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HOT TOPIC

Brain Mechanisms of Change in Addiction Treatment: Models, Methods, and Emerging Findings

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Abstract
Purpose of review Increased understanding of "how" and "for whom" treatment works at the level of the brain has potential to transform addiction treatment through the development of innovative neuroscience-informed interventions. The 2015 Science of Change meeting bridged the fields of neuroscience and psychotherapy research to identify brain mechanisms of behavior change that are "common" across therapies and "specific" to distinct behavioral interventions.

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Recent findings Conceptual models of brain mechanisms underlying cognitive behavioral therapy, mindfulness interventions, and motivational interviewing differ in targeting brain circuits representing "top-down" cognitive control and "bottom-up" processing of reward. Methods for integrating neuroimaging into psychotherapy research can reveal recovery of brain functioning with sustained abstinence, which may be facilitated by psychotherapy and cognitive training.
Summary Neuroimaging provides powerful tools for determining brain mechanisms underlying treatment effects, predicting and monitoring outcomes, developing novel neuroscience-informed interventions, and identifying for whom an intervention will be effective.

Keywords Neuroimaging psychotherapy · Addictive behaviors · Translational · Alcohol · Substance use disorder

Introduction

A critical barrier to progress in improving the magnitude and durability of treatment effects for addictive behaviors involves addressing gaps in knowledge regarding "how" treatment works and "for whom," at the level of the brain [1•, 2•, 3•]. Increased understanding of brain-based mechanisms of change has potential to revolutionize approaches to behavioral treatment through application of neuroscience principles of learning and motivation to amplify the effect of "active ingredients" of psychotherapy, identify "common" and "therapy-specific" processes of change, specify brain targets for intervention, optimize dosing and treatment duration, and sustain positive treatment outcomes.

Presentations at the 2015 Science of Change meeting, summarized in the following abstracts, covered conceptual models of brain mechanisms of change for behavioral interventions such as cognitive behavioral therapy [CBT], mindfulness, and motivational interviewing [MI]). Opening remarks and keynote speakers discussed how neuroimaging methods can provide important insights into specific brain targets for intervention. Integrating neuroimaging into clinical research, however, involves addressing basic methodologic and analytic challenges. Presentations covered the use of neuroimaging to predict treatment outcomes, to study brain changes that occur during treatment, and potential clinical applications of neuroimaging, for example, in neurofeedback and multimodal approaches to treatment.

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Opening Remarks: Brain Imaging as a Tool to Develop Effective Alcoholism Treatment

Antonio Noronha

This translational meeting brings together the fields of neuroscience and behavioral therapies to improve treatments, particularly for alcohol use disorders (AUDs). A tool such as brain imaging will support the development of more effective behavioral treatments for alcoholism by helping to understand brain-based mechanisms of why some treatments work and also individual differences in response to treatment [4•]. Neuropsychological studies of individuals in recovery from alcoholism have revealed a typical profile of functional impairments, which may improve with extended sobriety (see Dr. Nixon's abstract). In temporal parallel, brain structural changes associated with chronic heavy alcohol use are also reversible with sustained sobriety. Thus, some alcoholics typically endure "incomplete" lesions and therefore retain neural tissue with the potential for structural repair and enabling functional repair.

Damage to circuitry in one area can affect distal regions and functions. However, the healthy nodes and systems intersecting with affected circuitries have connections of their own and the potential of "taking over" affected function or compensating for dysfunction. Neural systems affected in alcoholism include frontostriatal, frontocerebellar, and limbic circuitry and present targets for retraining. For example, functional imaging studies have shown that for alcoholic individuals to perform certain tasks (e.g., spatial working memory), frontal and cerebellar regions are activated, whereas controls activate frontal regions alone. Another interesting potential source for functional enhancement is the coupling of task-activated networks with resting-state activity.

Treatments to repair neural circuitry affected in alcoholism include, for example, the combined use of transcranial magnetic stimulation (TMS) with direct current stimulation (tDCS). Combined TMS and tDCS provide a method to redirect selective regions of brain response to particular tasks or stimuli. In addition, multimodal imaging using diffusion tensor imaging (DTI) to determine the health of white matter microstructure together with functional magnetic resonance imaging (fMRI) for brain activation could assist in identifying brain networks that are viable and potentially supportive of retraining. Retraining the brain and its circuitry to overcome dysfunction is having success in stroke, reading disability, dyslexia, and traumatic brain injury. Tools such as brain imaging also can be used, for example, in the actual treatment process with circuit retraining and neurofeedback during functional imaging.

Keynote: Neuroimaging and Clinical Research Collaboration to Study Treatment Processes

Kathleen Carroll and Marc Potenza

Our collaborative research program involves systematically testing and refining a model of brain mechanisms of change for empirically validated therapies (cognitive behavioral therapy, contingency management) across a range of addictive disorders. We have been successful in integrating pre- and post-treatment neuroimaging into most of our ongoing randomized clinical trials via use of a range of practical strategies as well as integration of perspectives from multiple disciplines (imaging and neuroscience, addiction treatment and clinical trials, cognitive science, psychopharmacology). Over time, we have refined our paradigms to accommodate the complex nature of this work (see Fig. 1), reflecting the complicated and dynamic effects of patient premorbid functioning, effects of chronic substance use, ongoing use of substances, the interplay of common and unique aspects of treatment, treatment exposure and process, and selection of appropriate imaging tasks and analytic strategies. In our model, neural mechanisms of change for CBT are proposed to involve multiple circuits that relate to specific components of the therapy [3•]. For example, the acquisition of skills to better control response to internal and external cues associated with craving and addictive behaviors (substance use, gambling) may involve changes in brain circuitry (e.g., dorsolateral prefrontal and anterior cingulate cortices) that may promote more effective decision making. Alterations in the function of subcortical regions (including within cortical-striatal circuitry) may also be involved given that individuals may learn to exert greater cortical control over motivational drives to participate in addictive behaviors. Our preliminary studies suggest that brain activations in both cortical and subcortical regions underlying cognitive control and reward processing relate prospectively to improved treatment outcomes, with several of our recent studies suggesting that changes in brain function are associated with indicators of exposure to specific elements of CBT and contingency management. These findings provide insight into the neural mechanisms of CBT and, hence, improvements that may enhance its efficacy and durability, as well as prove useful to the development of novel targets and treatments.

Integrating Neuroimaging into Randomized Controlled Trials: Methodological and Analytical Issues

Kent Hutchison

The integration of randomized controlled trials (RCTs) with neuroimaging offers scientists the opportunity to test key theoretical constructs linking treatment, mechanistic targets in the brain, and behavioral outcomes. A successful integration of neuroimaging in the context of RCTs can only be accomplished with a detailed theoretical model linking the treatment to mechanisms in the brain and more distal behavioral outcomes. As an example, a mechanistic model of Mindfulness-Based Relapse Prevention (MBRP) illustrates the integration of neuroimaging into an RCT (Fig. 2). In this model, MBRP, compared to relapse prevention (RP), is hypothesized to have effects through two mechanisms: one mechanism involves reducing neuroinflammation, which then increases connectivity of cognitive control circuitry (resting state), and the other involves mitigating epigenetic modifications due to chronic alcohol exposure, which then impacts the reward network (cue reactivity). From a methodological perspective, the challenge is to integrate neuroimaging methods with RCT design considerations. RCTs usually involve sample sizes of >60 patients per group (medium to small effects) and follow-ups, typically at 3 and 6 months post-treatment. fMRI tasks need to

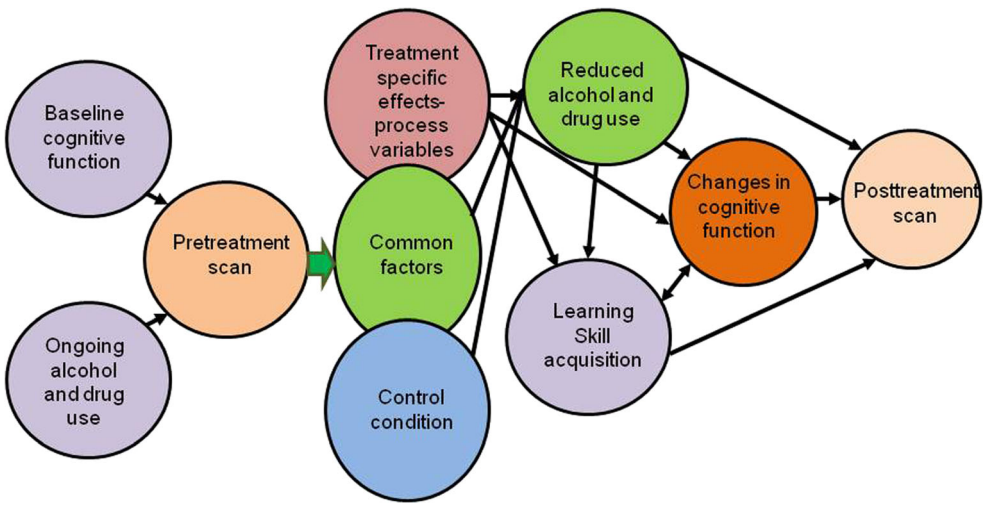

Fig. 1 Proposed model for studying brain mechanisms of change in psychotherapy for addictive behaviors (Kathleen M. Carroll)

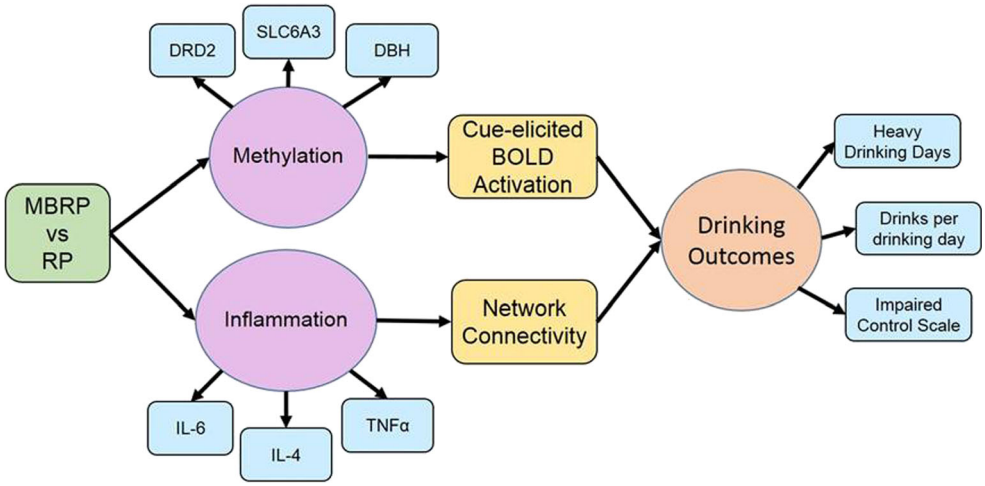

Fig. 2 Proposed mediation model of treatment effects on drinking outcomes (Kent Hutchison). *MBRP* Mindfulness-Based Relapse Prevention, *RP* relapse prevention

be selected to test the specific MBRP mechanisms involving cognitive control and reward sensitivity and reliably activate relevant circuitry. Neuroimaging sessions need to occur such that the treatment has adequate time to impact the brain mechanism, but prior to when the treatment is expected to impact behavioral outcomes, to establish temporal precedence of the mechanisms. Potential drawbacks to including neuroimaging in an RCT involve additional exclusionary criteria, which complicates sample ascertainment, imaging costs, increased type I error, and the need for analytic methods that reduce neuroimaging data in a way that allows for it to be used in traditional statistical models of treatment effects. While integrating neuroimaging into RCTs is definitely challenging, the potential scientific gains of understanding more precisely how a treatment leads to behavior change are worth the effort.

Maximizing Information in Brain Imaging Studies: Dynamics, Prediction, Data Fusion, Deep Learning, and Data Capture

Vince D. Calhoun

The brain imaging data collected to date encodes an incredible amount of information that we are only beginning to understand. Emerging approaches have begun to yield useful information from these data that were not conceived of when it was collected. For example, the field has fairly recently embraced the concept of whole-brain time-varying connectivity (i.e., the chronnectome [5]). As an example, the resting brain states of individuals using different substances such as alcohol, marijuana, or smoking manifest differently [6]. Secondly, there is a growing interest in using brain imaging data to make predictions at the level of the individual subject ranging from mild traumatic brain injury [7] to schizophrenia [8]. Thirdly, it is becoming increasingly clear that multimodal data fusion is able to provide more information for individual subjects by exploiting the rich multimodal information that exists, rather than an analysis of each modality alone. The complexity of the human brain coupled with the incomplete measurement provided by existing imaging technology makes multimodal fusion essential in order to increase our ability to characterize disease, mitigate against misdirection, and hopefully provide a key to finding the missing link(s) in complex mental illness [9]. Fourthly, approaches based on more complex models, so-called deep learning, have shown substantial improvements in certain domains. These approaches also show great promise for identifying hidden disease-related patterns in mental illness [10] or identifying the translation between brain structure and brain function [11]. And, lastly, there is a huge focus on sharing neuroimaging data [12]. As new tools come online for advanced data capture, management, processing, and sharing [13, 14], we will see a substantial increase in the information potential of existing and new data. In summary, we live in an exciting time of discovery during which a combination of factors enables us to leverage data collected from the living human brain in exciting and powerful ways.

Alcohol and Abstinence: Effects on Brain and Relevance to Treatment

Sara Jo Nixon

The chronic, excessive misuse of alcohol (i.e., alcoholism) is associated with significant compromise in neurobehavioral systems. An extensive literature documents alcohol-related deficits in brain structure including both gray and white matter [15]. Studies also show altered patterns of brain activation [16, 17] and neurophysiology [18, 19]. Although prefrontal and frontal areas may be differentially sensitive, other regions are also negatively affected [15].

Critically, neuropsychological/cognitive functions are also significantly impaired. A large body of work reveals alcohol-

related deficits across a variety of domains including executive function (e.g., problem-solving, behavioral inhibition, introspection, decision-making), visual-spatial functions, aspects of learning and learning, and balance/postural stability [16]. Executive functions, mediated by pre/frontal regions, appear to be more vulnerable than other domains [16, 20]. Taken together, alcoholism is associated with generalized diffuse brain dysfunction.

Given these patterns, two questions arise. The first concerns recovery of function. Importantly, improvement occurs with verbal skills recovering first, often in the first month. Other domains also demonstrate positive change across time. However, data also suggest that specific functions may not return to expected levels for months or years [19] and improvement is conditional on sustained abstinence [20].

The second question concerns the relevance of these deficits to treatment outcomes and programming. The relationship between neurocognition and treatment outcomes has been the focus of discussion for decades. Empirical studies have produced inconsistent results. Recent work by Bates and colleagues [21, 22] reveals a complex relationship influenced by interpersonal factors such as social support.

Similarly, there has been long-standing interest in whether cognitive remediation might be an active component of treatment programming [23]. Likely due to cost and staffing constraints, few studies have been conducted. Recently, there has been renewed interest and current findings indicate that cognitive training may enhance treatment processes [24, 25]. Further work is needed to determine if cognitive retraining improves sustained sobriety and adaptation.

Brain Training to Prevent and Treat Addictive Disorders

Bruce E. Wexler

Cognitive- and emotion-related processes emerge from dynamically configured neural systems or networks distributed widely throughout the brain. Hubel and Wiesel were awarded the Nobel Prize for demonstrating that connections among neurons that constitute neural systems are not genetically determined but, instead, are shaped and reshaped, after birth by stimulation from the environment. It is evident, for example, in volume expansion of the right sensorimotor cortex that controls the complex fingering movements of the left hand in violin players and altered inter-regional connectivity in gymnasts. Clinicians have begun harnessing this plasticity for therapeutics, dramatically, for example, allowing blind people to see through patterns of electrical stimulation delivered to their tongues from cameras worn like eyeglasses [26]. Furthermore, geriatric depressed patients who have executive dysfunction often fail to respond to medications. When these geriatric depressed patients, who failed to respond to 3 months of medications, were given our brain training, 90 % recovered in 4 weeks [27]. We also have developed a program of integrated computer-presented and physical exercises designed to activate and enhance neural systems associated with executive cognitive functions including sustained attention, working memory, cognitive flexibility, and response inhibition. Used three to four times per week by thousands of elementary school children, gains transfer to improvement on "gold standard" tests of focused attention, response inhibition, and working memory and to gains on school-administered tests of math and reading achievement. Children with attention-deficit hyperactivity disorder (ADHD) were twice as likely to show substantial decreases in symptoms after participating in the program than during a control period of similar duration. Moreover, those who improved clinically also showed significant improvement in all administered tests of executive function, while those who did not improve clinically did not improve on any of the tests. This cognitive training approach can provide new therapeutic tools for treating individuals with a substance use disorder.

Science of Change: Prediction as a Humanitarian and Pragmatic Contribution from Human Cognitive Neuroscience

John D.E. Gabrieli

Neuroimaging has greatly enhanced the cognitive neuroscience understanding of the human brain and its variation across individuals (neurodiversity) in both health and disease. Such progress has not yet, however, propelled changes in medical practices that improve people's lives [28•]. One way in which neuroimaging may contribute is predicting what kinds of treatment are beneficial for particular patients. We reviewed [28•] over 70 neuroimaging findings in which initial brain functional or structural measures (neuromarkers) correlated with or predicted future education, learning, and performance in children and adults; criminality; health-related behaviors; and responses to pharmacological or behavioral treatments. Neuromarkers often provide better predictions (neuroprognosis), alone or in combination with other measures, than traditional behavioral measures [28•]. For example, clinical responses to CBT in patients with social anxiety disorder are far better predicted from baseline measures of task-activated fMRI [29] or connectomics (the combination of structural connectivity measured by diffusion-weighted imaging and resting-state fMRI functional connectivity) [30] than by clinical rating scales. Variation in brain functions among adolescents correlates with future heavy use of alcohol [31, 32]. Brain measures made at the end of treatment programs for alcoholism have correlated with likelihood of future relapse (or abstinence) and were more

accurate than self-reported intensity of craving or history of intake [33, 34]. Thus, neuroimaging might improve the identification of adolescents at greatest risk for alcoholism and in need of preventive treatment or people with alcoholism who remain at high risk after treatment and who may benefit from further treatment. With further advances in study designs and analyses, neuromarkers may offer opportunities to personalize educational and clinical practices that lead to better outcomes for people [28•].

Imaging Mechanisms of Behavior Change in Motivational Interviewing

Sarah W. Feldstein Ewing and Francesca M. Filbey

While behavior change may seem straightforward, the journey between deciding to change and fully transitioning into modified behavior is fraught with difficulties. In addiction, intra-individual factors can either facilitate or interfere with movement toward reduced substance use; these factors have been called "mechanisms of change" [35].

Historically examined in behavioral investigations, recent studies have extended to neurobiological factors. Here, Filbey has shown that substances that can contribute to the intractability and severity of substance use (e.g., craving) may be driven by underlying neural adaptations in key reward areas including the orbitofrontal cortex, particularly among early-onset users [36•, 37]; as a result, individuals may experience heighted sensitivity to substance-related cues [38].

We extended this examination of neural adaptations to the treatment context. In one intervention, motivational interviewing (MI), within-session client language has been used as a proxy to determine how "well" this treatment is working, while a treatment session is underway [39•]. Work by our lab has supported that this behavioral "proxy" or "mechanism" is not only theoretically relevant, but also, in fact, increasingly accumulating neurobiological support [39•, 40].

Further, we have found differences in neural response to within-session client language by age group (adult versus adolescent), with adolescents showing greater activation in self-reflective regions (e.g., post-cingulate gyrus/precuneus) [41] and adults showing greater involvement of key reward regions (e.g., mesocorticolimbic systems) [40]. Moreover, for adolescents, we have found that these regions of response are robust across substances of abuse (cannabis vs. alcohol) (Feldstein Ewing et al., unpublished).

In sum, these data provide some empirical substantiation of behavioral processes observed in the treatment literature. Moreover, these data support that neural manifestations of addiction and behavior change have substantial developmental variation between adolescents and adults. Thus, these data underscore the importance of specifically examining models and mechanisms of behavior change by developmental period.

Candidate Neurobiological Mechanisms of Mindfulness Meditation

Judson Brewer

Operant conditioning is one of the most evolutionarily conserved learning processes currently known in science. Its "purpose" was likely to help us remember the types of food that are calorie-rich (and which ones are poisonous) and where to find them again. Fast-forward to modern day, when food is relatively plentiful, this process gets co-opted for learning how to eat as a result of stress (as compared to hunger), smoke cigarettes, and abuse drugs. We have found that mindfulness—the ability to see behavior and the results thereof in an unbiased manner—moderates the extinction of unhealthy behaviors [42, 43•]. Specifically, mindfulness training decouples the link between craving and smoking, leading to significantly increased quit rates compared to other behavioral treatments [43•, 44•]. In line with reinforcement of behavior, neurobiological correlates are now beginning to be mapped out [45]. In addition to typical brain pathways and regions associated with craving (e.g., mesolimbic dopaminergic system), the literature suggests that self-referential brain networks such as the default mode network (DMN) may be involved in operant conditioning [45]. Regions of the DMN, such as the posterior cingulate cortex (PCC), may be activated not necessarily by craving itself, but when individuals get "caught up in" it—the hallmark of addiction [46, 47]. Using fMRI, we have found that the PCC is deactivated in experienced meditators relative to novices and shows increased connectivity with cognitive control regions such as the dorsolateral prefrontal cortex and the dorsal anterior cingulate cortex [48•]. Using real-time fMRI neurofeedback, we have also found in neurophenomenological studies that the subjective experience of getting caught up in experience directly corresponds to PCC activation, while the opposite, letting go facilitated by mindfulness awareness, correlates with relative deactivation of the PCC [49•, 50•]. Taken together, these data suggest that mindfulness training targets core behavioral and brain mechanisms related to the addictive process.

Craving and the Regulation of Craving

Hedy Kober

Craving was recently added as a diagnostic criterion for addiction (DSM-5 [51]) but has long been considered a key motivating factor in drug use. Indeed, much research has

shown that craving correlates with and predicts drug use as well as relapse after treatment (see [52] for review). A recent meta-analysis showed that craving predicts smoking in laboratory studies of cigarette smokers [53]. With food, we similarly showed that cue reactivity and craving predict eating and long-term weight gain in the real world with a medium effect size across studies [54].

On the other hand, addiction is often conceptualized as a failure of cognitive control, with symptoms such as "using larger amounts/over longer time periods than intended." Consistent with this, treatments that include strategies for regulating craving are effective in reducing drug use and relapse [55••, 56]. Specifically, it has been shown that acquisition and application of such strategies are associated with greater abstinence [44•, 57, 58].

Taken together, these data suggest that craving, the ability to regulate craving, and the neural correlates of these processes may be important mechanisms of treatment-related change and could serve as biomarkers for such change over time. We developed the regulation of craving (ROC) task to first investigate these processes using fMRI. Findings suggest that cognitive regulation depends on recruitment of dorsolateral and ventrolateral prefrontal cortex and modulates activity in subcortical regions associated with craving including ventral striatum, amygdala, and subgenual anterior cingulate [59]. We continue to use the ROC in clinical trials for cigarette smoking and cocaine addiction to uncover treatment-specific neural mechanisms underlying reductions in drug use from pre- to post-treatment. One of our current hypotheses is that cognitive therapies are associated with increased "top-down" regulation in prefrontal regions, whereas mindfulness-based treatments may lead to reduced "bottom-up" reactivity during craving.

Imaging Mechanisms of Change: Medication Effects on Functional Connectivity During Cue Exposure

Lara Ray and Kelly Courtney

Developing novel medications for addiction remains a high-priority area. Efforts to refine and personalize the available treatments include the application of fMRI to understand the mechanisms of pharmacotherapy action. To that end, fMRI cue-reactivity paradigms represent an ideal platform to probe the involvement of neurobiological pathways sub-serving the reward/motivation system in addiction and potentially offer a translational mechanism by which interventions and behavioral predictions can be tested. This presentation demonstrated the utility of this approach by testing the effects of opioid blockade, via naltrexone, on fMRI measures during methamphetamine cue-reactivity to elucidate the role of endogenous opioids in the neural systems underlying drug craving. Non-treatment-seeking individuals with methamphetamine use disorders ($N = 23$, mean age = 34.7) completed a randomized, placebo-controlled, within-subject design and underwent a visual methamphetamine cue-reactivity task during two blood-oxygen-level-dependent (BOLD) fMRI sessions prior to and following 3 days of naltrexone (50 mg) and matched placebo. fMRI analyses tested naltrexone-induced differences in BOLD activation and functional connectivity during cue processing. Naltrexone administration reduced cue-reactivity in sensorimotor regions and altered functional connectivity of dorsal striatum, ventral tegmental area, and precuneus with frontal, visual, sensory, and motor-related regions. Naltrexone also weakened the associations between subjective craving and precuneus functional connectivity with sensorimotor regions and strengthened the associations between subjective craving and dorsal striatum and precuneus connectivity with frontal regions. This study provides the first evidence that opioidergic blockade alters neural responses to drug cues in humans with methamphetamine addiction and suggests that naltrexone may be reducing drug cue salience by decreasing the involvement of sensorimotor regions and by engaging greater frontal regulation over salience attribution. Importantly, this study demonstrates an approach to leveraging fMRI technology to advance treatment development for addiction, namely by elucidating neural mechanisms of change sub-serving medication effects during exposure to drug cues.

A Self-Regulation Risk Phenotype: Implications for Treatment

Timothy J. Strauman, Bruce Luber, and Sarah H. Lisanby

To date, there has been only limited success across psychiatric disorders in matching treatments to individual variation in pathophysiology. An alternative strategy is to identify intermediate states (*risk phenotypes*) hypothesized to convey risk for a specific "pathway" to disorder and then determine whether the putative phenotype predicts vulnerability to disorder as well as response to specific treatments. We are exploring one potential transdiagnostic risk phenotype: dysfunction of *self-regulation*, defined as the psychological and neural processes that enable pursuit of personal goals. Our approach is based on regulatory focus theory [60••], a model of the cognitive-motivational systems underlying goal pursuit that distinguishes between strategic approach (promotion) and strategic avoidance (prevention). Chronic promotion goal pursuit failure is discriminately associated with depressive symptoms [61], and depression is associated with attenuated left prefrontal cortex (PFC) activation in response to promotion goal priming [62]. Previously, we developed self-system

therapy (SST), a brief structured psychotherapy targeting self-regulatory problems that has shown specific efficacy for individuals characterized by regulatory system dysfunction [63]. We have begun to extend this model to consider whether the neural circuits associated with promotion system dysfunction can be modulated therapeutically using repetitive transcranial magnetic stimulation (rTMS). In particular, we are exploring whether individually targeted neurostimulation can be paired effectively with intentional engagement of promotion-related cognition. We are using fMRI to identify, on an individual basis, left PFC sites (Brodmann areas 9/10), which are maximally responsive to promotion goal priming. Our hypothesis is that increasing specifically targeted left PFC activation during intentional engagement of promotion-related cognition by simultaneous use of rTMS and SST will reduce depression by facilitating more effective promotion system function. Initial findings suggest that this combined treatment approach is feasible and safe and may be a tool for delineating a self-regulation risk phenotype for depression and other disorders.

Novel Approaches to Assessing Motivation Among Those Seeking AUD Treatment

Jon Morgenstern

Motivation to reduce or quit drinking is a key component of the AUD treatment process and a common target of most evidence-based AUD treatments [64]. Building on prior work in cognitive science, this study developed an implicit cognition task and an ecological momentary assessment (EMA) task to assess motivation to reduce drinking and examined their psychometric properties, including their ability to predict subsequent drinking. Implicit alcohol approach and avoidance tendencies were assessed using a modified version of the stimulus compatibility response (SCR: [65]) task. Daily ratings of commitment to not drink heavily were assessed as part of a twice-daily survey delivered via a smart phone. Problem drinkers ($N = 60$) completed the measures at baseline, during, and at end of the 8-week treatment period. Baseline approach and avoidance significantly predicted 3-month drinking outcomes, explaining an additional 12 % of variance in outcome over baseline drinking. Daily commitment to not drink heavily was a significant predictor of next day's drinking, even after controlling for prior drinking. Readiness to change [66], a standard measure used to assess motivation in AUD treatment research, was not a significant predictor of drinking outcomes in any analysis. In addition, the implicit cognition and EMA measures were weakly associated with other commonly used treatment process measures such as self-efficacy and coping. Finally, the implicit cognition and EMA measures were unique predictors of drinking outcome when entered simultaneously in a regression analysis. Findings suggest that motivation to reduce drinking is a multifaceted construct and that future research should examine ways to decompose motivation to its component parts. Future research also should include the use of neuroimaging to probe neural substrates associated with motivational processes identified in this study. Overall, findings strongly support the use of novel approaches including cognitive neuroscience to advance the study of mechanisms of behavior change in AUD [67–69].

Conclusions

Neuroimaging studies, in contrast to behavioral research [1•], have begun to identify therapy-specific mechanisms of action. For example, CBT strengthens cognitive control circuitry, whereas mindfulness may act primarily by reducing the salience of reward cues. Behavioral treatments, however, involve multiple components and mechanisms. For example, other models of mindfulness have proposed brain mechanisms (e.g., PCC activation) that are being targeted in neurofeedback or have proposed that MBRP impacts neuroinflammatory and epigenetic mechanisms, in addition to brain circuitry. Other interventions, such as cognitive training, target specific aberrations in brain functioning to "tune up" circuits affected by heavy substance use.

The models of brain mechanisms that were presented highlight key issues in a nascent field: the challenge of more precisely specifying "how" and "for whom" treatment works at the level of the brain; complexities in determining the effects of treatment in the context of recovery of brain functioning that occurs with abstinence; the need for valid research methods and novel analytic strategies; determination of the "added value" of neuromarkers in predicting and monitoring response to treatment [70]; the influence of development (adolescent versus adult), co-occurring psychopathology, and a disorder's dynamic course on brain mechanisms; and comparison of brain mechanisms underlying medication and behavioral treatment effects, for example, on craving and cue reactivity across addictive behaviors. Importantly, the conceptual models invoke transdiagnostic concepts of cognitive control, reward processing, and self-regulation and consider individual differences, in moving toward "personalized medicine" [71].

Future directions include refining multimodal approaches to treatment, in which the same neural circuitry is targeted for intervention by carefully selected combinations of psychotherapy, neuromodulation (e.g., rTMS, tDCS), and medication, to amplify and accelerate treatment effects. Another direction involves identifying brain mechanisms underlying implicit cognitions [72•], a novel predictor of treatment outcome. Despite evidence of promise, the use of brain imaging for clinical applications faces limitations such as high cost. Nevertheless, neuroimaging provides powerful tools for identifying brain mechanisms that drive and sustain therapeutic

change and for determining for whom an intervention will be effective.

Videos of the presentations in this article can be accessed at: www.scienceofchange.org.

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Compliance with Ethical Standards

Conflict of Interest Tammy Chung reports grants from the National Institute on Alcohol Abuse and Alcoholism during the conduct of the study. Kathleen M. Carroll reports grants and other fees from CBT4CBT LLC outside of the submitted work. In addition, Dr. Carroll has a patent copyright issued. Sara Jo Nixon reports grants from NIAAA, during the conduct of the study. Bruce E. Wexler has patent functionalities of brain training programs pending. Judson Brewer reports grants from the National Institutes of Health during the conduct of the study and other fees from Claritas MindSciences outside the submitted work. Dr. Potenza reports other fees from Springer, Oxford Press, and American Psychiatric Press; fees from Opiant/Lakelight Therapeutics, RiverMend Health, INSYS, and Shire; grants from Pfizer; and fees from Gambling and legal entities, outside the submitted work.

Antonio Noronha, Kent Hutchison, Vince D. Calhoun, John D. E. Gabrieli, Jon Morgenstern, Lara Ray, Francesca Filbey, Timothy J. Strauman, Hedy Kober, and Sarah W. Feldstein Ewing declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent Cited studies comply with research protections for human and animal subjects, as required by the specific journal in which the study was published.

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