techniques should be revised to safely allow a time delay to be set. This would involve using a maintenance agent, such as an intravenous narcotic or an inhalational agent to follow the induction agent, thereby maintaining unconsciousness beyond the action of the induction agent. A longer acting muscle relaxant would be needed or alternatively the administration of suxamethonium could be delayed until just prior to the ECT stimulus (but allowing adequate time for full relaxation to occur). We believe that these changes to ECT practice would improve efficacy and cognitive outcomes.

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A Cross Species Approach to Understanding DBS Modulation of Fear

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 (Fig. 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 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 (Fig. 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 (Fig. 1B) [11]. However, at more dorsal sites, convergence of fibers from dACC and OFC may be important for clinical improvement during DBS.

Using rodent models 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 dorsal sites reduced conditioned freezing and enhanced extinction memory, whereas stimulation at more ventral sites increased freezing to ceiling levels (Fig. 1A) [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 (Fig. 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-mediated inhibition of cortical sources in the dorsal sites may tend to inhibit fear-enhancing circuits; whereas DBS of the ventral sites may tend to inhibit fear-inhibiting circuits (Fig. 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].

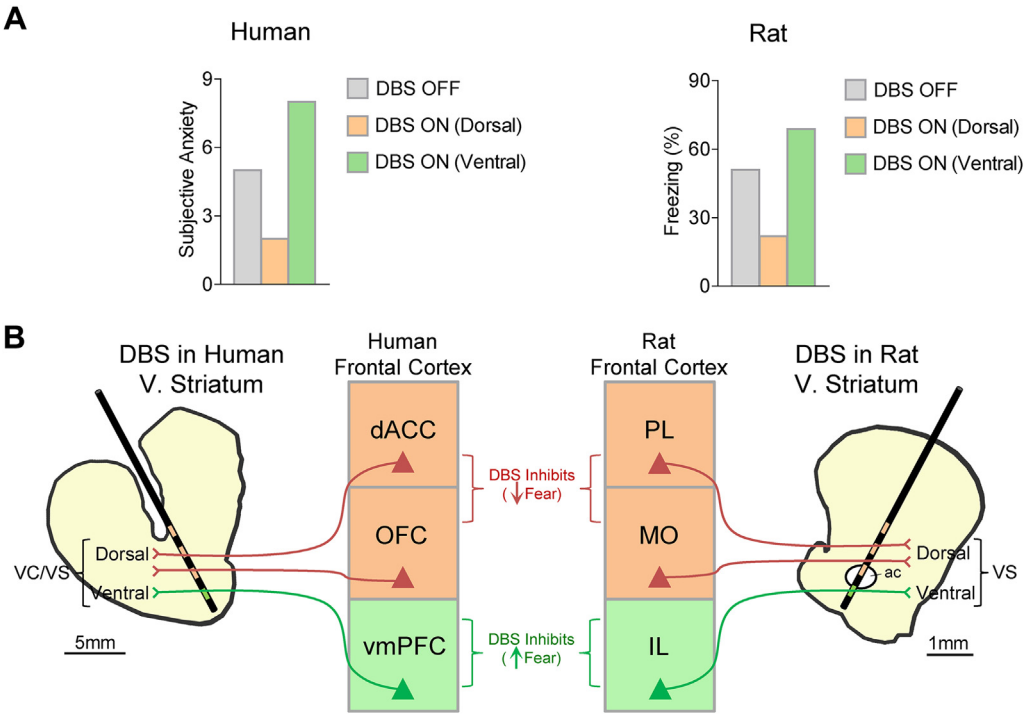

Figure 1. A model by which DBS modulates fear circuits in OCD. A) DBS of Dorsal-VS & Ventral-VS in humans has opposite effects on anxiety (*left*). DBS of Dorsal-VS & Ventral-VS in rats has opposite effects in freezing behavior (*right*). B) Homology of cortical sources targeted by DBS of Dorsal-VS & Ventral-VS in both humans (*left*) and rats (*right*). DBS of dorsal-VS increases anxiety/fear via inhibition of dACC (PL in rat) and OFC (MO in rat) targets, whereas DBS of ventral-VS increases anxiety/fear via inhibition of vmPFC (IL in rat).

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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Trigeminal Nerve Stimulation (TNS) for Major Depressive Disorder in Pregnancy: A Case Study

Dear Editor,

Following the rationale of the first report on transcranial direct current stimulation for auditory verbal hallucinations during pregnancy recently published in Brain Stimulation [1], our group has satisfactorily evaluated a Trigeminal Nerve Stimulation (TNS) protocol for Major Depressive Disorder (MDD) during pregnancy. MDD has an estimated prevalence ranging from 8.3% to 12.7% during pregnancy of US women. Those figures are estimated to be higher in poor women in developing countries [2]. In addition to the core depressive symptoms, MDD in pregnancy is associated with preterm birth, preeclampsia, low birth weight, tobacco, alcohol, and illicit drug use, decreased prenatal vitamin use, and decreased prenatal physician visits [2]. MDD treatment is always indicated. However, no oral antidepressant medication has been shown to be completely safe for use during pregnancy [3]. Conflict among pregnant women regarding psychotropic use during pregnancy has been previously reported [4]. In fact, treatment adherence decreases during pregnancy [4]. Neuromodulation strategies arise as new possibilities for the treatment of MDD during pregnancy.

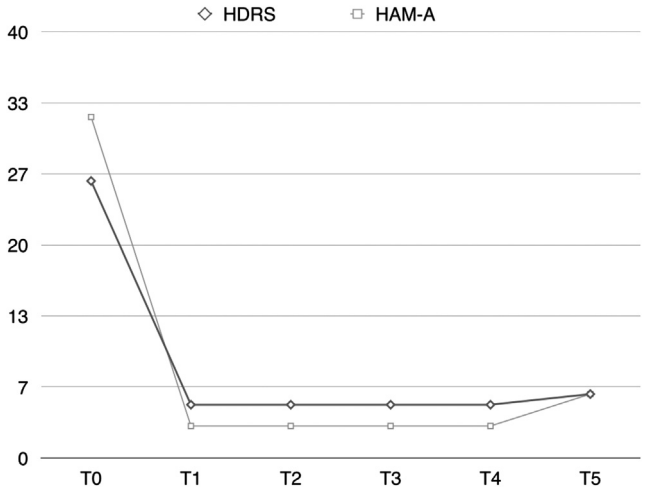

Figure 1. Hamilton Depression Rating Scale – 17 items (HDRS), Hamilton Anxiety Rating Scale (HAMA). T0 = baseline; T1 = end of Treatment; T2 = one-month follow-up; T3 = two-month follow-up; T4 = three-month follow-up (before child-birth); T5 = four-month follow-up (one month after child-birth).

TNS applies an electric current over the supraorbitary branch of the trigeminal nerve of the trigeminal nerve. Further stimuli propagates toward brain areas that are related to mood and anxiety symptoms, such as the amygdala and the frontal lobe [5]. TNS has been successfully associated with the treatment for MDD [6].

A 40-year-old patient with 26 weeks of pregnancy with MMD successfully underwent a TNS intervention protocol, with amelioration of her symptoms. “Ms. S.” experienced depressive and anxiety symptoms 12 months prior to stimulation and initiated a pharmacological treatment with fluoxetine 60 mg/day, with successful amelioration of her symptoms. However, three months after remission, pregnancy was diagnosed, at six weeks gestation. The patient refused to continue the fluoxetine treatment due to her fear of fetal malformations and discontinued the medication. Two months after the antidepressant discontinuation she presented depressive and anxiety symptoms, such as insomnia, sadness, hyporexia, anergia and anhedonia. Considering the severity of her symptoms and the wish not to use pharmacological treatments, TNS was started after she provided written informed consent (IRB approved) and was informed of the lack of scientific data on the subject.

Ten consecutive daily TNS sessions were performed. Electric stimulation was performed at 120 Hz with a pulse wave duration of 250 μs for 30 min per day. We used retangular autoadhesive rubber electrodes of 20 cm^2 placed over supraorbital trigeminal branches (V1) bilaterally following our previously tested protocol [5]. For assessing MDD symptoms we used the Hamilton Depression Rating Scale – 17 items (HDRS). We also assessed cognitive functions with the Montreal Cognitive Assessment (MOCA) and anxiety symptoms with the Hamilton Anxiety Rating Scale.