volitional inhibitory control

of action. Importantly, the same system seems to be involved in volitional inhibitory control of cognition (i.e., suppression of unwanted memories) and negative affect (i.e., suppression of negative emotions) [35,46-49]. The right lateral inferior frontal gyrus (rIFG) is an important hub of this brain system. The circuit involving motor inhibitory control includes the pre-supplementary motor area (preSMA) with direct connectivity with rIFG [48] and projections from these cortical areas to the striatum and subthalamic nucleus (STN) [47,48] (Fig. 1).

Low CON, or disinhibition, has been consistently found in individuals with SUD (see Box 2). In a recent study, individuals with SUD and their biological siblings (without history of drug abuse) had very similar deficits in a measure of response inhibition (stop-signal reaction time), and they also showed similar prefrontal-striatal brain abnormalities, compared to unrelated healthy volunteers [50]. Those abnormalities included reduced integrity in the fiber tracts adjacent to the rIFG. In SUD there is an impairment of volitional control of negative emotion, which correlates with decreased grey matter in rIFG [49]. Thus, patients with SUD show impairment of both non-volitional (see above) and volitional control of negative emotions (inability to withstand craving).

VNTR polymorphisms of the dopamine $D_4$ receptor gene sequence that codes for the third intracellular loop of the receptor (presence of the $D_{4.7}$ allele, with seven repeats, which is associated with a less functional $D_4$ receptor [51]) and the 3′-untranslated region of the dopamine transporter (DAT) gene (homozygous for the DAT-10 allele, with 10 repeats, which is associated with high DAT expression and, therefore, lower dopaminergic tone [52]) have been associated with disinhibition [53,54]. Additionally, a significant DAT-by-$D_4$ gene interaction exists, as healthy adults expressing the homozygous DAT-10/10 genotype and $D_{4.7}$ allele show a significant impairment in motor inhibitory control [54]. A long literature suggests that disinhibition is an endophenotype for Attention Deficit Hyperactivity Disorder (ADHD) and studies draw associations between ADHD and the same $D_4$ and DAT polymorphisms [53,54]. As for 5-HTT polymorphisms (see above), no clear evidence exists for a direct link between $D_4$ and DAT polymorphisms and SUD. Nevertheless, the clear evidence for a moderation of CON by $D_4$ and DAT genes through their regulation of specific prefrontal-striatal circuits implies that low CON constitutes an endophenotype for SUD (Fig. 2).

Some studies have also shown that striatal $D_2$ receptor availability inversely correlates with measures of impulsive action in animals and in healthy and addicted individuals [33,55,56]. How can we reconcile that dopamine, and more specifically $D_2$ receptors, modulates two orthogonal personality traits? Possibly, postsynaptic $D_2$ receptors localized in striatal GABAergic efferent neurons modulate PEM/E, presynaptic $D_2$ receptors localized in cortico-striatal glutamatergic neurons would be involved in CON. In fact, one main functional role of $D_4$ receptors is modulating striatal glutamatergic neurotransmission and this function depends on molecular interactions (heteromerization) with presynaptic $D_2$ receptors [51].

## Conclusion: a new frame to study resilience and vulnerability to SUD

We now appreciate that specific brain circuits modulate well-defined higher-order personality traits, and that these circuits have been inextricably linked to specific gene associations. This heuristic model is based on a continuum of three independent variables (constituted by three main orthogonal personality traits) that interact dynamically and with the environment to determine the degree of vulnerability to the development of SUD. Individuals with low PEM/E, high NEM/N and low CON would be most vulnerable (least resilient) and individuals with high PEM/E, low NEM/N and high CON would be least

vulnerable (most resilient). We believe that the use of this framework will yield important advances in the field of psychiatric genetics. Traditional approaches would shift to a goal of connecting personality traits and genes, shortening the causal link between genetics and complex disease states. Additionally, this framework affords more approachable questions with testable animal models with measurable aspects of personality that are currently in use (for example, with the use of laboratory tests of impulsivity or stress reactivity). Our approach represents an auspicious paradigm shift that is compatible with a recent invocation by the National Institute of Mental Health to the study of endophenotypes [57]. Our framework is unique, however, in that it allows for a dissection with factors that are completely orthogonal, each with biological traction. Priorities for future work in line with this approach should incorporate the identification of additional genes that moderate the circuits involved in the expression of personality traits. Another open question is the contribution of the environment and more provocatively, of drugs themselves to personality. Finally, our focus is restricted to the study of the personality traits as endophenotypes of SUD, but this framework should be extended to all other mental health disorders.

## Acknowledgments

Supported by the NIDA Intramural Research Program

## References

1. Belcher, AM., et al. Society and Addiction: Bringing understanding toward appreciation of a mental disorder. In: Gazzaniga, MS., editor. The Cognitive Neurosciences. 5th edn. MIT Press; 2013. in press
2. Lopez-Quintero C, et al. Probability and predictors in transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 2011; 115:120–130. [PubMed: 21145178]
3. Kendler KS, et al. Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. Nat. Neurosci. 2012; 15:181–189. [PubMed: 22281715]
4. Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. Am. J. Psychiatry. 2003; 160:636–645. [PubMed: 12668349]
5. Bearden CE, Freimer NB. Endophenotypes for psychiatric disorders: ready for primetime? Trends Genet. 2006; 22:306–313. [PubMed: 16697071]
6. Levy Y, Ebstein RP. Research review: crossing syndrome boundaries in thesearch for brain endophenotypes. J. Child. Psychol. Psychiatry. 2009; 50:657–668. [PubMed: 19175806]
7. Wise RA. Dopamine, learning and motivation. Nat. Rev. Neurosci. 2004; 5:483–494. [PubMed: 15152198]
8. Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. Neuron. 2012; 76:470–485. [PubMed: 23141060]
9. Depue RA, Collins PF. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behav. Brain Sci. 1999; 22:491–517. [PubMed: 11301519]
10. Depue RA, et al. Dopamine and the structure of personality: relation of agonist-induced dopamine activity to positive emotionality. J. Pers. Soc. Psychol. 1994; 67:485–498. [PubMed: 7965602]
11. Depue RA, Fu Y. On the nature of extraversion: variation in conditioned contextual activation of dopamine-facilitated affective, cognitive, and motor processes. Front. Hum. Neurosci. 2013; 7:288. [PubMed: 23785330]
12. Taylor JR, et al. Spontaneous blink rates correlate with dopamine levels in the caudate nucleus of MPTP-treated monkeys. Exp. Neurol. 1999; 158:214–220. [PubMed: 10448434]
13. Fitzgerald P, Dinan TG. Prolactin and dopamine: what is the connection? A review article. J. Psychopharmacol. 2008; 22:12–19. [PubMed: 18477617]

14. Volkow ND, et al. High levels of dopamine D2 receptors in unaffected members of alcoholic families: possible protective factors. Arch. Gen. Psychiatry. 2006; 63:999–1008. [PubMed: 16953002]
15. Baik SH, et al. Extraversion and striatal dopaminergic receptor availability in young adults: an [18F]fallypride PET study. Neuroreport. 2012; 23:251–254. [PubMed: 22257904]
16. Treadway MT, et al. Dopaminergic mechanisms of individual differences in human effort-based decision-making. J. Neurosci. 2012; 32:6170–6176. [PubMed: 22553023]
17. Volkow ND, et al. Addiction: beyond dopamine reward circuitry. Proc. Natl. Acad. Sci. USA. 2011; 108:15037–15042. [PubMed: 21402948]
18. Wills TA, et al. Activity and mood temperament as predictors of adolescent substance use: test of a self-regulation mediational model. J. Pers. Soc. Psychol. 1995; 68:901–916. [PubMed: 7776186]
19. Wills TA, et al. Sandy JM, Yaeger A, Shinar O. Family risk factors and adolescent substance use: moderation effects for temperament dimensions. Dev. Psychol. 2001; 37:283–297. [PubMed: 11370906]
20. Trifilieff P, Martinez D. Imaging addiction: D(2) receptors and dopamine signaling in the striatum as biomarkers for impulsivity. Neuropharmacology. 2014; 76(PtB):498–509. [PubMed: 23851257]
21. Volkow ND, et al. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology. 2009; 56(Suppl 1):3–8. [PubMed: 18617195]
22. Volkow ND, et al. Positive emotionality is associated with baseline metabolism in orbitofrontal cortex and in regions of the default network. Mol. Psychiatry. 2011; 16:818–825. [PubMed: 21483434]
23. Volkow ND, et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature. 1997; 386:830–833. [PubMed: 9126741]
24. Martinez D, et al. Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. Am. J. Psychiatry. 2007; 164:622–629. [PubMed: 17403976]
25. Colzato LS, et al. Reduced spontaneous eye blink rates in recreational cocaine users: evidence for dopaminergic hypoactivity. PLoS One. 2008; 3:e3461. [PubMed: 18941515]
26. Thompson J, et al. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics. 1997; 7:479–484. [PubMed: 9429233]
27. Pohjalainen T, et al. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol. Psychiatry. 1998; 3:56–60.
28. Ozkaragoz T, Noble EP. Extraversion. Interaction between D2 dopamine receptor polymorphisms and parental alcoholism. Alcohol. 2000; 22:139–146. [PubMed: 11163121]
29. Lee HJ, et al. D2 and D4 dopamine receptor gene polymorphisms and personality traits in a young Korean population. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2003; 121B:44–49. [PubMed: 12898574]
30. Cohen MX, et al. Individual differences in extraversion and dopamine genetics predict neural reward responses. Brain Res. Cogn. Brain Res. 2005; 25:851–861. [PubMed: 16289773]
31. Wang F, et al. A large-scale meta-analysis of the association between the ANKK1/DRD2 Taq1A polymorphism and alcohol dependence. Hum. Genet. 2013; 132:347–358. [PubMed: 23203481]
32. Nader MA, et al. Positron emission tomography imaging studies of dopamine receptors in primate models of addiction. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2008; 363:3223–3332. [PubMed: 18640923]
33. Everitt BJ, et al. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2008; 363:3125–3135. [PubMed: 18640910]
34. Lucantonio F, et al. The impact of orbitofrontal dysfunction on cocaine addiction. Nat. Neurosci. 2012; 15:358–366. [PubMed: 22267164]
35. Phan KL, et al. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol. Psychiatry. 2005; 57:210–219. [PubMed: 15691521]

36. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am. J. Psychiatry. 2007; 164:476–488.
37. Kim MJ, Whalen PJ. The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. J. Neurosci. 2009; 29:11614–11618. [PubMed: 19759308]
38. Cremers HR, et al. Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. Neuroimage. 2010; 49:963–970. [PubMed: 19683585]
39. Terracciano A, et al. Five-Factor Model personality profiles of drug users. BMC Psychiatry. 2008; 8:22. [PubMed: 18405382]
40. Kotov R, et al. Linking “big” personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychol. Bull. 2010; 136:768–821. [PubMed: 20804236]
41. Ersche KD, et al. Cognitive dysfunction and anxious-impulsive personality traits are endophenotypes for drug dependence. Am. J. Psychiatry. 2010; 169:926–936. [PubMed: 22952072]
42. Lesch KP, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science. 1996; 274:1527–1531. [PubMed: 8929413]
43. Caspi A, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 301:386–389. [PubMed: 12869766]
44. Hariri AR, et al. Serotonin transporter genetic variation and the response of the human amygdala. Science. 2002; 297:400–403. [PubMed: 12130784]
45. Pezawas L, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat. Neurosci. 2005; 8:828–834. [PubMed: 15880108]
46. Aron AR, et al. Inhibition and the right inferior frontal cortex. Trends Cogn. Sci. 2004; 8:170–177. [PubMed: 15050513]
47. Aron AR, et al. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J. Neurosci. 2007; 27:3743–3752. [PubMed: 17409238]
48. Swann NC, et al. Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: electrophysiological responses and functional and structural connectivity. Neuroimage. 2012; 59:2860–2870. [PubMed: 21979383]
49. Tabibnia G, et al. Different forms of self-control share a neurocognitive substrate. J. Neurosci. 2011; 31:4805–4810. [PubMed: 21451018]
50. Ersche KD, et al. Abnormal brain structure implicated in stimulant drug addiction. Science. 2012; 335:601–604. [PubMed: 22301321]
51. González S, et al. Dopamine D4 receptor, but not the ADHD-associated D4.7 variant, forms functional heteromers with the dopamine D2S receptor in the brain. Mol. Psychiatry. 2012; 17:650–662. [PubMed: 21844870]
52. Kang AM, et al. Global variation of a 40-bp VNTR in the 3′-untranslated region of the dopamine transporter gene (SLC6A3). Biol. Psychiatry. 1999; 46:151–160. [PubMed: 10418689]
53. Cornish KM, et al. Association of the dopamine transporter (DAT1) 10/10-repeat genotype with ADHD symptoms and response inhibition in a general population sample. Mol. Psychiatry. 2005; 10:686–698. [PubMed: 15809660]
54. Congdon E, et al. Analysis of DRD4 and DAT polymorphisms and behavioral inhibition in healthy adults: implications for impulsivity. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2008; 147B:27–32. [PubMed: 17525955]
55. Lee B, et al. Striatal dopamine D2/D3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. J. Neurosci. 2009; 29:14734–14740. [PubMed: 19940168]
56. Ghahremani DG, et al. Striatal dopamine D2/D3 receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. J. Neurosci. 2012; 32:7316–7324. [PubMed: 22623677]
57. Insel T, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry. 2010; 167:748–751. [PubMed: 20595427]

58. MacQueen DA, et al. Variation in the α5 nicotinic acetylcholine receptor subunit gene predicts cigarette smoking intensity as a function of nicotine content. Pharmacogenomics J. 2013 doi: 10.1038/tpj.2012.50.
59. Flint J, Munafò MR. Candidate and non-candidate genes in behavior genetics. Curr. Opin. Neurobiol. 2013; 23:57–61. [PubMed: 22878161]
60. Manolio TA. Bringing genome-wide association findings into clinical use. Nat. Rev. Genet. 2013; 14:549–558. [PubMed: 23835440]
61. Visscher, PM. Nat. Genet. Vol. 40. Psychological Assessment Resources; Odessa, FL: 2008. Sizing up human height variation; p. 489-490.
62. Hall FS, et al. Implications of genome wide associationstudies for addiction: are our a priori assumptions all wrong? Pharmacol. Ther. 2013; 140:267–279. [PubMed: 23872493]
63. Tellegen, A. Unpublished manuscript. University of Minnesota; Minneapolis: 1982. Brief Manual for the Differential Personality Questionnaire.
64. Costa, PT.; McCrae, RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory Professional Manual. 1992.
65. Tellegen, A. Structures of mood and personality and their relevance to assesing anxiety, with emphasis on self-report. In: Tuma, AH.; Maser, JD., editors. Anxiety and the Anxiety Disorders. Erlbaum; 1985. p. 681-706.
66. Clark, LA.; Watson, D. Temperament: An organizing paradigm for trait psychology. In: Pervin, LA.; John, OP., editors. Handbook of Personality: Theory and Research. 2nd edn. Guilford; 1999. p. 399-423.
67. Church AT. Relating the Tellegen and five-factor models of personality structure. J. Pers. Soc. Psychol. 1994; 67:898–909. [PubMed: 7983581]
68. Tellegen A, et al. Personality similarity in twins reared apart and together. J. Pers. Soc. Psychol. 1988; 54:1031–1039. [PubMed: 3397862]
69. Jang KL, et al. Heritability of the big five personality dimensions and their facets: a twin study. J. Pers. 1996; 64:577–591. [PubMed: 8776880]
70. Krueger RF. The structure of common mental disorders. Arch. Gen. Psychiatry. 1999; 56:921–926. [PubMed: 10530634]
71. Krueger RF. Personality traits in late adolescence predict mental disorders in early adulthood: a prospective-epidemiological study. J. Pers. 1999; 67:39–65. [PubMed: 10030020]
72. Krueger RF. Phenotypic, genetic, and nonshared environmental parallels in the structure of personality: a view from the multidimensional personality questionnaire. J. Pers. Soc. Psychol. 2000; 79:1057–1067. [PubMed: 11138754]
73. Moeller FG, et al. Psychiatric aspects of impulsivity. Am. J. Psychiatry. 2001; 158:783–1793. [PubMed: 11329402]
74. Dalley JW, et al. Impulsivity, compulsivity, and top-down cognitive control. Neuron. 2011; 69:680–694. [PubMed: 21338879]
75. Kjome KL, et al. Relationship between impulsivity and decision making in cocaine dependence. Psychiatry Res. 2010; 178:299–304. [PubMed: 20478631]
76. Gerfen CR, Surmeier DJ. Modulation of striatal projection systems by dopamine. Annu. Rev. Neurosci. 2011; 34:441–66. [PubMed: 21469956]
77. Obeso JA, et al. Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. Mov. Disord. 2008; 23(Suppl 3):S548–S559. [PubMed: 18781672]
78. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 1996; 29:162–173. [PubMed: 8812068]

**Box 1**

## Psychiatric genetics

Traditional methods used in psychiatric genetics include genome wide association studies (GWAS) and the search for candidate genes [3]. The candidate gene approach is hypothesis driven, studying genes thought to be involved in a CNS disorder, such as a single nucleotide polymorphism (SNP; *genetic polymorphism* is a synonym for *common genetic variant*, referring to the co-occurrence in the same population of two or more genetically determined phenotypes, in such proportions that the rarest of them cannot be maintained merely by recurrent mutation) that is likely to influence some specific neurotransmission. Several polymorphisms (often with allelic frequencies above 10% in the general population) have been found and claimed to increase vulnerability to SUD [3]. Among the most robust findings is an association between a polymorphism of the $\alpha_5$ nicotinic acetylcholine receptor gene (rs16969968 genotype) and vulnerability to nicotine addiction [58]. However, most studies have yielded associations difficult to replicate [2,59].

GWAS is a hypothesis-free method which tests for the presence of genetic association throughout the genome, whether variation in any of the ~20,000 human genes might contribute to disease susceptibility or other individual differences. GWAS analyzes from several hundred to more than a million SNPs in thousands of individuals, representing a powerful tool for investigating the genetic architecture of complex diseases or traits [60]. A first general conclusion from GWAS is that most polymorphisms confer little risk increments and explain only a small proportion of heritability. For example, more than 40 loci have been associated with human height, a complex trait with a heritability of about 80%, but those variants can only explain about 5% of the phenotypic variance [61]. One main problem with GWAS is the need for a level of multiple statistical comparisons that are unprecedented in biology, with stringent analyses demanding individual SNPs with extremely low *p* values to achieve genome-wide significance [62]. Nevertheless, novel GWAS approaches aimed at decreasing false negative results are enhancing confidence in SUD-gene associations (e.g., identification of multiple SNP markers in each locus and replication across multiple samples and multiple marker densities) [62] and are uncovering possible associations not previously identified by candidate gene studies (such as genes for cell adhesion molecules) [62].

**Box 2**

### Relationship of the structure of personality and structure of adult psychopathology

The most popular models of personality are the big-three and big-five models, operationalized by the Multidimensional Personality Questionnaire (MPQ) [63] and the revised NEO Personality Inventory (NEO-PI-R) [64], respectively. MPQ includes 11 primary trait scales that coalesce around three orthogonal higher-order factors: Positive Emotionality (PEM), Negative Emotionality (NEM), and Constraint (CON) [63,65,66]. The PEM and NEM dimensions are explicitly temperamental in nature. They incorporate dispositions toward positive and negative emotions, respectively, and are linked conceptually to the brain systems underlying appetitive-approach and defensive-withdrawal behaviors. CON encompasses traits related to the construct of behavioral restraint, behavioral control; the other end of the spectrum implies disinhibition or impulsive action. NEO-PI-R [64] consists of 30 facets, six for each five higher-order factors: Neuroticism (N), Extraversion (E), Openness (O), Agreeableness (A) and Conscientiousness (C). N and E highly correlate with NEM and PEM [66,67], basically constituting the same personality constructs. ‘O’ means openness to experience and ‘A’ implies an empathic personality. Finally, ‘C’ implies persistence. ‘C’ appears to be most similar to CON, but also includes elements of ‘O’ and ‘A’ [64].

Behavior genetic studies have demonstrated substantial heritability from the various traits assessed by MPQ and NEO-PI-R. For all higher-order factors of the big-three and big-five models, the broad genetic influence ranges between 40% and 60% [68,69]. Several studies have linked the structure of psychopathology to the structure of personality as defined by the MPQ or NEO-PI-R. Krueger [70] factor analyzed patterns of comorbidity among mental disorders and reported evidence for two broad dimensions in psychopathology: an ‘internalizing’ dimension, encompassing anxiety and depression, and an ‘externalizing’ dimension, encompassing SUD and antisocial behavior. Krueger also demonstrated that the internalizing and externalizing dimensions were correlated positively with NEM, and the externalizing dimension was correlated negatively with CON [71,72]. Using the big-five higher order traits plus CON, a recent meta-analysis of the relationship between anxiety, depression and SUD identified high ‘N’ as a common trait, with CON specifically low in SUD [40].

**Box 3**

### Decomposing the concept of impulsivity

Impulsivity is defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the individual or others [73]. Embedded in this definition is the fact that impulsivity is a complex construct, which includes at least two different components: 'impulsive action' and 'impulsive choice'. Impulsive action can be operationally defined as a failure of motor inhibition (disinhibition), a failure of volitional motor control, the opposite of constraint (CON; see Box 2 and text), while impulsive choice implies a tendency to accept small immediate or likely rewards in favor of large delayed or unlikely ones [74]. Impulsive choice overlaps conceptually with impairment in decision-making [34]. Several clinical studies support the existence of the two-component impulsivity construct in the pathogenesis of SUD. In cocaine-dependent subjects, there is no correlation in the measurements of decision-making and behavioral inhibition, underscoring the notion that the two constructs are independent, and can be differentially affected in SUD [75].

Impulsive choice in SUD individuals correlates with impaired function of prefrontal cortical areas, such as the orbitofrontal cortex (OFC) [17]. In fact, low metabolism in OFC and anterior cingular cortex (ACC) is a persistent finding in these subjects, which correlates with a reduced striatal dopamine $D_2$ receptor availability [17,21]. We postulate that reduced function of striatal postsynaptic $D_2$ receptors (either premorbid or drug-induced) is the initial mechanism that leads to a low metabolism and function of OFC/ACC, by reducing the thalamo-cortical disinhibition induced by tonic activation of postsynaptic inhibitory $D_2$ receptors, localized in GABAergic striato-pallidal neurons [76,77].

## Highlights

- Clear evidence supports a genetic basis for Substance Use Disorders (SUD).
- The search to identify individual gene contributions to SUD has been unsuccessful.
- Three high-order personality traits can be used as endophenotypes for SUD.
- These personality traits are tied to specific brain systems and genes.
- These brain systems determine vulnerability or resilience to developing SUD.

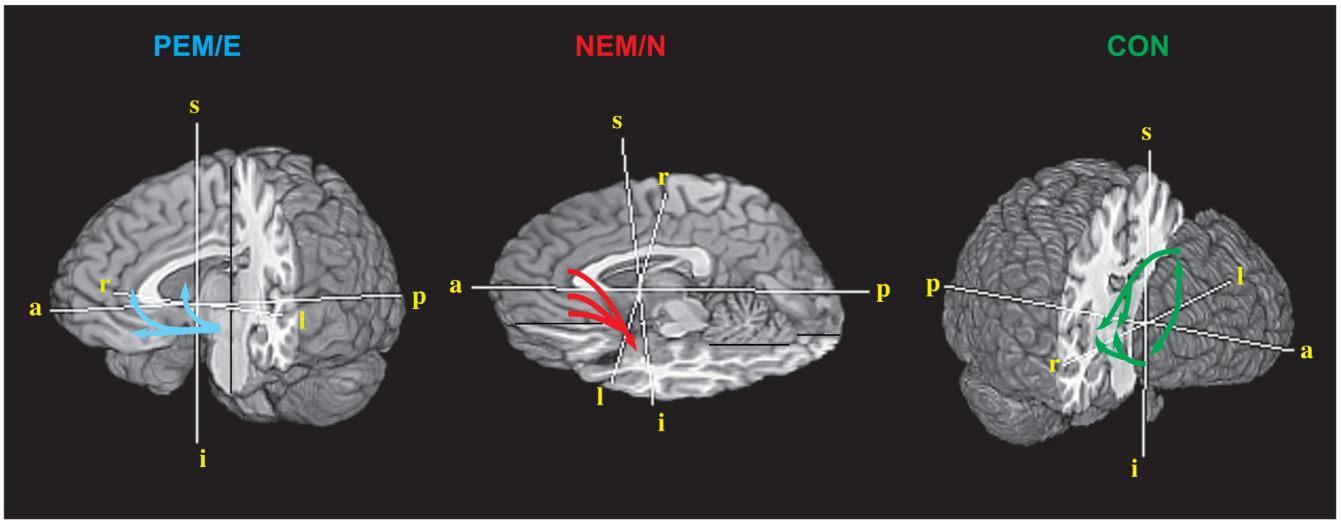


**Figure 1. Brain systems involved in dimensions of personality**

Three putative systems involved in personality are schematized, with major output and input brain regions designated by the arrows: (i) Positive Emotionality/Extraversion (PEM/E), which includes the ascending dopaminergic system originating from the mesencephalon and innervating the striatum, rostral anterior cingulate (rACC) cortex, and ventromedial prefrontal cortex (vmPFC); (ii) Negative Emotionality/Neuroticism (NEM/N), which incorporates glutamatergic outputs from the rACC and vmPFC to the amygdala and insula (insula not shown); and (iii) Constraint (CON), which involves a circuit from the pre-Supplementary Motor Area (preSMA) and right Inferior Frontal Gyrus (rIFG) to the striatum and the subthalamic nucleus (STN). All images were created in AFNI [78] with the Tailarach-Tournoux template of the human brain. Directional axes are centered at the 0-origin of the template, and designate the superior (s), inferior (i), left (l), right (r), anterior (a) and posterior (p) directions.

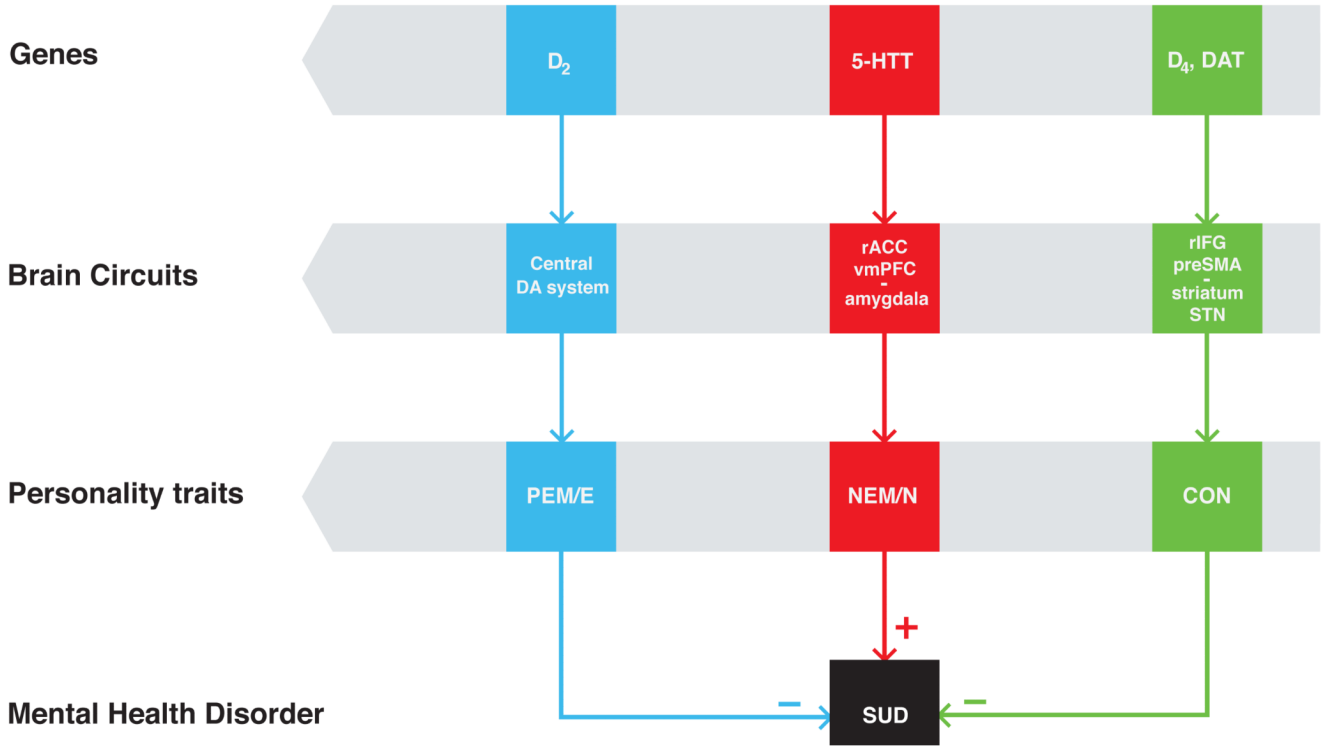


**Figure 2. Personality traits as endophenotypes of SUD**

High Negative Emotionality/Neuroticism (NEM/N) increases, while high Constraint (CON) and high Positive Emotionality/Extraversion (PEM/E) decreases, vulnerability to SUD. We can link genes to these personality traits and to the brain circuits that modulate these traits, which can therefore be used as endophenotypes of SUD. PEM/E is modulated by the function of the central dopaminergic system and is moderated by the $D_2$ receptor gene. NEM/N is modulated by the glutamatergic outputs from the right anterior cingulate cortex (rACC) and ventromedial prefrontal cortex (vmPFC) to the amygdala and insula and is moderated by the serotonin transporter (5-HTT) gene. CON is modulated by a circuit including the pre-Supplementary Motor Area (preSMA) and right Inferior Frontal Gyrus (rIFG) to the striatum and the subthalamic nucleus (STN) and is moderated by the genes of the $D_4$ receptor and the dopamine transporter (DAT).