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A cross species approach to understanding DBS modulation of fear

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Standard treatments for patients suffering from obsessive-compulsive disorder (OCD) are pharmacotherapy and behavior therapies based on the principle of extinction, i.e. exposure with response prevention (ERP) (1), or both combined. For patients who do not respond to these modalities, deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) region (2, 3) is an approved treatment in the E.U. and has humanitarian approval in the U.S.A. The VC/VS target has been developed empirically since 1998, using anterior capsulotomy ablation as the starting point, rather than targeting of specific pathways within this densely innervated zone. We have therefore applied a cross-species (rat, monkey, human) approach to identify the key circuits to target, with the goals of better understanding mechanisms of action and thereby refining DBS treatment to enhance effectiveness and reduce potential adverse effects.

Deep brain stimulation of VC/VS for refractory OCD

Some clinical effects of DBS can be immediate, while others develop slowly. For example, DBS at dorsal regions of VC/VS may reduce nonspecific anxiety intraoperatively (Figure 1A) (4); the maximal reductions in core OCD symptoms typically take weeks to months (2, 3). Importantly, OCD symptoms are further reduced when patients receiving DBS engage in ERP, where patients are exposed to symptom triggers but coached to refrain from

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compulsive actions (3). Because all DBS candidates must have failed to respond to ERP before surgery, DBS may in essence facilitate responses to a previously failed therapy.

It is possible that ERP, intended to extinguish compulsions (1), was ineffective pre-DBS due to dysfunction in fear extinction circuits. In support of this, OCD patients exhibit impaired extinction memory, as well as failure to activate the ventromedial prefrontal cortex (vmPFC) (5, 6). Furthermore, OCD patients also exhibit hyperactivity in dorsal anterior cingulate cortex (dACC, area 32) and the orbitofrontal cortex (OFC), areas which drive fear and OCD symptoms, respectively (7, 8).

The striatum is organized into specific patterns based on cortical input (8, 9). In the last 10 years, clinicians have noted that more ventral VC/VS targets produced fear and panic in some patients (Figure 1A) (4, 10). Targets near or dorsal to the junction of the white matter of the anterior limb of the internal capsule have been more commonly (albeit not universally) associated with better clinical responses (2, 3). Functional and anatomical differences within VC/VS targets need to be better understood on both the group and individual levels to determine which fibers to target and which to avoid. Recent advances using 3-D tract tracing techniques in monkeys have suggested that fibers from the ventral medial prefrontal cortex (vmPFC) may be responsible for the fear seen with ventral DBS (Figure 1B) (11). However, at more dorsal sites, convergence of fibers from dACC and OFC may be important for clinical improvement during DBS.

Using rodent model to understand the mechanism of DBS

Rodent studies of DBS have found opposite behavioral effects of dorsal vs. ventral stimulation sites within the ventral striatum. In auditory fear conditioning, stimulation at ventral sites increased conditioned freezing to ceiling levels, whereas stimulation at more dorsal sites reduced freezing (Figure 1A), and enhanced extinction memory (12). Paralleling monkey and human anatomy, we observed that the infralimbic prefrontal cortex (IL, vmPFC homologue) projects through the more ventral sites, whereas prelimbic prefrontal cortex (PL, dACC homologue) and the medial orbitofrontal cortex (MO, OFC homologue) converge at the more dorsal sites (Figure 1B) (13). Activity in both PL and mOFC is necessary for fear expression (13, 14), whereas activity in IL is necessary for fear inhibition (14). Thus, in both rodents and humans, DBS-like stimulation of the dorsal sites may tend to inhibit fear-enhancing circuits; whereas DBS of the ventral sites may tend to inhibit fear-inhibiting circuits (Figure 1B). A similar mechanism has been proposed for Parkinson's disease, where DBS of the sub thalamic nucleus (STN) leads to rapid inhibition of motor cortex which projects to STN (15).

Rodent models can also provide clues about potential neurochemical mediators of DBS's beneficial long-term effects. DBS-mediated inhibition of fear circuits may lead to activation of fear-inhibiting structures. In support of this, DBS of dorsal-VS (but not ventral-VS) increases the expression of brain derived neurotrophic factor (BDNF) in IL neurons (16). BDNF is important for long-term memory processes and is needed for fear extinction memory within IL (17). DBS of dorsal-VS also increases the expression of plasticity marker pERK in IL, as well as in the lateral portion of central amygdala (CeL) (12), both of which

are important for fear extinction memory (18). Furthermore, serum levels of BDNF are reduced in OCD (19), and a BDNF genetic polymorphism is correlated with impaired response to ERP therapy (20), suggesting ERP failure may involve dysfunctional BDNF regulation. Therefore, DBS-induced increases in prefrontal BDNF, may repair faulty extinction circuits in OCD.

In summary, cross-species homology of cortico-striatal circuits in humans, monkeys and rodents allows us to test hypotheses regarding the circuitry by which DBS of the VC/VS might modulate fear expression and extinction in humans. This approach reveals key circuits that, in future, may be modulated by non-invasive/circuit-based neuromodulation approaches such as transcranial magnetic stimulation.

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Figure 1.

A model by which DBS modulates fear circuits in OCD. **A.** DBS of Dorsal-VS & Ventral-VS in humans has opposite effects on anxiety (*left*). DBS of Dorsal-VS & Ventral-VS in rats has opposite effects in freezing behavior (*right*). **B.** Homology of cortical sources targeted by DBS of Dorsal-VS & Ventral-VS in both humans (*left*) and rats (*right*). DBS of ventral-VS increases in fear are due to inhibition of vmPFC (IL in rat), whereas DBS decreases in fear effects are due to inhibition of dACC (PL in rat) and OFC (MO in rat) targets.