RUNNING HEAD: IMPLICIT COGNITION

Chapter x

Implicit Cognition: An Intermediate Phenotype for Addiction?

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3. Genetics and Implicit Cognition (and Executive Control)

3.1 Findings on genetic variation and implicit cognition

Any relationship between genetic factors and implicit cognition would be expected to be indirect – for instance, it seems unlikely that a genetic variant would be associated with automatically attending bottles of beer. Various types of implicit cognition may well involve common genetic influences, and different genetic pathways may result in common cognitive biases. Genetic variants in several genes have been found to be associated with addiction. Although the functional pathways via which these genetic variants increase the risk for addiction remain to be further elucidated we will propose a theoretical framework for the role of the genes involved in addiction-related implicit cognition (see Figure 1). We identify and briefly discuss three broadly defined, interconnected pathways: i) variations related to the acute hedonic value[1] of potentially addictive substances or behavior (or "addictors" for short); ii) variations related to emotion regulation that indirectly affect negative reinforcement value; and iii) variations related to reward (in)sensitivity that affect positive reinforcement value. These pathways may provide a foundation for understanding findings concerning genetic variation and addiction-related implicit cognition. Subsequently, we tentatively link these pathways to the few existing studies directly relating genetic variation to implicit cognition.

3.2 Genetic variations related to the acute hedonic value of potentially addictive substances or behavior

[1] While the term "hedonic" suggests that the strength of positive feelings following the addictor is crucial, research on expectancies (29) and implicit associations (69, 70) suggests that addictors are associated with a combination of positive and arousing feelings.

First, genetic variation can impact the metabolism of addictive substances, and thereby the extent to which their use will be reinforcing, which will impact the associations between cues signaling the drug and reward. A well-known example is the set of *ADH* and *ALDH* genes, which code for enzymes involved with alcohol metabolism. Certain alleles of these genes are associated with facial flushing and other aversive effects as a consequence of drinking alcohol, and, accordingly, have been shown to be protective against alcoholism in various populations (133, 134). Single Nucleotide Polymorphisms (SNPs) in the *GABRA2* gene associated with alcoholism (135) are also associated with weaker subjective sensations (such as "getting high") due to alcohol consumption (136), possibly due to relatively weak signals to stop drinking.

3.3 Genetic variants related to negative reinforcement

The second pathway concerns negative reinforcement. Genetic variants related to the serotonin transporter gene *SLC6A4* (also referred to as 5-HTT)(137) and the brain-derived neurotrophic factor (*BDNF*)(138) gene appear to be related to general stress sensitivity, for instance such that they influence the chance that childhood adversity will lead to depression (139, 140). The "short" repeat of a stress-related polymorphism of the promotor region of the SCL6A4 gene (5-HTTLPR), results in slower reuptake of serotonin and hence desensitization of serotonin receptors, and is also related to higher sensitivity to nicotine withdrawal (141), which would seem likely to be due to an enhancement of the acute effect of smoking in terms of negative reinforcement. Indeed, the 5-HTT short-allele has been shown to interact with stress to predict alcohol and drug use in college students (142). Further, two different polymorphisms related to serotonin, which are located in the *HTR2C* (also referred to as *5-HT(2C))* gene, have been found to affect the odds of smoking initiation (143).

The *BDNF* gene is involved in neuronal growth and differentiation, and has a Val/Met polymorphism (Val66Met) in which the Met allele is associated with more robust fear and anxiety behavior in mice (144, 145), and anatomically with smaller amygdala and hippocampus volume in humans (146), possibly due to reduced BDNF production associated with the Met allele. Concerning its relationship to addiction, low *BDNF* serum levels are associated with an increased chance of addiction to cocaine (147), methamphetamine (148), and the severity of alcohol withdrawal (149). In line with these findings, the MET variant of the *BDNF* gene is associated with violence and delirium tremens in addiction. We note that changes in BDNF protein levels over time, as opposed to variation over subjects, are also related to addiction: craving is associated with increases in *BDNF* protein levels, and *BDNF* protein levels rise after abstinence (150), possibly reflecting the activation of mechanisms related to drug-seeking (151).

3.4 Genetic variants related to positive reinforcement value

Genetic variation may affect addictor-sensitivity via acute effects involving enhanced positive reinforcement. Such enhancement has been argued to result from dopaminergic deficiencies, for which the stimulatory effects of addictive drugs on the endogenous opioid system can compensate (152). Low dopamine (DA) receptor density is associated with various clinical disorders as well as with personality characteristics such as novelty seeking (153) and approach tendencies (154). Genetic polymorphisms in the *ANKK1* gene (TaqI A and B) have been associated with low receptor density as well as with alcohol addiction, specifically a severe form of addiction, obesity, and addiction to other substances including cocaine (152, 155). In addition, the Taq1A polymorphism has been suggested to interact with parental rule-setting regarding adolescent alcohol use (156, 157). The Taq1A and B polymorphisms

are also in strong linkage disequilibrium (LD) with the D2 dopamine receptor (*DRD2*) gene and were previously considered to be in the promotor region of *DRD2*. Due to the strong LD in this region, it is unclear whether associations between clinical disorders and Taq1A and B polymorphisms indicate the involvement of *ANKK1* or *DRD2*.

A polymorphism (-521 C/T) in the promotor region of the dopamine D4 receptor (*DRD4*) gene has been found to affect novelty seeking in a meta-analysis (153). Reduced receptor density may result in increased novelty seeking or related personality changes, which has been proposed as a consequence of DA genetic variation that may mediate increased risk for drug use (158, 159). Some studies have found evidence for a role of the 7-repeat VNTR polymorphism in *DRD4* in novelty seeking and approach behavior, but these relationships were found to have relatively weak evidence in meta-analyses (153, 154). However, there are indications that the *DRD4* 7-repeat VNTR may involve more general processes, such as tendency to imitate, which would only lead to heavy drinking in the presence of heavy drinking peers (160), in line with the idea of plasticity genes (161).

A similar pathway involving positive reinforcement involves genetic variation in a gene coding for the mu-opioid receptor. The A118G polymorphism of the *OPRM1* gene has been shown to confer functional differences to mu-opioid receptors, such that the G allele binds beta-endorphin three times more strongly than the A allele. The G allele of this polymorphism has been shown to be associated with relatively strong craving for alcohol (162, 163) and with relatively strong automatically activated approach tendencies to alcohol and other appetitive stimuli (103), assessed with the alcohol-AAT (as discussed above). An fMRI study showed relatively strong reactions to alcohol in mesolimbic areas, both for carriers of the

OPRM1 G-allele and for carriers of the *DRD4* 7+ repeat VNTR (164). In a recent PET study, smokers with the G-allele of the *OPRM1* gene were found to have reduced receptor availability of opioid receptors in brain regions involved with reinforcement (165). The relationship between *OPRM1* and addiction may thus, similarly to DRD genes, reflect an enhanced positive reinforcement of drug use due to a baseline deficiency in the reward system. Of possible interest is the disinhibitory effect of mu-opioid receptors on dopamine release, suggesting a possible interaction with dopamine-related aspects of addiction.

3.3 Modulating influences via executive functions

Modulating effects involving the above biological network concern the executive control functions (ECFs). As discussed above, relatively strong ECFs concerns a protective factor in addiction: less impulsive individuals are less likely to develop addiction, and stronger ECFs appears to "uncouple" automatic addictor-related associations from behavior (35, 110, 112, 113, 116, 117). ECFs are highly heritable (166, 167). There are indications that the Val158Met polymorphism of the catechol-O-methyltransferase (*COMT*) gene may explain part of the genetic variation. *COMT* is involved with the clearance of prefrontal dopamine, the Met allele is associated with relatively low enzyme activity, and hence an increase in tonic dopamine levels and decrease in dopamine sensitivity compared to the Val allele. Individuals carrying a Met versus Val allele have better ECFs (168) and more efficient prefrontal processing (i.e., more deactivation) during tasks that tax ECFs (169). The effect of the COMT variations appear to be specific to ECFs as opposed to component processes such as attention or short term memory capacity without executive components (168, 170). Interestingly, the negative effects of the Val-allele of the *COMT* gene appear to

be modifiable via methylation (171), which could be an interesting epigenetic effect from the present perspective (see for a review on epigenetic effects in addiction, 172).

3.4 Implicit cognition as an endophenotype?

While current evidence is scarce and indirect, we suggest that the pathways described above may connect various genetic variations influences to implicit cognition in addiction. Initial findings have connected some of the above genes to some forms of addiction-related implicit cognitive processes. Genetic influences involving attentional bias for alcohol have been found in a study with young adolescents and young adults (177). A dot probe task with alcoholic drinks and soft drinks was used to assess attentional bias to alcohol pictures. The risk variant in the *OPRM1* gene (the G-allele) was associated with a relatively strong attentional bias for alcohol in young adolescents, while the *DRD4* *DRD4* 7+ repeat VNTR was found to be associated with an attentional bias for alcohol in young adults. While we know of no other study relating attentional bias for alcohol to genetic factors, it should be noted that in research on anxiety, one of the above sources of genetic variation – serotonin-related polymorphisms related to stress - has been associated with attentional bias for emotional stimuli (178-181), see for a meta-analysis (182). A stronger attentional bias could be explained from increased emotional salience of stimuli and thereby a stronger influence on learning processes. It is well possible that in a subgroup of individuals with an attentional bias for threatening stimuli, this bias is coupled with a bias to approach alcohol (as a way to cope with the stress). Similar processes could influence the development of automatic associations, in two ways matching the basic dichotomy of internalizing and externalizing pathways to addiction. Interactions involving genes and implicit cognition have also been found for implicit memory associations (183). Only for subgroups with high-risk variants in *ALDH2* or *COMT*,

were alcohol-coping associations (assessed with an IAT, see above) predictive of drinking behavior. Finally, as mentioned above, the risk variant of a polymorphism in the *OPRM1* gene has been found to be related to relatively strong automatic approach tendencies for alcohol and other appetitive stimuli in male heavy drinkers (103). Hence, individuals for whom drug use compensates for a genetic lack of sensitivity to normal reinforcement would form a group at risk for developing addiction-related approach tendencies. Individuals with a genetic tendency to experience strong negative emotions could experience greater reinforcement for drug use because it helps them avoid those emotions. In both cases, individuals with strong executive function would be better able to overcome the effects of these tendencies (see Figure 1).

To account for interactions between the various influences that are likely involved in addictive behaviors, an endophenotype for addiction would have to be defined in terms of constellations of pathways, with the common result of a tendency to develop difficult-to-control implicit cognitions directed towards addictive behaviors. There are two such constellations which we argue should be distinguished: the positive and negative reinforcement endophenotype. The positive endophenotype revolves around heritable biological deficits that drug use ameliorates (e.g., decreased ability for dopaminergic stimulation), while the core of the negative endophenotype is a general stress vulnerability that confers added negative reinforcement value on the acute effects of drugs. For example, coping drinking would be considered an expression of the latter pathway, and would be expected to be associated with different genes than individuals with different drinking motivation. On the other hand, other genetic factors would be expected to have common effects in either

endophenotype: genetic variation that renders drug metabolism aversive should always be protective, as would factors that increase ECFs.

4. Conclusion

From an implicit cognition or dual-process perspective, the endophenotype for addiction vulnerability would consist of a set of interrelated genetically influenced factors: (1) non-aversive metabolism of the addictor; (2) enhanced (positive or negative) reinforcement of acute effects; (3) relatively weak ECFs. The "perfect storm" would involve all factors working towards a tendency to addiction. This vulnerability would be expected to be expressed at a behavioral level as a common endophenotype, defined in terms of automaticity development: the ease with which hard-to-control cognitive biases arise from addictor-related reinforcement. The measurement of such an endophenotype would require novel methods for detecting such vulnerability, possibly involving experimentally controlled tests of automaticity development (for an example of such an approach, see 184). From the perspective sketched above, research focusing on genetic variation and implicit cognition, and in particular the development of implicit cognitive processes, may be highly relevant to understanding the biological basis of the vulnerability to addiction.

We briefly note that genetic influences on neural plasticity may well modulate many of the pathways discussed above. The hippocampus has been linked to associative processes supporting addiction in animal studies: stimulation of the hippocampus reinstates cocaine seeking after extinction (173) and suppression of hippocampal activity reduces cue-evoked cocaine seeking (174). As neural plasticity in the hippocampus is heritable, related genes may influence vulnerability for addiction via associative processes. Further, variations in dopamine transporter (*DAT1*) and receptor (*DRD4*) genes (175) and *COMT* (176) may play a role in

plasticity via effects on error-related feedback processing; variants leading to either very high or very low dopamine availability appear to cause increased reactivity to errors (176). If these effects on errors could be generalized to include unexpected consequences in general, such variation may affect learning processes caused by the acute effects of addictive substances or experiences.

A particularly important application of the development of an endophenotype in terms of implicit cognition would be targeted interventions. If it is known what type of vulnerability has likely led to an individuals' addiction, this may indicate which type of implicit cognition to target in interventions. For example, the patients with relatively strong automatically activated approach-tendencies may benefit most from approach bias re-training (108), and it is an interesting question whether patients could better be selected with respect to the strength of their approach tendencies or with respect to the associated genetic factor (presence of the *OPRM1* G-allele). Similarly, patients with weak working memory capacity could benefit more from a specific training, either aimed at increasing their working memory (130) or aimed at changing their dysfunctional automatic cognitive processes, as has been found in the domain of anxiety (185). In this domain, a first study also found genetic moderation of trainability: individuals with a low-expression form (S/S, S/Lg, or Lg/Lg) of the *SCL6A4* (5-HTTLPR) gene developed stronger biases for both negative and positive affective pictures through attentional re-training compared to those with the high-expression (La/La) form of the gene (186). These first findings can be interpreted as initial support that implicit cognitive processes may constitute a malleable endophenotype in addiction and related disorders. However, clearly more research is needed to critically test this claim and its associated therapeutic consequences. We believe this is an intriguing avenue for further research.

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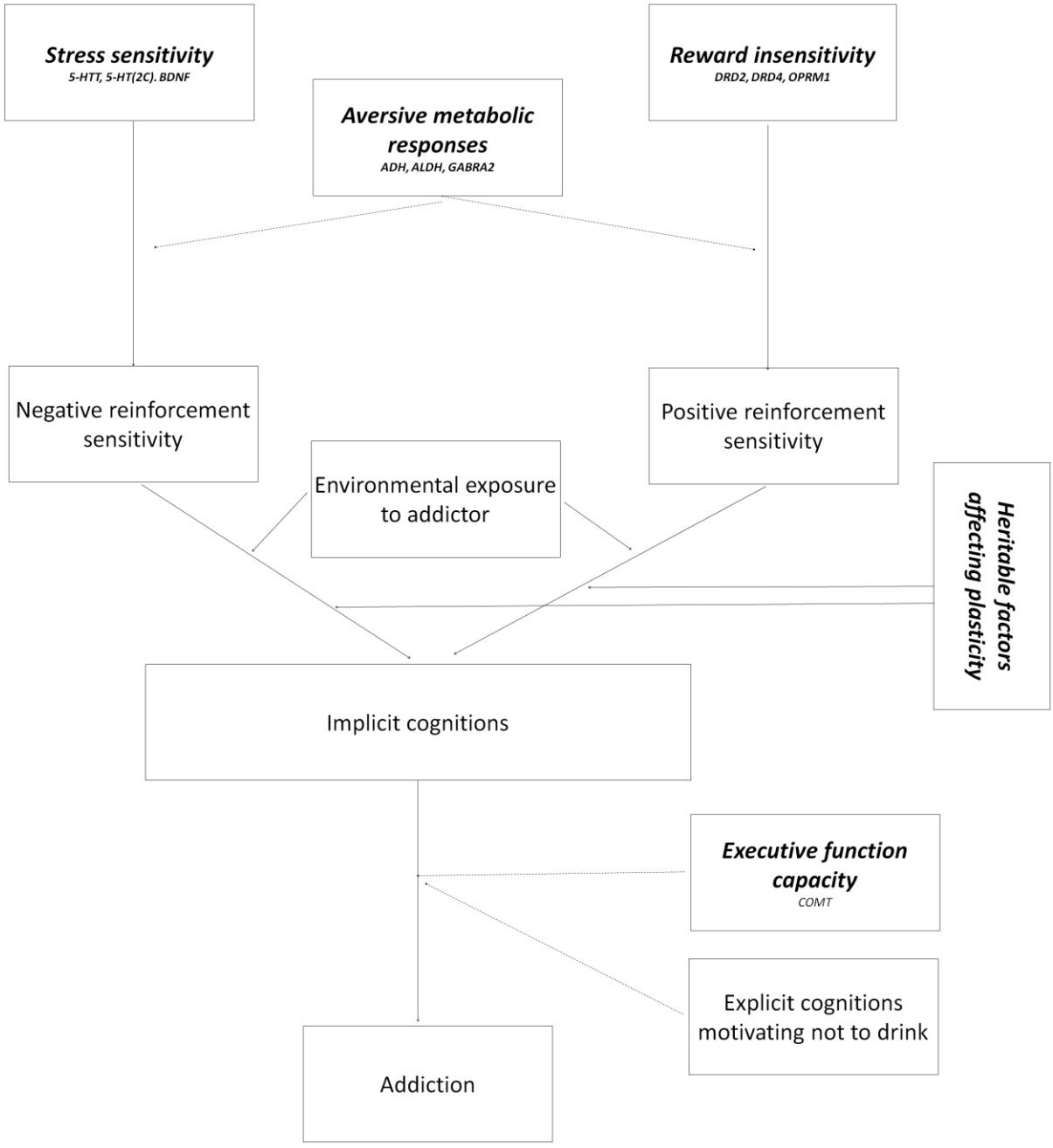
Figure Caption

A heuristic model illustrating possible pathways to addiction, involving implicit cognitive processes.


Stress sensitivity
5-HTT, 5-HT(2C). BDNF
Aversive metabolic responses
ADH, ALDH, GABRA2
Reward insensitivity
DRD2, DRD4, OPRM1
Negative reinforcement sensitivity
Positive reinforcement sensitivity
Environmental exposure to addictor
Heritable factors affecting plasticity
Implicit cognitions
Executive function capacity
COMT
Explicit cognitions motivating not to drink
Addiction