Commentary on Latvala et al (2016)

What can genetic cognitive epidemiology tell us about substance misuse and addiction?

Michelle Luciano [1]

[1] Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, Edinburgh, UK

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Concise statement: Multivariate methods (extending the range of addiction traits and including endophenotypes) and gene functional studies are needed to understand the genetic correlation between cognitive ability and risk of substance misuse. Such studies would enable us to better distinguish between models of biological pleiotropy and mediated pleiotropy.

Latvala et al. (2016) use three diverse family designs to provide evidence for a largely genetic relationship between early cognitive ability and risk of substance misuse. Their finding is in line with the rapidly growing molecular genetic literature which supports an overlap of common genetic variants influencing cognitive ability and a host of psychiatric and physical disorders (1, 2). However, the basis of this genetic association remains speculative. The two main competing hypotheses are: 1) biological pleiotropy, where the same genes have direct effects on each of the correlated traits—cognitive ability and substance misuse—through the same or different biological pathways, and 2) mediated pleiotropy, where genes directly influence one trait and this trait influences the second trait (3).

In a model of biological pleiotropy one might hypothesise that genes influencing executive functioning processes, such as response inhibition, could be candidates for common genetic effects because these measure have been phenotypically associated with cognitive abilities (4) and alcohol/illicit drug use (5). One strategy then would be to focus on endophenotypes of addiction, which are arguably easier to map in terms of biology than the addiction endpoint and are less likely to be direct outcomes of cognitive ability; one might instead consider them components of cognitive ability, which could fit with a model of biological pleiotropy. Ultimately, functional studies of relevant candidate genes are needed to establish mechanism and thus the likelihood of any individual gene having direct effects on both cognitive ability and substance misuse. Given that Latvala et al. (2016) tested a prospective relationship between cognitive ability in young adulthood and later substance misuse, a mediated pleiotropy model should expect the causal direction to be from cognitive ability to substance misuse. This could function via a host of factors, including increased health awareness, internal locus of control, resilience, and positive coping

strategies that might be facilitated by better cognitive processing capacities. The direction of causation between variables can be explicitly tested in twin (6) and Mendelian Randomisation (7) studies assuming key assumptions are met. Such studies, coupled with genetically informative longitudinal studies, will provide further evidence for a particular causal direction. The inclusion of multiple endophenotypes of addiction within a multivariate longitudinal framework has the capacity to increase the reliability and the relations between variables in the analysis (see 8).

Another avenue of research to explore the cognitive ability- substance misuse genetic relationship is to focus on other forms of addiction—both physiological and behavioural. A substance such as caffeine could be particularly informative because it will be subject to less confounding from socio-economic factors, it has fewer negative effects on physical health than alcohol and illicit substances, and may even enhance cognitive ability (e.g., protection against dementia, 9)—so indeed one might observe a positive genetic correlation. Behavioural addictions such as gambling and internet gaming can tell us whether the genetic correlation between cognitive ability and substance misuse is limited to substances with physiological effects, or psychological effects, too. Perhaps these relationships are mediated to a greater extent by the environment; would we uncover the same positive nonshared environmental correlation reported by Latvala et al. (2016) for cognitive ability and substance misuse? The positive nonshared environmental correlation is certainly an interesting finding, could it be related to the personality trait openness to experience with which cognitive ability positively correlates. This trait shows a large contribution of variance from the nonshared environment, although in adolescence this is largely independent of cognitive abilities (10). There is some evidence which shows that people who are more open-minded, liberal and willing to try new experiences are more likely to use some types of

illicit drugs (11). Comparing the environmental covariance between cognitive ability with licit and illicit drug use would help evaluate the strength of such a hypothesis. Latvala et al. (2016) used a combined index of alcohol and illicit drugs in their genetic analysis, but their phenotypic analysis showed a stronger association between cognitive ability and drug-related than alcohol-related medical events; differences in their constituent genetic and environmental variance components (and covariance with cognitive ability) might also exist. To further investigate environmental factors, family designs, such as those used by Latvala et al. (2016) are needed in which cognitive ability and multiple substance use and addiction measures have been sampled; such designs are typically rare but would be valuable to establish. Genetic correlations, on the other hand, can be estimated using genome-wide association results of the measures of interest from independent samples, thus bypassing the need for multiple measures to be collected in a single sample. Large genome-wide studies of cognitive ability (e.g., 12) and some substance use variables (e.g., caffeine, 13) are currently available with others fast following suit. This linkage disequilibrium regression method for establishing genetic correlation will complement family designs by confirming how much shared genetic variance is due to common genetic variation as opposed to rare and/or structural variants.

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