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A human brain circuit for addiction remission

Substance addiction is a major public health crisis. Neuromodulation treatments show promise, but the therapeutic targets remain unclear. Studying human brain lesions that led to addiction remission with the lesion-network-mapping approach resulted in the identification of a brain circuit shared across addiction disorders that may have therapeutic potential.

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The problem

Substance addictions are a public health problem worldwide and are one of the leading causes of death in the young. Addiction (a chronic compulsion to use a substance or engage in a behavior despite adverse consequences) is considered a brain-wide disorder, and treatments that target the neurobiological mechanisms of addiction are lacking. New treatment options for substance addiction are urgently needed. Brain stimulation and even neurosurgical brain lesioning (therapeutic removal or destruction of a brain area) have shown promise in relieving addiction, but it is unclear which brain areas should be targeted by these interventions and whether different targets are needed for different substance addictions[1]. One approach that could help to identify therapeutic targets would be to study patients who undergo spontaneous addiction remission after focal brain damage, such as a stroke[2]. However, lesions that lead to addiction remission have occurred in multiple different locations, which has left localization of the optimal therapeutic target unclear. A new technique, called 'lesion network mapping', combines lesion locations with an atlas of human brain connectivity (the normative connectome, which is created from a large dataset of resting-state functional magnetic resonance images of healthy volunteers) to map lesion-induced effects to brain circuits rather than to individual brain regions[3]. This technique has helped to identify brain circuits causally linked to many different neurological and psychiatric symptoms, such as movement disorders and mood disorders[4], and can help to identify effective therapeutic targets on the basis of brain lesions that provide symptom relief[5].

The solution

In this study, we investigated brain lesions that resulted in remission of smoking addiction and compared them with brain lesions in patients who were unable to quit smoking, across two independent cohorts. The brain connections disrupted by these lesions were identified through the use of a human brain connectome (Fig. 1). Although lesions occurred in different brain locations, they mapped to a common human brain circuit that includes regions previously linked to addiction neurobiology, such as the insula and paracingulate cortex, which showed positive connectivity (Fig. 1c, d), and the medial prefrontal cortex, which showed negative connectivity (Fig. 1c, d). Positive connectivity refers to regions with parallel changes in brain activity; negative connectivity refers to regions with coincidental but opposite changes. This circuit was commonly involved in other substance addictions, suggestive of a neural substrate shared across addiction disorders. The main regions of this circuit aligned well with prior neuromodulation targets that were demonstrated to be effective in improving substance addiction, but also suggested modifications to the locations of previous targets that might optimize the therapeutic effects.

The implications

Our study identifies a human brain circuit causally linked to addiction remission. This circuit may be common across different substance abuse disorders and provides a testable therapeutic target for addiction treatment in patients. This circuit could potentially be targeted directly by neuromodulation or brain-stimulation interventions. It could also help to guide the search for pharmacological agents that selectively modulate this circuit.

Of note, our results are based solely on retrospective analysis of existing datasets. These datasets covered only specific substances of abuse, and it is unclear whether our findings can be generalized to all substances of abuse or behavioral addictions. Prospective validation of our findings is needed, as are clinical trials that test whether neuromodulation targeting this circuit provides clinical benefit. These trials are necessary before translation of these findings into clinical practice for substance addiction. Identifying the most effective approaches for modulating this circuit by testing different targets within this network and neuromodulation protocols is needed to begin the translation of these findings into therapy.

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EXPERT OPINION

"The discovery of remission of nicotine addiction after structural damage to the insula provided a major clue on the neural circuitry underlying addiction. However, lesions of many other structures have comparable effects. The breakthrough reported here, using a sophisticated approach based on revealing a common neural circuitry among effective lesions by elegant neuroimaging analyses, may provide a causal circuitry underlying nicotine addiction and clinically useful loci for treatments such as transcranial magnetic stimulation." **Trevor Robbins, University of Cambridge, Cambridge, UK.**

FIGURE

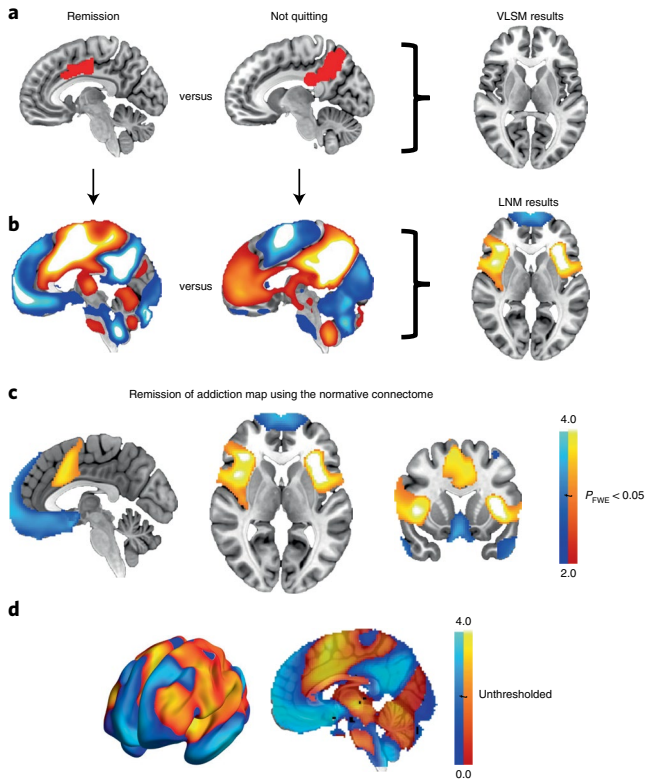

Fig. 1 | Addiction remission circuit. a,**b**, Examples of lesions that did (left) or did not (middle) result in remission of smoking addiction. No regions were significantly associated with addiction remission, as assessed by traditional voxel-lesion symptom mapping (VLSM) (**a**), whereas lesion-network mapping (LNM) of the same lesions showed a significant difference in connectivity (**b**). **c**, Brain regions significantly associated with addiction remission. Key: red scale, positive connectivity; blue scale, negative connectivity; pFWE, family-wise error-corrected *P* value. **d**, Whole-brain map of the addiction remission circuit without statistical thresholding; *t* value indicates the significance of the main effect. © 2022, Joutsa, J., CCBY 4.0.

BEHIND THE PAPER

We have long been puzzled by the fact that despite the wealth of available information on the neurobiological mechanisms of addiction, treatment targets have remained unknown. Although lesion-network mapping had proved useful in identifying brain circuits involved in neurological and psychiatric symptoms[4], it was not immediately clear how to best use this approach for finding new treatments. We were thrilled when we discovered that lesions that had improved essential tremor were connected to a specific spot in the thalamus that precisely matched the most efficacious neurosurgical target for treating this condition[5]. Inspired by this finding, we recognized the potential of the approach for identifying treatment targets in conditions with unclear localization in the brain. For this work, researchers from multiple institutions joined forces and combined several datasets in a true team effort to solve this problem. **J.J. and M.D.F.**

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FROM THE EDITOR

"The findings of this paper from Jousta, Moussawi, Siddiqi and colleagues are particularly exciting, as the authors make use of the lesion-network-mapping approach to identify a potential brain circuit that could be a target for neuromodulation therapies aimed at treating addiction." **Editorial Team, *Nature Medicine***