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## Alcohol Dependence: Neuroimaging and the Development of Translational Phenotypes

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Significant advances in the prevention and treatment of alcohol dependence will require a greater understanding of individual differences in the neurobiological mechanisms that underlie the effects of alcohol on the brain. A greater understanding of these mechanisms will allow researchers to identify genetic variation that corresponds to a specific biological vulnerability to substance abuse. However, 1 of the most significant barriers to realizing the promise of the human genome is the lack of translational phenotypes and a translational framework that link changes at the molecular level (e.g., genetic variation), to changes in neuronal function, and ultimately to changes at the behavioral and clinical levels. Translational phenotypes are important for 3 reasons. First, translational phenotypes are biological in nature, and are therefore much more likely to reflect the function of genetic variation as opposed to phenotypes based on DSM IV criteria, which are much more distal to the functional effects of genetic variation. Second, translational phenotypes provide important information about the neurobiological mechanisms that are the targets of medication development. Third, translational phenotypes can be empirically linked to both basic science and the clinical course of addiction. Thus, translational phenotypes can serve as a natural bridge between basic pre-clinical and clinical research as these phenotypes reflect basic mechanisms that are closely tied to the neurobiology of alcohol dependence, relapse, and treatment outcome.

Translational phenotypes can be identified through the use of both animal and human studies that are designed to elucidate the neuroanatomical and pharmacological mechanisms that underlie the etiology of addiction (e.g., Kalivas and Volkow, 2005). Animal models can help identify and evaluate mechanisms on a neuroanatomical and pharmacological level through lesion studies and dose-response studies of new or existing compounds. In humans, functional neuroimaging can be used to examine homologous brain mechanisms in humans and to examine the effect of genetic variation and/or pharmacological compounds on these mechanisms. In humans, the primary advantage of neuroimaging over other approaches is that the phenotype is more directly analogous to the animal models. Therefore, it more directly reflects underlying neurobiological and genetic mechanisms as compared with the subjective self-report or behavioral measures that have historically been employed.

In fact, the integration of genomic and neuroimaging methods has already proven to be very valuable in terms of identifying and translating the function of important genetic variants (Filbey et al., 2006; Glahn et al., 2007; Hariri and Weinberger, 2003; McClernon et al., 2007). Further integration of imaging genomics with the testing of pharmacological compounds will make the approach even more powerful because it allows for an

experimental test of a particular pharmacological mechanism and an evaluation of whether genetic factors predict response to a particular pharmacological compound. Not only does this integration offer a natural extension of animal models, but it also creates the opportunity to link basic science with clinical applications. Ultimately, research on these phenotypes and their underlying genetic variation is directly relevant for the development of new medications and models to guide the matching of medications with individuals most likely to benefit from them.

A number of investigators have been using neuroimaging approaches to identify translational phenotypes related to alcohol dependence (Filbey et al., 2007; Heinz et al., 2007; Tapert et al., 2004; Wrase et al., 2007). Investigators in the alcohol field have begun to emphasize the integration of neuroimaging and genetic approaches (e.g., Boettiger et al., 2007; Heinz et al., 2007; Hutchison et al., in press). This special topic section of ACER features the work of four groups who are developing translational phenotypes based on neuroimaging. Bragulat et al. present a unique approach that involves the combination of intravenous ethanol infusion and the presentation of olfactory cues in the scanner. This study represents a thoughtful approach to investigating the effects of a highly controlled priming dose of ethanol on brain activation in response to alcohol cues. A unique advantage of this approach is that the priming dose is highly controlled with the intravenous infusion, which is likely to yield a phenotype that is sensitive to genetic variation that may influence the effects of ethanol on cue-elicited brain activation. Filbey et al. utilize an approach that involves exposing individuals to the taste of alcohol versus a novel control taste (litchi juice) in the scanner to examine the effects of genetic variations on cue-elicited activation in mesocorticolimbic circuits. In addition, they test the effects of genetic variations before and after an oral priming drink.

Also in this issue, researchers are extending the neuroimaging approach to predictors of alcohol use in adolescents. In a thoughtful discussion on the default network and family history of alcohol use disorders (AUD) in adolescents, Spadoni et al. argue that adolescents with a family history of alcoholism may have greater difficulty moderating the default network in response to cognitive load, which may result in poor neurocognitive function and/or inhibitory control, and thus increased risk for AUD. Finally, in the last feature in this special section, Meyerhoff and Durazzo present a thoughtful review of how magnetic resonance spectroscopy (MRS) and genetics can be combined to study alcohol dependence.

In summary, the integration neuroimaging studies and genetic approaches has great potential for advancing research on alcohol dependence. It is worth noting that, while genetic advances and the genetic tools that drive these advances are developing at a fast pace, these tools are most useful in the context of well-defined, biologically based phenotypes. Phenotypes derived from neuroimaging can be readily integrated with the rapidly expanding repertoire of genetic tools. For example, it is likely that future studies will combine high density genetic arrays and genome wide association with neuroimaging. Based on the studies presented in this special section, the alcohol field is in an excellent position to take advantage of these developments.

## REFERENCES

- Boettiger CA, Mitchell JM, Tavares VC, Robertson M, Joslyn G, D'Esposito M, Fields HL. Immediate reward bias in humans: fronto-parietal networks and a role for the catechol-O-methyltransferase 158(Val/Val) genotype. *J Neurosci* 2007;27:14383–14391. [PubMed: 18160646]
- Filbey FM, Claus ED, Audette AR, Niculescu M, Banich MT, Tanabe J, Du YP, Hutchison KE. Exposure to the taste of alcohol elicits robust activation of the mesocorticolimbic neurocircuitry. *Neuropsychopharmacology* 2008;33:1391–1401. [PubMed: 17653109]

- Filbey FM, Slack KJ, Sunderland TP, Cohen RM. Functional magnetic resonance imaging and magnetoencephalography differences associated with APOEepsilon4 in young healthy adults. *Neuroreport* 2006;17:1585–1590. [PubMed: 17001273]
- Glahn DC, Paus T, Thompson PM. Imaging genomics: mapping the influence of genetics on brain structure and function. *Hum Brain Mapp* 2007;28:461–463. [PubMed: 17471577]
- Hariri AR, Weinberger DR. Imaging genomics. *Br Med Bull* 2003;65:259–270. [PubMed: 12697630]
- Heinz A, Friedel E, Muller DJ, Puls I, Wrase J. Genetic research with intermediate phenotypes: phenocopies, perspectives and pitfalls. *Addiction* 2007;102:1696–1697. [PubMed: 17935576]
- Hutchison KE, Haughey H, Niculescu M, Schacht J, Kaiser A, Stitzel J, Horton WJ, Filbey F. The incentive salience of alcohol: translating the effects of genetic variant in CNR1. *Arch Gen Psychiatry*. 2008 in press.
- Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* 2005;162:1403–1413. [PubMed: 16055761]
- McClernon FJ, Hutchison KE, Rose JE, Kozink RV. DRD4 VNTR polymorphism is associated with transient fMRI-BOLD responses to smoking cues. *Psychopharmacology (Berl)* 2007;194:433–441. [PubMed: 17611740]
- Tapert SF, Brown GG, Baratta MV, Brown SA. fMRI BOLD response to alcohol stimuli in alcohol dependent young women. *Addict Behav* 2004;29:33–50. [PubMed: 14667419]
- Wrase J, Kahnt T, Schlagenhauf F, Beck A, Cohen MX, Knutson B, et al. Different neural systems adjust motor behavior in response to reward and punishment. *Neuroimage* 2007;36:1253–1262. [PubMed: 17521924]