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Section I

Introduction
1 Translational Approaches to Addiction Treatment

Sarah W. Yip, Kathleen M. Carroll, and Marc N. Potenza

I. Background

Addiction is a leading cause of disability worldwide (WHO, 2009). Despite important advances in identification and dissemination of evidence-based treatments (Vocci & Montoya, 2009; Vocci, 2008; Dutra et al., 2008; NIDA, 2012) including behavioral therapies like Contingency Management (CM), Motivational Interviewing (MI), and Cognitive Behavioral Therapy (CBT), the efficacy of these treatments varies significantly across individuals (Dutra et al., 2008; Carroll & Onken, 2005).

In recent years, researchers have increasingly utilized translational approaches to study the neurobiological mechanisms associated with optimal treatment response following psychotherapy for addictive disorders. Such research may be particularly important in the a priori identification of individuals who respond preferentially to specific behavioral interventions. This may be critical in reducing the overall burden of care for both therapist and patient. Similarly, by enhancing the understanding of biological mechanisms associated with positive treatment response, this area of research may help refine existing treatment methodologies and improve treatment efficacy. In this introduction, we will discuss how translational approaches have been applied to the study of addiction and behavioral treatments for these disorders, focusing on functional and structural MRI-based approaches.

II. Functional Magnetic Resonance Imaging (fMRI) and Behavioral Treatments

Functional MRI (fMRI) facilitates the in vivo assessment of changes in regional cerebral blood flow that reflect changes in neural activity
Neuroimaging and Psychosocial Addiction Treatment during different mental states (i.e., during task performance) (Ogawa et al., 1990). This methodology has been applied extensively to study addiction, and the resulting research has identified key brain regions in the development and maintenance of addictive behaviors (see Chapter 2) (Koob & Volkow, 2010; Goldstein & Volkow, 2011; Garavan & Weierstall, 2012). Emerging research suggests that the effectiveness of treatments for addictions may depend on individuals’ ability to engage these circuits. In general, behavioral therapy seeks to enhance ‘top-down’ control over behavior (e.g., strengthening cognitive/behavioral control strategies, curbing impulsive responding, shoring up motivation for abstinence) and, to some extent, diminish ‘bottom-up’ drives (e.g., reducing salience of cues, attending to alternate rewards) (Carroll & Rounsaville, 2006). Both processes may be important for effecting behavioral changes within the context of addiction treatment (Feldstein Ewing & Chung, 2013; Potenza et al., 2011), and data suggests that individual differences in functionally connected networks subserving both top-down and bottom-up processes may be related to treatment outcomes (Worhunsky et al., 2013). Below, we highlight findings from fMRI studies of behavioral treatment interventions as predictors of response to treatment and as indicators of treatment-related change over time.

A. Cognitive Behavioral Therapy and fMRI
While multifaceted, Cognitive Behavioral Therapy (CBT) involves the identification of behavioral and cognitive factors that may promote substance use, along with the learning and practice of cognitive and behavioral control strategies (e.g., limiting exposure to substance-related stimuli, learning to cope with craving) (Carroll, 1998; Carroll & Onken, 2005; Carroll & Rounsaville, 2006). Emerging evidence suggests that pre-treatment neural function within both the dorsolateral and ventrolateral components of the prefrontal cortex (PFC) during performance of a cognitive control task (i.e., Stroop color-word interference test) may relate to treatment outcomes following CBT for cocaine dependence (Brewer et al., 2008) and other substance use disorders (SUDs) (DeVito et al., 2012). This has been hypothesized to relate to the PFC’s role in cognitive control processes. Future studies are needed to determine the extent to which individuals with alterations within top-down neurocircuitry may respond preferentially to CBT versus other behavioral interventions for the treatment of addiction.

B. Motivational Interviewing and fMRI
Motivational Interviewing (MI) (Miller & Rollnick, 2013), an empirically validated treatment for addiction, involves the use of therapist-prompted
behaviors to generate sustained behavioral change (Jensen et al., 2011; Rubak et al., 2005; Vasilaki et al., 2006). Research suggests that MI’s efficacy might relate to inhibition of known reward processing regions (e.g., striatum, orbital PFC) during exposure to one’s own change talk as observed with adults with alcohol dependence (Feldstein Ewing et al., 2011b). In a separate study, neural responses (within the posterior cingulate and precuneus) to one’s own change talk among adolescent cannabis users were significantly associated with reductions in cannabis use behaviors at one-month follow-up (Feldstein Ewing et al., 2013). While further research is needed, these data highlight the feasibility of identifying distinct patterns of neural activity associated with key components of behavioral interventions using fMRI.

C. Contingency Management and fMRI

Contingency Management (CM), a therapy involving the encouragement and reinforcement of abstinence via the provision of contingent rewards, has received support as an effective treatment for addiction (Lussier et al., 2006; McDonell et al., 2013, Petry et al., 2005; Prendergast et al., 2006). To our knowledge, no studies have systematically assessed longitudinal neural changes associated with CM treatment for addiction, although such research is ongoing (Stanger et al., 2013). Given CM’s focus on reward-related learning, it has been hypothesized that the efficacy of this treatment may be related to individual differences within corticostriatal reward neurocircuitry (Martinez et al., 2011; Bickel et al., 2010).

D. fMRI summary

Evaluation of neural mechanisms associated with empirically supported behavioral therapies is in its infancy, and there are multiple opportunities for innovative research in this area. In particular, research into the neural correlates of specific components of different therapies (e.g., as has been done with change talk in MI) (Feldstein Ewing & Chung, 2013) is needed to provide greater knowledge of the mechanisms of change. Similarly, longitudinal studies (e.g., direct pre- versus post-treatment comparisons of fMRI data) are needed to isolate the neurobiological changes associated with optimal responses, as well as the effects of recent substance use versus abstinence on these brain-behavior relationships. Moreover, the extent to which optimal treatment responses are reliant on pre-treatment neural integrity is largely unexplored. Such research may have significant clinical implications for the a priori assignment of behavioral therapies on an individual basis. Current findings, nonetheless, suggest that fMRI is a useful tool for the elucidation
III. Structural MRI and Behavioral Treatment Responses

Pre-treatment neurostructural characteristics may relate to treatment outcomes among individuals with addiction. Neurostructural research typically utilizes either voxel-based or surface-based morphometric approaches to assess gray matter volume or cortical thickness, respectively. White matter in vivo is most commonly assessed using diffusion tensor imaging (DTI), a technique that characterizes organized white matter at high spatial resolutions (see Chapter 2). Here, we introduce findings from these methodologies and the implications for behavioral treatments of addiction.

A. Gray matter: Findings from morphometric and cortical thickness studies

Cortical thickness and gray matter volumetric reductions have been reported among individuals with SUDs (most notably among individuals with alcohol use disorders; AUDs) (Fein et al., 2002; Mechtcheriakov et al., 2007; Durazzo et al., 2011). These alterations have been traditionally interpreted as resulting from prolonged exposure to substances of abuse and have been found to be partially reversed following sustained abstinence (Bühler & Mann, 2011; Demirakca et al., 2011). Additionally, emerging evidence suggests that individual differences in gray matter structures may relate to behavior, addictions vulnerability (Rando et al., 2013), and risk taking (Schneider et al., 2012), particularly during adolescence.

To our knowledge, no studies have examined the longitudinal effects of behavioral treatments for addiction on gray matter volume. However, time to relapse has been associated with extent of volumetric gray matter alterations among individuals with AUDs (Rando et al., 2011; Durazzo et al. 2011). Similarly, data indicate differences in pre-treatment gray matter volumes between individuals who achieved abstinence following nicotine replacement therapy versus those who did not (Froeliger et al., 2010). And pre-treatment putaminal volume may relate to the successful achievement of sustained abstinence (three or more weeks) among individuals with cannabis dependence (Yip et al., 2014). Together, this suggests that gray matter volumes may also relate to response to behavioral treatments. However, the questions of how individual differences in gray matter macrostructures might relate to specific aspects of different...
behavioral interventions and/or how gray matter might change as a function of behavioral treatment are largely unexplored.

**B. White matter: Findings from diffusion tensor imaging studies**

As with gray matter, alterations in white matter tissue have been reported across a range of addictive disorders (Moeller et al., 2005; Arnone et al., 2008). Importantly, data suggest that these measures may relate to treatment outcomes among individuals with addiction. For example, decreases in fractional anisotropy (FA), a commonly used scalar index of white matter integrity, within frontal white matter structures have been reported among individuals who relapsed following CBT treatment for alcohol dependence versus those who did not (Sorg et al., 2012). Similarly, in a study of treatment-seeking individuals with cocaine dependence, Xu and colleagues found significant positive associations between pre-treatment white matter tissue integrity (FA values within the frontal and parietal lobes) and measures of abstinence (maximum durations of abstinence, percent cocaine-negative urines during treatment) (Xu et al., 2010).

**C. Structural summary**

Findings from structural MRI and DTI studies suggest that individual differences in gray and white matter tissues may relate to treatment response among individuals with addiction. However, more research is needed to determine the extent to which white and gray matter tissue might change as a function of behavioral treatments and how such changes might relate to treatment response. Given that structural differences may be related to the recency and duration of substance exposure (Beveridge et al., 2008) and may be partially ameliorated following prolonged abstinence (Bühler & Mann, 2011; Demirakca et al., 2011; Alhassoon et al., 2012), a particular challenge of such research will be disentangling the effects of abstinence from those of treatment.

**IV. Ligand-Based Imaging: Assessing Endogenous Neurochemistry in Relation to Treatment Responses**

Ligand-based imaging methods – namely positron emission tomography (PET) and single-photon emission computed tomography (SPECT) – allow for in vivo assessment of receptor binding and neurotransmitter release. Using PET, Martinez and colleagues recently demonstrated a significant positive association between DA D_{2/3} receptor binding and DA release within the striatum and treatment outcomes following CM
for cocaine dependence (Martinez et al., 2011), suggesting a relationship between individual variability in endogenous DA functioning and reward-based treatment responses. While further research is needed to determine the extent to which endogenous DA levels might change as a function of CM treatment, these data suggest important avenues for further research. For example, given that the combination of CM with dopaminergic medications (e.g., levodopa) may enhance treatment response (Schmitz et al., 2010), future studies could explore the relationship between baseline levels of endogenous DA, use of dopaminergic medications, and treatment response to CM. Additional areas of important future research will be the determination of whether baseline DA levels relate to treatment outcomes for non-reward-based therapies, along with the assessment of the relationship between treatment response and endogenous functioning of other neurotransmitter systems (e.g., serotonin).

V. Genetic Influences on Behavioral Treatment Response

Genetic factors influencing dopaminergic neurotransmission may influence treatment response to behavioral interventions including CBT for panic disorder (Lonsdorf et al., 2010). Within the context of addiction, Feldstein Ewing and colleagues demonstrated an association between genes encoding for DA D₄ receptors and treatment responses to Motivational Enhancement Therapy (MET) (Feldstein Ewing et al., 2009). In a later study, Feldstein Ewing and colleagues further demonstrated differential neural responses to change talk between individuals with cannabis dependence with different single nucleotide polymorphisms (SNPs) in the gene coding for the 5-HT 2A receptor (Feldstein Ewing et al., 2012). Taken together, these findings suggest that individual genetic differences may relate to variability in behavioral treatment response. However, replication of these findings using larger sample sizes is needed.

VI. Emerging Therapies: Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation

Non-surgical brain stimulation techniques, including transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) methodologies, may be used to probe and/or alter neural function (see Chapter 5 for further description of these techniques). Stimulation of the dorsolateral prefrontal cortex (dlPFC), a region involved in motivational control and craving processes (Goldstein & Volkow, 2011), may reduce
cravings for and consumption of substances of abuse (for reviews, see Bellamoli et al., 2013; Wing et al., 2013; Nardone et al., 2012). However, not all studies have found reductions in craving (Xu et al., 2013), and the effects of transcranial brain stimulation techniques on the achievement of abstinence appear limited (Bellamoli et al., 2013). Thus, rTMS and tDCS may be most effective for the treatment of addiction if used alongside other validated treatment methodologies, such as CBT (Bellamoli et al., 2013; Feil & Zangen, 2010). As the addition of tDCS to cognitive-based training improves response inhibition in healthy individuals (Ditye et al., 2012), an important future step will be to test the effectiveness of combined rTMS or tDCS with behavioral treatments for addiction. This approach may improve treatment outcomes, particularly among individuals with differences in cognitive control-related neurocircuitry.

VII. Summary, Clinical Implications, and Future Directions

Significant advances have been made in translational approaches, furthering our understanding of the neural mechanisms associated with evidence-based behavioral treatments for addiction. Data from fMRI, structural MRI, and DTI suggest that individual differences in fronto-cortical limbic reward circuitry relate to treatment response. Similarly, individual differences in dopaminergic neurotransmission within the striatum may relate to responses to CM (Martinez et al., 2011). Translational research has also helped to elucidate the neural correlates of specific aspects of behavioral therapies (Feldstein Ewing & Chung, 2013), which may be used to refine existing treatments.

Despite these advances, several limitations characterize much of this research. To begin, the relationship between different neurobiological factors (structural and functional integrity within the PFC, for example) and treatment mechanisms and outcomes among individuals with addiction remains largely unknown. For example, it is possible that decreases in dIPFC activity during cognitive control processes (i.e., Stroop performance) following treatment (DeVito et al., 2012) might relate to increases in frontal white matter integrity (Xu et al., 2010) and/or that both of these factors might relate to similar aspects of treatment response (such as the acquisition of new skills to down-regulate craving). Thus, future studies must integrate multiple translational approaches within the context of behavioral treatments for addictions, including, for example, both task-based and resting state data before and after treatment (Frewen et al., 2008).
In addition, much of this research is still in early stages and is therefore limited by small sample sizes and methodological issues including an absence of pre-post comparisons and use of well-characterized control groups (Frewen et al., 2008). Existing studies have typically conducted comparisons of patient groups based on their responses to treatment post hoc. While these comparisons inform the field regarding the neurobiology of treatment responders versus non-responders, the predictive validity of such findings remains largely untested. Thus, an important future challenge will be the identification of those factors that not only relate to treatment outcome but that are also detectable on an individual basis (rather than observable when averaged across a group of patients) prior to treatment. Finally, translational research is often expensive, which may be a prohibitive factor to consider in the practical implementation or use within real-world clinical settings. Thus, future studies evaluating the cost-effectiveness of translational methodologies in the implementation into clinical practice are needed.

VIII. Conclusions

Translational research methodologies are developing rapidly. They have a high potential to enhance our understanding of addictions and their treatment. Additional research is needed to translate neurobiological findings into day-to-day clinical practice. However, existing data suggests that translational research may significantly improve treatment outcomes over the long term via identification of individual factors relating to optimal treatment response.

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