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# Commentary

# Indirect Targeting of Subsuperficial Brain Structures With Transcranial Magnetic Stimulation Reveals a Promising Way Forward in the Treatment of Fear

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Symptoms of fear and anxiety disorders are frequently elicited by environmental stimuli, most often the result of the association these stimuli have with past negative events. This has spawned a multidecade search for neuroscience-based approaches to reduce the influence that these associations have on affected individuals or to erase these associations entirely. Findings from an exciting new study by Raij *et al.* (1) suggest that exposure therapy, which targets the strength of fear memories, might be enhanced using transcranial magnetic stimulation (TMS) of the prefrontal cortex (PFC).

Exposure therapy is the most widely used method for diminishing fear in a clinical setting. This form of therapy capitalizes on the phenomenon of extinction, wherein repeated exposure to fear-inducing stimuli in the absence of ensuing aversive events gradually reduces responses to them. Extinction is believed to be supported by a new form of learning that inhibits the initial fear memory but does not erase it (2). Although exposure therapy is effective, because extinction learning is labile—it does not fully transfer to novel environments (e.g., outside the therapist's office), and fear is prone to spontaneously re-emerge with time or in response to sensitizing stimuli after extinction—the gains made from exposure therapy are also labile (2). In addition, extinction learning may itself be impaired in those with fear and anxiety disorders (3). These factors have motivated a search to augment the biological processes that support fear extinction. Preclinical studies have revealed that the ventromedial PFC (vmPFC) of the rodent supports the extinction of learned fear responses: excitation and inhibition of the vmPFC during extinction enhances and diminishes the efficacy of extinction, respectively (4,5). Moreover, human imaging studies have linked both functional and morphological changes in the vmPFC to individual differences in extinction (6,7), substantiating the notion that rodent and human vmPFC are homologous. The contribution of the vmPFC to extinction has been hypothesized to result from direct projections of neurons in the vmPFC to the amygdala, which is thought to be the critical site of plasticity supporting the acquisition of fear memories (8). Indeed, optogenetic approaches for directly targeting vmPFC–amygdala connections demonstrate the ability of this pathway to support extinction and inhibit fear (9). In light of this, the ability to selectively stimulate the human vmPFC represents a promising approach to facilitate exposure therapy.

There are several issues with targeting the vmPFC of humans during extinction. First, the absence of known molecules specific to the vmPFC limits the likelihood that a systemically administered drug might selectively alter vmPFC function. Second, the deep location of the subregion of the vmPFC associated with extinction in humans makes it inaccessible to contemporary methods like TMS, which enable the excitation/inhibition of superficial brain regions. Because of this, the translational utility of altering vmPFC function has been elusive up to this point.

Raij *et al.* (1) take an innovative new approach to circumvent the problem of the vmPFC being inaccessible to TMS. Capitalizing on functional connectivity analysis, a superficial region of the left posterolateral PFC was identified that is coupled to the region of the vmPFC that is activated during extinction. Next, in a laboratory setting, healthy subjects were conditioned to fear multiple stimuli paired with an electric shock. Fear of these stimuli was then extinguished, and during extinction the presentation of one of the conditioned stimuli was paired with TMS, either of the aforementioned region or a region immediately rostral to it that was not functionally connected with the vmPFC. Remarkably, when subjects were re-exposed to these stimuli the next day in the absence of stimulation, they showed reduced responses to the stimulus paired with TMS of the target brain region. The elegant inclusion of an adjacent control site at which stimulation was ineffective helps eliminate concerns about nonspecific effects. These findings suggest that stimulation of a vmPFC extinction circuit in humans can facilitate extinction.

This is a preliminary study, and much remains to be done before this approach can be used with confidence in a clinical setting. One of the major problems with extinction is that it is typically context specific. If the stimulation protocol used also enhanced the context specificity of extinction, exposure therapy could be hindered because the reduction in fear would not transfer beyond the therapy session. In addition, the finding that fear was reduced only to the conditioned stimulus paired with TMS could be problematic. Given that the cues were very similar (lights of different colors), the fact that the reduction in fear did not transfer between stimuli calls into question the generalizability of the benefits gained. Future studies will need to explore how the benefits in extinction produced by TMS are related to the stimuli used, how these benefits transfer to similar stimuli, and how long these gains last.

Moreover, technical/monetary hurdles may limit the utility of TMS as an adjunct to exposure therapy. It is notable that the targeted region was only 23 mm away from the control region

SEE CORRESPONDING ARTICLE ON PAGE 129

 
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whose stimulation had no impact on extinction. Precise targeting of this structure is therefore far from trivial in a clinical setting. In light of this, the magnitude of effects observed will need to be weighed against the cost and difficulty of such an approach.

Finally, from a theoretical standpoint, it is interesting that although a functional interaction was observed between the vmPFC and the region targeted in the PFC, diffusion tensor imaging did not confirm a direct projection between these regions, nor was it demonstrated that the stimulation protocol changed the activity of the vmPFC. Therefore, it is possible that the vmPFC did not contribute to the observed effect on extinction. This does not limit the potential relevance of the targeted brain region, but much remains to be addressed with respect to how it influences the activity of the vmPFC or other components of the circuitry that supports extinction. The answers to these questions will be important for understanding the future applicability of using functional connectivity as a guide for indirectly targeting subsuperficial brain structures with TMS.

While the work of Raij *et al.* (1) is in the early stages, the potential utility of this approach to augment fear extinction is tremendously exciting.

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