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Stimulating social interest: The translational value of basic investigations into frontal cortex function

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<https://doi.org/10.1016/j.neuron.2024.07.004>

Fan et al. use electrical stimulation during a novel social interaction paradigm to demonstrate a role for the orbitofrontal cortex in directing social attention. Their results shed new light on the basic functions of the orbitofrontal cortex and have translational value in understanding circuit modulation for psychiatric disorders.

Some of our earliest insights into the localization of brain function came from applying electrical stimulation to the brains of humans and other animals. Although acute effects on motor and sensory areas were immediately discernable, frontal areas beyond the motor cortex did not produce clear behavioral or perceptual changes and were deemed to be “silent.” However, decades later, there is renewed interest in stimulation of these “silent” areas, spurred in part by clinical observations that applying stimulation to nodes of frontal and limbic circuits might improve symptoms of otherwise refractory psychiatric disorders. While promising, many relevant factors remain poorly understood. For instance, it is unclear what cognitive or emotional processes might be affected by stimulating frontal cortex targets in a healthy brain, let alone in a disease state.

In this issue of *Neuron*, Fan et al.¹ take steps to address these gaps by investi-

gating the effects of frontal cortex stimulation on social behavior in rhesus monkeys. Using a novel social paradigm and closed-loop approach, they demonstrate that stimulation of the orbitofrontal cortex (OFC) consistently increases socially directed gaze. These results open the door to new investigations of the OFC's role in dynamic social interaction, as well as the impact of modulating the OFC's functions with exogenous stimulation.

The authors targeted a circuit of frontal areas including the OFC, dorsomedial prefrontal cortex (dmPFC), and anterior cingulate cortex gyrus (ACCg). These targets were selected based on their previous work showing that neurons in these regions discriminate faces from objects, eyes from other facial landmarks, and track one's own gaze relative to a partner's.² In the present study, brief trains of electrical stimulation were delivered to each region separately when the stimulated monkey (M1) moved their gaze

to the region around the eyes of a partner monkey seated opposite them. The closed-loop element of the design is particularly novel, as it relied on tracking the monkey's natural gaze pattern and, in real time, using it to trigger stimulation to the same subject's brain. Doing the experiment in a closed loop allowed the monkeys to view each other naturally and spontaneously, while also constraining variables such as eye position and visuospatial attention at the moment that stimulation was delivered.

The authors found that only stimulation of the OFC resulted in short-latency changes in gaze behavior. Within 1.5 s following stimulation, M1's spontaneous fixations shifted closer to the eyes of the other monkey and increased in frequency compared to sham stimulation. M1 subjects also showed a shorter “reciprocity latency,” meaning that if the partner monkey looked at them within 5 s following stimulation, it took M1 less



time to look back toward the partner's face. In no case did stimulation elicit a stereotyped eye movement as if it were directly affecting saccade execution. Instead, stimulating the OFC at the time when the actor monkey's eyes were directed toward their partner's appeared to increase their propensity to look at them again.

Similar effects were not found with stimulation applied to the dmPFC nor ACCg. In the dmPFC, there were longer timescale effects, in which the tendency for M1 to follow gaze patterns of their partner increased as gaze was directed closer to the face, and this effect became more pronounced as the session went on. Coupled with a lack of short-latency changes, this suggests that repeated dmPFC stimulation has a modulating effect on social gaze exchanges. Critically, the effects of OFC and dmPFC stimulation were specific to social settings. There were no changes in gaze when M1 looked at a random dot motion stimulus placed in the same location as the partner's eyes. This served as a nonsocial control that included a moving stimulus that elicited fixations from M1 similar to the live partner monkey. In addition, there were no effects when OFC stimulation was triggered by M1 gazing at the partner's mouth region, consistent with a more relevant role for the eyes in social interactions among primates.

Together, these results suggest a direct causal link between OFC function and social gaze exchanges. Although the OFC is commonly studied in the context of subjective decision-making, it has also been implicated in social behavior generally and social gaze monitoring specifically. Fan et al.'s combination of temporally precise stimulation with naturalistic social viewing provides further insight into the potential role played by the OFC in the social domain. For instance, the fact that frequency and proximity of socially directed fixations increased but fixation duration did not suggests that stimulation affected mechanisms of social attention. In primates, more frequent eye contact is found with heightened interest or attention, perhaps because it allows one agent to monitor another for changes in their state.³ Long duration eye contact, however, is more often associated with aggression, particularly in non-human primates.

Therefore, it is possible that OFC stimulation increased the tendency to attend to or monitor informative features of a social partner. Given the importance of the OFC in valuation and the links between valuable stimuli and attention, one possibility is that stimulation had an activating effect on the OFC and boosted the perceived value of cues from a social partner, thereby increasing the tendency for M1 to pay attention to those cues.

On the other hand, experimental lesions of the OFC have been found to increase spontaneous visual exploration of static images of human and non-human primate faces.⁴ This includes longer gaze times at the eyes as well as inanimate objects with face-like features that elicit face pareidolia. Although this effect was not replicated with more focal OFC lesions,⁵ it is counter to the interpretation that heightened social attention results from activation of the OFC and instead suggests that engagement with social cues may increase with loss of OFC function. In parallel, human patients who have sustained OFC damage display interpersonal interactions with strangers that have been described as inappropriately familiar, including overly personal speech, intrusive body language, and sustained eye contact.⁶ Therefore, another possibility is that stimulation temporarily inhibited the OFC, reducing the animals' normal tendency to avoid eye contact, which in many settings is socially appropriate among non-human primates.

These possible interpretations illustrate how applying current to an interconnected network of heterogeneous but electrically excitable cells can produce consequences that defy simple explanation. Electrical stimulation can elicit behavioral effects associated with either activation or inhibition of the stimulated brain region, and effects appear to depend on the stimulation parameters used. The parameters in this study are more in line with those believed to be activating (high frequency and mid-low current), but they are something of a middle ground, and a net inhibitory effect is also possible. Moreover, voltage-sensitive dyes have shown that electrical stimulation can cause an initial activation of neurons, followed by suppression, suggesting that behavioral manifestations may arise from a mix of

processes rather than pure activation or inhibition.⁷

Clearly, electrical stimulation does not have the specificity of approaches like optogenetics, which can selectively target certain cell types (though consequences of optogenetic perturbations are likely underestimated as well⁸). Despite this, it is a translational method with unmatched potential to impact human health. Stimulation of the OFC in epilepsy patients with mild to moderate symptoms of depression acutely boosted mood, and the OFC is among the areas being considered for future therapeutic interventions.⁹ In this context, understanding how stimulation of the OFC and other clinical targets affects ongoing behavior, including social attention, could help refine clinical approaches to achieve therapeutic goals while avoiding undesirable side effects. Perhaps OFC stimulation dials up the perceived value of social cues in the environment, and this helps to override social withdrawal that accompanies severe depression. Perhaps OFC stimulation reduces social inhibition or self-monitoring tendencies that become overactive in the case of depression and anxiety. Non-human primates are particularly important model species for investigating these possibilities because they have brain anatomy similar to humans, meaning that homologous stimulation targets can be identified.¹⁰ They also have complex social behaviors, including the use of gaze, that bear resemblance to our own.

Overall, Fan et al.'s results expand our understanding of the OFC's role in social behaviors, and as with any novel approach, also raise new and important questions. Beyond discerning the mechanism within the OFC that links stimulation to social gaze, there are questions of how stimulation at one node affects larger brain networks that allow us to perceive and interpret faces as relevant social cues. For instance, connections between the OFC and amygdala, which is also involved in mutual gaze, might be important in facilitating this behavior. Pursuing these investigations has the potential to advance our understanding of basic function in healthy brains by illuminating mechanisms of natural social interactions. But there is also a pressing translational need for more answers to these

basic science questions, and Fan et al. move the field one step closer to both of these goals.

ACKNOWLEDGMENTS

We would like to thank Peter Rudebeck and Catherine Elorette for comments on the manuscript. Funding support was provided by NIH D-SPAN award NS125826 to J.S.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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