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Neuroimaging mechanisms of change in psychotherapy for addictive behaviors: Emerging translational approaches that bridge biology and behavior:

Introduction to the Special Issue

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Abstract

Research on mechanisms of behavior change provides an innovative method to improve treatment for addictive behaviors. An important extension of mechanisms of change research involves the use of translational approaches, which examine how basic biological (i.e., brain-based mechanisms) and behavioral factors interact in initiating and sustaining positive behavior change as a result of psychotherapy. Articles in this special issue include integrative conceptual reviews and innovative empirical research on brain-based mechanisms that may underlie risk for addictive behaviors and response to psychotherapy from adolescence through adulthood. Review articles discuss hypothesized mechanisms of change for cognitive and behavioral therapies, mindfulness-based interventions, and neuroeconomic approaches. Empirical articles cover a range of addictive behaviors, including use of alcohol, cigarettes, marijuana, cocaine, and pathological gambling and represent a variety of imaging approaches including fMRI, magneto-encephalography, real time fMRI, and diffusion tensor imaging. Additionally, a few empirical studies directly examined brain-based mechanisms of change, whereas others examined brain-based indicators as predictors of treatment outcome. Finally, two commentaries discuss craving as a core feature of addiction, and the importance of a developmental approach to examining mechanisms of change. Ultimately, translational research on mechanisms of behavior change holds promise for increasing understanding of how psychotherapy may modify brain structure and functioning and facilitate the initiation and maintenance of positive treatment outcomes for addictive behaviors.

Keywords

translational; psychotherapy; neuroimaging; fMRI; MEG; real time fMRI; DTI; adolescence; addictive behaviors

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Currently, the gold-standard psychosocial interventions for addictive behaviors are only moderately successful in initiating and sustaining behavior change (e.g., Miller, Walters, & Bennett, 2001), leaving a substantial proportion of the treated population facing significant substance use problems even within 12 months post-intervention (e.g., Anton et al., 2006; Hendershot et al., 2011; Magill & Ray, 2009). This modest success rate is due, in part, to our

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limited understanding of how and why psychotherapy works. One potential avenue to improve outcomes is through examining mechanisms of change (e.g., http://commonfund.nih.gov/behaviorchange/). Not only can this research help elucidate therapy-specific processes of change, importantly, it also provides an innovative avenue to modify and improve intervention approaches, as well as ways to better achieve treatment goals (Kazdin, 2007; Kraemer et al., 2002). While many researchers have discussed the importance of considering both biology and behavior in therapeutic models and practice (Goldstein et al., 2009; Hutchison, 2010; Potenza et al., 2011), to date, earnest interdisciplinary interchanges and empirical integrative evaluations have been limited. This is important because innovative translational studies are vital to elucidating how basic biological and behavioral factors interact to catalyze the initiation and maintenance of positive behavior change in psychosocial addictions treatment.

Efforts to examine brain-based mechanisms underlying psychotherapeutic change fit into an emerging conceptual framework, Research Domain Criteria (RDoC; Insel et al., 2010). This framework proposes the use of brain circuits as an important level of analysis in an ambitious attempt to integrate data across scale, from genes through self-report, and broader social influences and developmental contexts, in order to understand the etiology and course of mental health conditions (Insel et al., 2010). In this regard, to improve the effectiveness of substance use treatment, the National Institutes of Health (NIH) are investing in translational approaches, integrating and supporting brain science and addictions treatment research (e.g., RFA DA-10-003, RFA-NR-11-007; NIAAA-09-07; 2011 NIDA workshop on “Integrating Neuroscience and Adolescent Substance Abuse Treatment”). In the timely context of these recent developments, this special issue showcases emerging theoretical and empirical translational approaches to addictions treatment.

The term “translational,” as it is used here, refers to the integrated study of basic biological mechanisms (e.g., brain-based factors) and behavior (e.g., treatment outcome, clinical symptoms). Just as addiction can be conceptualized as a disorder involving learning and memory, in which drug-related cues may be entrained through long-term neuroadaptive changes (e.g., Koob & Volkow, 2010), psychotherapy can be considered a specialized form of learning, which may involve specific neuroadaptive changes (Kandel, 1979, 1998). A translational approach can help to illuminate changes, at the level of brain structure and function, that are associated with treatment response and sustained behavioral change. In particular, a key mechanism that may underlie psychotherapy effects involves neural plasticity, that is, modifications in brain structure and circuitry that may occur as a result of experience or learning (Bryck & Fisher, 2012; Cramer et al., 2011; Huttenlocher, 2002; Keller & Just, 2009).

A goal of this special issue was to take a first step toward integrating brain science and addictions treatment research to begin to understand processes by which “active ingredients” of psychotherapy might have an impact at a more basic biological level--the level of brain structure and functioning. A rapidly expanding literature reviews brain-based changes associated with the transition into and maintenance of addiction (e.g., Koob & Volkow, 2010; Naqvi & Bechara, 2009; Everitt & Robbins, 2005; Robison & Nestler, 2011). In contrast, substantially less is known about brain-based processes of psychotherapy change for addictive behaviors. A handful of pioneering papers have proposed or examined models of psychotherapy effects on brain functioning and structure in the treatment of mood and anxiety disorders (e.g., Baxter et al., 1992; DeRubeis, Siegle, & Hollon, 2008; Felmingham et al., 2007; Frewen, Dozois, & Lanius, 2008; Goldapple et al., 2004; Porto et al., 2009; Roffman et al., 2005; Strauman et al., in press). Articles addressing brain-based mechanisms of psychotherapy change in addictive behaviors have appeared more recently (e.g., Brewer et al., 2010; Feldstein Ewing et al., 2011; Goldstein et al., 2009; Hutchison, 2010; Potenza et al., 2011), but the topic clearly warrants greater attention. In an effort to focus the special issue on translational models and research, we refer the reader to other sources for in-depth reviews of the neurobiology of addictive behaviors (e.g., Everitt & Robbins, 2005; Koob & Le Moal, 2008; Koob & Volkow, 2010; Naqvi & Bechara, 2009; Sinha, 2008) and methodological issues related to the use of neuroimaging in translational research (e.g., Carrig, Kolden, & Strauman, 2009; Hari & Salmelin, 2011; Linden, 2008; Logothetis, 2008; Walter, Berger, & Schnell, 2009).

This special issue of *Psychology of Addictive Behaviors* features conceptual reviews and empirical research on brain-based mechanisms that may underlie risk for substance use and effective psychotherapy interventions for addictive behaviors in adolescence through adulthood. The review articles discuss hypothesized mechanisms of behavior change for addictive behaviors associated with cognitive and behavioral therapies (Morgenstern, Bechara, & Breiter, 2013; Wetherill & Tapert, 2013; Potenza et al., 2013), mindfulness-based interventions (Brewer, Elwafi, & Davis, 2013; Stanger, Budney, & Bickel, 2013; Wetherill & Tapert, 2013; Witkiewitz, Lustyk, & Bowen, 2013), and neuroeconomic approaches, focusing on contingency management (Stanger et al., 2013). The conceptual reviews converge in referencing two overarching processing pathways that are relevant to addictive behavior: “top-down” and “bottom-up” processing. Top-down processing refers to the role of cognitive control circuitry (which may involve, for example: orbitofrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex) in modulating the processing of sensory information (e.g., craving and response to reward). Bottom-up processing refers to the primacy of sensory information processing and salience of drug cues (circuitry relevant to the incentive salience system may involve, for example: the insula, ventral tegmental area, putamen, and caudate) relative to modulation of sensory processing by cognitive control systems. The interplay of top-down and bottom-up processes dynamically influences the onset, maintenance, and effective treatment of addictive behaviors. Ideas proposed in the conceptual reviews with regard to how specific interventions impact top-down and bottom-up processes may be controversial, but aim to provide heuristic frameworks to guide testing of novel concepts regarding brain-based psychotherapy mechanisms of change.

Empirical articles in the special issue cover a range of addictive behaviors, including alcohol use (Houck, Moyers, & Tesche, 2013; Monnig et al., 2013; Xiao et al., 2013), smoking (Hartwell et al., 2013; Krishnan-Sarin et al., 2013; Wilson, Sayette, & Fiez, 2013), marijuana use (Feldstein Ewing et al., 2013), co-occurring alcohol and marijuana use (Chung, Pajtek, & Clark, 2013; Jacobus et al., 2013), cocaine dependence (Worhunsky et al., 2013), pathological gambling (Potenza et al., 2013), and risk for substance use (Banich et al., 2013). The studies also represent a variety of imaging approaches: fMRI to examine task-related brain functioning and treatment outcome (e.g., cue-elicited craving: Feldstein Ewing et al., 2013; Wilson et al., 2013; Stroop color word task: Krishnan-Sarin et al., 2013; Worhunsky et al., 2013; Iowa gambling task: Xiao et al., 2013), and pilot studies of magneto-encephalography (MEG) (Houck et al., 2013) and real time fMRI (Hartwell et al., 2013) to examine stimulus-related regional brain activity. Other studies examined brain structure (i.e., integrity of white matter tracts) using diffusion tensor imaging (DTI) as a predictor of risk taking behavior in youth (Jacobus et al., 2013), a correlate of current or remitted alcohol use disorder (Monnig et al., 2013), and as a predictor of adolescent treatment outcome (Chung et al., 2013).

Given the early stage of research on neuroimaging mechanisms of behavior change for addictive behaviors, many of the empirical studies in the issue characterized brain functioning or structure associated with addictive behavior (e.g., Monnig et al., 2013; Xiao et al., 2013) or examined brain-based indicators as predictors of treatment response more generally (e.g., Chung et al., 2013; Krishnan-Sarin et al., 2013; Worhunsky et al., 2013).

Although these studies do not directly address mechanisms of psychotherapy change, they do indicate specific impairments in brain structure and functioning associated with addictive behaviors that could be used to match individuals to specific interventions based on the nature and severity impairment. A few cutting-edge studies in the special issue examined the effect of specific intervention components on brain functioning (e.g., client change language as an "active ingredient" of motivational interviewing in Feldstein Ewing et al., 2013, and Houck et al., 2013; self- versus other-focusing coping among smokers in Wilson et al., 2013; effects of real time feedback on modulation of regional brain activation in response to smoking cues in Hartwell et al., 2013). The special issue's data-based papers report some intriguing preliminary findings that warrant replication and extension.

The special issue also includes two commentaries, which discuss craving as a core feature of addiction (Thayer & Hutchison, 2013), and the importance of a developmental approach to examining mechanisms of treatment change for addictive behaviors (Boyce & Lynne-Landsman, 2013). The commentary by Thayer and Hutchison (2013) provides a compelling integration of findings across empirical studies of craving in the special issue. Specifically, Thayer and Hutchison (2013) suggest that multiple interventions to address craving will need to be developed, each of which targets a specific neurobiological vulnerability (e.g., neural systems associated with incentive salience and cognitive control). In addition to the need for targeted interventions, the commentary by Boyce and Lynne-Landsman (2013) highlights the importance of a developmental perspective, particularly in the context of on-going brain development in adolescence into young adulthood, for understanding risk for addictive behaviors and guiding the design of developmentally sensitive interventions. Boyce and Lynne-Landsman (2013) also discuss the importance of cross-discipline collaboration in conducting translational research across the lifespan, and the critical role of NIH in supporting these pioneering efforts. Taken together, the special issue's articles provide an interdisciplinary foundation for future empirical evaluation of psychotherapy mechanisms of change for addictive behaviors.

An important theme across the special issue articles is the plasticity of brain structure and functioning, specifically as a result of environmental factors such as heavy substance use and psychotherapy, both of which have potential to produce sustained brain-based and behavioral changes (Etkin et al., 2005; Koob & Volkow, 2010). The basic concept that learning, which occurs in the context of psychotherapy, might be associated with a change in brain functioning (e.g., change in activation, patterns of regional connectivity) and brain structure (e.g., greater white matter integrity) has only begun to be explored. The following paragraphs briefly review mechanisms of neural plasticity to provide a context for discussing future directions for studying brain-based mechanisms of treatment change for addictive behaviors.

Mechanisms of neural plasticity operate at multiple levels, and may involve, for example, alterations in network efficiency and activation thresholds, within and across neural systems, such as the cognitive control and incentive salience systems (Cicchetti & Blender, 2006; Koob & Volkow, 2010). Further, whereas short-term modulations may occur at neural synapses, longer-term changes may be reflected in brain structure and functioning (Cicchetti & Blender, 2006; Markham & Greenough, 2004). One recent study, however, observed regional microstructural changes in white matter detected by DTI after only two hours of task-related training (Sagi et al., 2012), possibly reflecting rapid, activity-dependent structural changes (i.e., swelling) in astrocytes that are associated with learning (Johansen-Berg, Baptista, & Thomas, 2012). Alternatively, certain learning or psychotherapy effects may not be observable at the level of brain structure and functioning covered by the methods used in the special issue articles, such as MRI, DTI, or fMRI (Markham & Greenough, 2004; Zatorre, Fields, & Johansen-Berg, 2012). Findings may depend on the specific fMRI task used, including whether no task-related activation (i.e., resting state), is analyzed (Li et al., 2009). In addition, some neural systems may be more plastic or responsive to psychosocial intervention than others, on-going brain development and neurotoxic effects of chronic substance use on the brain may impact response to interventions, and each component of an intervention may involve a different time course for specific effects (Cicchetti & Blender, 2006; Markham & Greenough, 2004). Effects of sustained abstinence from a substance, which may occur in the absence of an intervention (e.g., natural recovery) also need to be considered when examining changes in brain structure and functioning (Mon et al., 2011). We are only beginning to see how learning sculpts the brain at cellular through systems levels (Zatorre et al., 2012). Future efforts need to consider how psychotherapy, as a specialized form of learning, might impact specific brain-based mechanisms (i.e., functioning, structure), and the anticipated time course and duration of these effects (cf. reading intervention for children: Meyler et al., 2008).

Understanding how psychotherapy interventions work at the level of brain functioning and structure also requires a high degree of specification of the “active ingredient” (e.g., client talk in support of behavior change, Feldstein Ewing et al., 2011) in relation to specific targets of change (e.g., decreased reactivity to drug cues), and hypothesized brain-based mechanisms of change (e.g., increase in cognitive control systems). Studies of the effects of specific types of treatment (e.g., behavior therapy, mindfulness-based relapse prevention) on brain functioning (e.g., DeVito et al., 2012) need to be complemented by research that uses a micro-intervention strategy (Strauman et al., in press). Micro-interventions focus on the time-limited application of a specific therapeutic technique (e.g., eliciting client change talk), derived from an explicit model of therapeutic change (e.g., motivational enhancement), to more precisely test predictions about how and for whom an intervention component works (Feldstein Ewing et al., 2011; Strauman et al., in press). A micro-intervention approach permits greater specificity in establishing links between theory, a well-defined “active ingredient,” hypothesized brain-based mechanisms, and key outcomes (cf. alcohol cue-exposure intervention: Vollstadt-Klein et al., 2011; specialized spelling intervention for children: Gebauer et al., 2012; proposed micro-mechanisms of mindfulness: Vago & Silbersweig, 2012). Micro-intervention strategies have the advantage of greater precision through targeting smaller units of cause (e.g., eliciting client change talk) and effect (e.g., reduced drug-related cue reactivity), whereas studies of a specific type of treatment (e.g., cognitive behavior therapy) may have greater external validity, and can usefully indicate the overall effects of integrated intervention components delivered as a standardized “package” on brain functioning and structure.

A brain-based approach to understanding mechanisms of psychotherapy change has limitations. Neuroimaging remains costly, and studies of treatment process require repeated scans over time; studies typically include small, carefully selected samples, which limit external validity. Greater attention needs to be given to analyses of brain circuitry (cf. Worhunsky et al., 2013), rather than examining isolated regions of activity. In addition to studies of stimulus-related brain activation (e.g., cue reactivity studies: Feldstein Ewing et al, 2013; Wilson et al., 2013), research is needed to better characterize the functional connectivity of the addicted brain “in resting state” (i.e., default mode network, e.g.: Ma et al., 2011). Few studies have examined change at the molecular level as a result of psychotherapy (cf. depression: Hirvonen et al., 2011). Integration of data, across scale from molecules to behavior (Carandini, 2012; Zatorre et al., 2012) and across modalities (e.g., fMRI, DTI, EEG), represents an important future direction. Although neuroimaging may provide brain-based biomarkers to facilitate diagnosis, predict treatment response, and track treatment progress (Berkman, Falk, & Lieberman, 2011; Etkin et al., 2005; Reske & Paulus, 2011), these biomarkers need to demonstrate “added value,” due to cost, in relation to traditional, less expensive, measures for day-to-day clinical utility. The reliability and validity of neuroimaging methods also warrants attention (e.g., Bennett & Miller, 2010; Desmond & Chen, 2002), with corresponding caution used to prevent premature translation to clinical practice (Desmond & Chen, 2002). Finally, despite the importance of the interpersonal context in which psychotherapy typically occurs, few studies have examined simultaneous brain activity of individuals engaged in social interaction (e.g., using fMRI: Hasson & Honey, in press) to understand how interpersonal interactions may modify an individual's brain response, and help to shape that person's thoughts and behavior (e.g., interactions between therapist and client, or parent and child; Davidson & McEwen, 2012).

Addiction involves long term neuroadaptive changes in brain structure and circuitry. Effective treatment likely requires an equal and opposite effect for sustained recovery. Brain-based research on mechanisms of treatment change holds promise for increased understanding of how psychotherapy, as a specialized form of learning, can modify brain structure and functioning to facilitate sustained positive treatment outcomes. Specifically, brain-based research could inform the matching of patients to specialized intervention based on nature and severity of brain-related impairments in structure and functioning (Hutchison, 2010); could guide the optimal content, intensity, and duration of interventions to promote sustained behavior change based on tracking changes in brain functioning and structure over time; and could inform the design of more effective interventions for youth in the context of on-going brain development.

Efforts to leverage neural plasticity (e.g., "brain training") to promote health are gaining momentum in the fields of cognitive science (Chein & Schneider, 2012), education (e.g., Berkman, Graham, & Fisher, in press; Diamond & Lee, 2011; Keller & Just, 2009), substance use prevention (Fishbein, 2011), and the treatment of psychopathology (e.g., Vinogradov, Fisher, & de Villers-Sidani, 2012) and addictive behaviors (e.g., Potenza et al., 2011). Emerging technologies, based on brain science, such as neurofeedback (e.g., Siegle, Ghinassi, & Thase, 2007; neurofeedback using real time fMRI: Caria, Sitaram, & Birbaumer, 2012; Weiskopf, 2012), and neuromodulation (e.g., transcranial magnetic stimulation, transcranial direct current stimulation, which involve non-invasive brain stimulation), may be useful as adjuncts to therapy (e.g., Brunoni et al., 2012; Vallar & Bolognini, 2011), but are not without critics or skepticism. Developments in brain science will increasingly inform mental health interventions, and typically involve cross-discipline collaboration not only due to the complexity of psychotherapy processes of change, but also the need to integrate data across scale, from "neurons to neighborhoods" in order to facilitate sustained positive behavior change (Shonkoff & Phillips, 2000).

This special issue addresses a number of empirically supported treatments for the addictions from a translational perspective. We thank the contributors and reviewers for fostering a cross-disciplinary exchange of ideas, a collaboration across fields that is essential to increased understanding of brain-based mechanisms of psychotherapy change. We hope that the special issue continues to stimulate dialogue between fields and to spark ideas for the design of innovative brain-based treatments for addictive behaviors.

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