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Regional cerebral blood flow predictors of relapse and resilience in substance use recovery: A coordinate-based meta-analysis of human neuroimaging studies

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ABSTRACT

Background: Predicting relapse vulnerability can inform level-of-care and personalized substance use treatment. Few reliable predictors of relapse risk have been identified from traditional clinical, psychosocial, and demographic variables. However, recent neuroimaging findings highlight the potential prognostic import of brain-based signals, indexing the degree to which neural systems have been perturbed by addiction. These proposed “neuromarkers” forecast the likelihood, severity, and timing of relapse but the reliability and generalizability of such effects remains to be established.

Methods: Activation likelihood estimation was used to conduct a preliminary quantitative, coordinate-based meta-analysis of the addiction neuroprediction literature; specifically, studies wherein baseline measures of regional cerebral blood flow were prospectively associated with substance use treatment outcomes. Consensus patterns of activation associated with relapse vulnerability (greater activation predicts poorer outcomes) versus resilience (greater activation predicts improved outcomes) were specifically investigated.

Results: Twenty-four eligible studies yielded 134 foci, representing 923 subjects. Consensus activation was identified in right putamen and claustrum ($p < .05$, cluster-corrected) in relation to positive and negative treatment outcomes – likely reflecting variability in measurement context (e.g., task, sample characteristics) across datasets. A single cluster in rostral-ventral anterior cingulate cortex (rACC) was associated with relapse resilience, specifically ($p < .05$, cluster-corrected); no significant vulnerability-related clusters were identified.

Conclusions: Right putamen activation has been associated with relapse vulnerability and resilience, while increased baseline rACC activation has been consistently associated with improved treatment outcomes. Methodological heterogeneity within the existing literature, however, limits firm conclusions and future work will be necessary to confirm and clarify these results.

1. Introduction

Most individuals with substance use disorders (SUDs) experience relapse (Finney and Moos, 1992; Hubbard et al., 2003) – the consequences of which can impede or end individual progress in recovery. Unfortunately, relapse involves dynamic interplay between intrinsic and extrinsic risk factors that can be extremely unpredictable, making long-term management of SUDs particularly challenging. To better characterize relapse risk, cognitive-behavioral, psychosocial, clinical, and demographic factors have been investigated but demonstrate limited predictive utility with respect to treatment outcomes (Reske and Paulus, 2008). In search of more reliable, proximal predictors of

relapse, attention has increasingly turned to brain-based measures or “neuromarkers” representing neurocognitive resilience and vulnerability factors of relevance to addiction (Garrison and Potenza, 2014; Moeller and Paulus, 2018; Reske, 2013).

Neuroimaging has revealed alterations in brain function that accompany addiction – underlying both compulsive use (e.g., drug cue sensitization) and failure of higher-order inhibitory processes (Goldstein and Volkow, 2011). The degree to which reward- and control-related brain functions reflect addiction propensity (or severity) may therefore serve as a powerful prognostic indicator, forecasting the likelihood, extent, and even timing of relapse (Gabrieli et al., 2015). Beyond predicting relapse, patient-level vulnerability and resilience

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factors may also clarify novel treatment targets to support sustained recovery; e.g., neural loci implicated in inhibitory control or craving to be strategically up- or down-regulated by pharmacotherapy, cognitive training, or noninvasive brain stimulation. Findings from relapse neuroprediction studies can thus advance evidence-based personalized care for addictive disorders by (1) informing enhanced assessment of individual risk and resilience factors and (2) identifying precision interventions from such factors to improve outcomes.

The relapse neuroprediction literature has grown steadily over the past decade, spurring several contemporary reviews (Garrison and Potenza, 2014; Moeller and Paulus, 2018; Volkow and Baler, 2013). Most recently, Moeller and Paulus (2018) provided a comprehensive summary and synthesis of previously described event-related brain signals, prospectively associated with relapse versus abstinence, and noted frequent inconsistency in the direction of predictive effects. For example, response to drug-related cues or messages within medial prefrontal cortex (mPFC) and/or rostral-ventral anterior cingulate cortex (rACC) has been associated with both vulnerability to relapse (Beck et al., 2012; Reinhard et al., 2015) and improved treatment outcomes (Chua et al., 2011; Wang et al., 2015), as has dorsal-caudal ACC activation in the context of inhibitory control (Luo et al., 2013; Marhe et al., 2013) and striatal activation in both cue reactivity and control-related paradigms (Beck et al., 2012; Brewer et al., 2008; Kober et al., 2014; Li et al., 2015; Mann et al., 2014; Reinhard et al., 2015). Such findings suggest that the task and treatment context in which brain signals are measured may determine prognostic meaning; however, the authors conclude that relapse vulnerability is generally characterized by (1) increased activation to substance-related cues and decreased activation to non-substance-related stimuli across several cortical and subcortical regions, (2) prefrontal hyperactivation and striatal hypoactivation during execution of inhibitory control, and (3) reduced prefrontal activation during performance monitoring.

Findings summarized by Moeller and Paulus (2018) can be considered in the context of pharmacological and cognitive-behavioral interventions for SUDs – aiming to reduce craving and exposure to substance-related triggers, increase exposure to non-substance rewards, and improve self-control. Indeed, a recent quantitative meta-analysis of substance use treatment targets (Konova et al., 2013) suggests substantial overlap between brain regions associated with prospective substance use treatment outcomes and those modulated by treatment engagement. Konova and colleagues specifically investigated neural effects of acute or longitudinal exposure to substance use interventions and identified distinct targets of pharmacotherapy versus cognitive-behavioral treatment options (e.g., the latter being more likely to engage ACC, posterior cingulate cortex, and middle frontal gyrus). When considered alongside person-level neural predictors of relapse, these findings could guide individualized treatment planning and may also highlight promising new approaches to relapse prevention. However, while Konova et al. utilized a data-driven approach to identify consensus patterns of neural activation in existing substance use intervention studies, a similar quantitative meta-analysis has not yet been undertaken with respect to the relapse neuroprediction literature.

Herein, we utilized the same quantitative coordinate-based Activation Likelihood Estimation (ALE) meta-analytic method (Eickhoff et al., 2012; Eickhoff et al., 2009; Turkeltaub et al., 2012) employed by Konova et al. (2013) to objectively evaluate inter-study consistency in patterns of neural activation associated with prospective substance use treatment outcomes. This data-driven approach to evaluating the aggregate literature enables determination of statistical significance for consensus regions of interest identified across studies, making ALE an important complement to scholarly reviews. Lack of consistency within the current literature may also be informative, both with respect to issues of treatment and task effects raised by Moeller and Paulus (2018), as well as predictive effects that differ between SUDs. We reviewed the literature for prospective clinical outcome studies, wherein baseline neuroimaging data were associated with longitudinal

substance use outcomes – either through comparison of relapsing versus abstinent individuals or association with treatment outcome measures (e.g., frequency/severity of substance use during follow-up). To determine if enhanced activation of specific brain areas (such as those previously identified by Moeller and Paulus (2018) and Konova et al. (2013)) consistently and reliably forecasts better or worse treatment outcomes, effects were categorized as reflecting either relapse vulnerability (increased baseline activation associated with relapse, greater use, or other negative treatment outcome) or resilience (increased baseline activation associated with abstinence, reduced use, or other positive treatment outcome). Effects related to task type (i.e., cue reactivity versus non-cue-related paradigms) and well-represented diagnostic categories (i.e., stimulant use disorders (StimUDs) versus alcohol use disorder (AUD)) were also specifically evaluated.

2. Methods

2.1. Dataset selection and classification

Additional information regarding our methods is provided in Supplementary Materials (see Supplementary Fig. S1 for selection process flowchart). Briefly, the online database, PubMed (<https://www.ncbi.nlm.nih.gov/>), was used to identify peer-reviewed addiction neuroprediction studies, published between January 1, 2000 and October 1, 2017. A total of 953 research articles were identified using search terms: treatment outcome, relapse, recovery, prediction, addiction, dependence, substance use disorder, PET, positron emission tomography, fMRI, functional magnetic resonance imaging, and neuroimaging. Articles that were selected for inclusion: (1) reported activation foci¹ for a whole-brain search space using Montreal Neuroimaging Institute (MNI) or Talairach coordinates, (2) examined baseline functional neuroimaging data with respect to prospective substance use outcomes following treatment, (3) reported group-, correlational-, or survival-based between-subjects effects differentiating relapse versus abstinence or other treatment outcome (e.g., level/frequency of use, latency of relapse, treatment adherence), and (4) did not include a dataset (sample and task) reported in another included study. Included datasets are summarized in Table 1. To be maximally inclusive, “relapse” was defined as any negative treatment outcome (e.g., greater/earlier/more frequent use, treatment dropout); specific outcome measures are summarized in Supplementary Table S1. Each of the 24 studies identified for inclusion were subsequently re-reviewed and relevant foci were extracted, categorized as representing relapse vulnerability (increased baseline activation associated with poorer treatment outcomes) or resilience (increased baseline activation associated with improved outcomes),² and (if necessary) converted to MNI using the MNI2TAL web-based conversion tool (<http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html>).

Pooling vulnerability and resilience effects, 25 datasets were identified (from 24 publications), yielding 134 foci and representing 923 subjects. A total of 58 vulnerability-related foci were identified from 18 datasets (575 subjects) and 76 resilience-related foci were identified from 15 datasets (588 subjects). In keeping with Konova et al. (2013), we additionally explored task effects by identifying datasets from (1)

¹ Consistent with previous work (e.g., Chase et al., 2011; Konova et al., 2013), no statistical threshold was specified for foci selection; this approach is recommended because false negatives are more problematic for ALE than false positives (see Supplementary Materials).

² Because reduced activation can reflect improved processing efficiency, vulnerability effects identified herein may also reflect resilience, as has previously been demonstrated for the control-related fronto-cingulate network (Worhunsky et al., 2013) and individual control-related regions such as dorsolateral prefrontal cortex (Brewer et al., 2008). While functional interpretation of brain-based prognostic signals is necessary to translate results into clinically-meaningful applications, this was beyond the scope of the current meta-analysis. Consequently, our approach to categorizing foci was chosen to facilitate objective, expedient evaluation of the literature.

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