Archival Report

An Avoidance-Based Rodent Model of Exposure With Response Prevention Therapy for Obsessive-Compulsive Disorder

Jose Rodriguez-Romaguera, Benjamin D. Greenberg, Steven A. Rasmussen, and Gregory J. Quirk

ABSTRACT

BACKGROUND: Obsessive-compulsive disorder is treated with exposure with response prevention (ERP) therapy, in which patients are repeatedly exposed to compulsive triggers but prevented from expressing their compulsions. Many compulsions are an attempt to avoid perceived dangers, and the intent of ERP is to extinguish compulsions. Patients failing ERP therapy are candidates for deep brain stimulation (DBS) of the ventral capsule/ventral striatum, which facilitates patients' response to ERP therapy. An animal model of ERP would be useful for understanding the neural mechanisms of extinction in obsessive-compulsive disorder.

METHODS: Using a platform-mediated signaled avoidance task, we developed a rodent model of ERP called extinction with response prevention (Ext-RP), in which avoidance-conditioned rats are given extinction trials while blocking access to the avoidance platform. Following 3 days of Ext-RP, rats were tested with the platform unblocked to evaluate persistent avoidance. We then assessed if pharmacologic inactivation of lateral orbitofrontal cortex (lOFC) or DBS of the ventral striatum reduced persistent avoidance.

RESULTS: Following Ext-RP training, most rats showed reduced avoidance at test (Ext-RP success), but a subset persisted in their avoidance (Ext-RP failure). Pharmacologic inactivation of lOFC eliminated persistent avoidance, as did DBS applied to the ventral striatum during Ext-RP.

CONCLUSIONS: DBS of ventral striatum has been previously shown to inhibit lOFC activity. Thus, activity in lOFC, which is known to be hyperactive in obsessive-compulsive disorder, may be responsible for impairing patients' response to ERP therapy.

Keywords: Deep brain stimulation, Obsessive-compulsive disorder, Orbitofrontal cortex, Platform-mediated avoidance, Rat, Ventral striatum

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Obsessive-compulsive disorder (OCD) is a devastating illness affecting an estimated three million individuals in the United States alone (1). Many of the compulsive behaviors in OCD (e.g., hand washing, lock checking) are viewed as protective against perceived threats (e.g., infection, intruders) (2). The standard behavioral therapy for OCD is exposure with response prevention (ERP), in which patients are repeatedly exposed to triggers for their compulsions but are prevented from expressing the compulsion (3). The goal of repeated sessions of ERP is to extinguish compulsive behaviors (2). ERP is effective in the majority of OCD patients; however, approximately 40% either drop out or fail ERP (4,5). Little is known about the mechanisms of ERP therapy failure or the interactions between extinction and compulsive behaviors, thereby necessitating an animal model.

Patients failing to respond to ERP, as well as to pharmacotherapies, are candidates for deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS). DBS of VC/VS reduces OCD and anxiety symptoms (6) and facilitates patients' response to ERP therapy (7,8). OCD is associated with excessive activity in the orbitofrontal cortex (OFC) [for reviews see (9,10–12)], and DBS has been shown to reduce blood oxygen level–dependent signaling in OFC together with compulsions (13–15). In rodents, DBS of dorsal VS (a rodent homologue of VC/VS) has been shown to reduce the firing rate of neurons within the lateral OFC (lOFC) (16). However, the role of lOFC in ERP has not been studied. Therefore, to further explore the roles of lOFC and DBS in ERP, we developed a rodent model of ERP therapy using a platform-mediated avoidance task (17). This allowed us to characterize persistent avoidance and its response to manipulations of OFC, both directly and indirectly via DBS of the ventral striatum.

METHODS AND MATERIALS

Subjects

One hundred ten male Sprague Dawley rats (~325 g; Harlan Laboratories, Indianapolis, IN) were housed and handled as previously described (18). Rats were fed standard rat chow in

a restricted manner (18 g/day) to facilitate pressing a bar for food on a variable-interval schedule of reinforcement (variable interval 30 seconds). All procedures were approved by the Institutional Animal Care and Use Committee of the University of Puerto Rico School of Medicine in compliance with the National Institutes of Health guidelines for the care and use of laboratory animals.

Behavior

Rats were initially trained to press a bar to receive food pellets on a variable-interval reinforcement schedule (variable interval 30 seconds) inside standard operant chambers (Coulbourn Instruments, Whitehall, PA) located in sound-attenuating cubicles (MED Associates, St. Albans, VT). Bar pressing was used to maintain a constant level of activity against which avoidance and freezing could reliably be measured. Food was available throughout all phases of the experiment.

For platform-mediated avoidance, rats were trained as previously described (17). Briefly, rats were conditioned with a pure tone (30 seconds, 4 kHz, 75 dB) coterminating with a shock delivered through the floor grids (2 seconds, 0.4 mA). The intertrial interval was variable, averaging 3 minutes. The platform was fixed to the floor and was present during all stages of training (including bar–press training). Rats were conditioned for 10 days, with nine tone–shock pairings per day with the reinforcement schedule changed to a continuous schedule of reinforcement during the tone. The availability of food on the side opposite to the platform motivated rats to leave the platform during the intertrial interval, facilitating trial–by–trial assessment of avoidance.

Once platform-mediated avoidance was learned, rats underwent extinction (tones with no shock) in the presence of a transparent Plexiglas barrier that prevented access to the platform. During extinction with response prevention (Ext-RP), rats underwent sessions consisting of 15 tone-alone presentations across 3 consecutive days with a variable interval 30 seconds food schedule. After 3 days of Ext-RP, the barrier was removed and rats were again exposed to the tone.

Surgery and Histology

Rats were initially anesthetized with isoflurane inhalant gas (5%) in an induction chamber and positioned in a stereotaxic frame. Isoflurane (2% to 3%) was delivered through a facemask for anesthesia maintenance. For our inactivation experiment, rats were bilaterally implanted with 26-gauge guide cannulas (Plastics One, Roanoke, VA) in the lOFC using the following coordinates: +3.20 mm anterior-posterior; ±3.30 mm medial-lateral; and +4.40 mm dorsal-ventral to bregma (19). Cannulas were fixed to the skull with anchoring screws and acrylic cement. After surgery, a topical triple antibiotic was applied around the surgery incision, and an analgesic (ketoprofen, 5 mg/kg) was injected intramuscularly. Stainless steel obturators (33 gauge) were inserted into the guide cannulas to avoid obstructions until infusions were made. Rats were allowed 5 to 7 days to recover from surgery before behavioral testing.

For our DBS experiment, a similar surgical procedure as above was used, except that rats were implanted with concentric bipolar stimulating electrodes (NEX-100; Rhodes Medical Instruments, Santa Barbara, CA) as previously described (20). Electrodes were aimed at a dorsal VS site (+1.2 mm anterior-posterior, ±2.0 mm medial-lateral, and −6.5 mm dorsal-ventral to bregma). Rats were allowed 5 days to recover from surgery before behavioral testing.

After behavioral experiments, rats were deeply anesthetized with sodium pentobarbital (450 mg/kg intraperitoneal) and transcardially perfused with 0.9% saline followed by a 10% formalin solution. Brains were removed from the skull and stored in 30% sucrose for cryoprotection for at least 72 hours before sectioning and Nissl staining. Histology was analyzed and correct placement of cannulas and stimulating electrodes was assessed.

Pharmacologic Inactivation

Fluorescent muscimol (MUS) (0.2 μL; BODIPY TMR-X Conjugate; Sigma-Aldrich, St. Louis, MO) was infused to enhance gamma-aminobutyric acid type A receptor activity, thereby temporally inactivating lOFC. On the day of infusion, 0.2 μL of MUS or saline (SAL) (vehicle) was infused at a rate of 0.2 μL/min. Injector tips extended 1.0 mm beyond the guide cannula. After infusion, injectors were left in place for 1 minute to allow the drug to diffuse. Eight rats were eliminated from our MUS experiment because the injections were located outside of our area of interest (lOFC).

Deep Brain Stimulation

Stimulation was monophasic, with the deeper contact as negative. We used DBS parameters similar to those used in humans (100 μA, 0.1-ms pulse duration, 130 Hz), which have been used in previous rat models studying DBS-like stimulation (16,20–22). Stimulation was generated with an S88X stimulator (Grass Instruments, Warwick, RI) and a constant-current unit (SIC-C Isolation Unit; Grass Instruments). Three rats were eliminated from DBS experiments because placements were not located in dorsal VS, as previously described (20).

Data Collection and Analysis

Behavior was recorded with digital video cameras (Micro Video Products, Bobcaygeon, Ontario, Canada). Freezing was quantified from digitized video images using commercially available software (Freezescan; Clever Systems, Reston, VA). Platform avoidance was quantified by observers blinded to experimental group, where avoidance was defined as the rat having at least two paws on the platform. The time spent avoiding during the tone (percent time on platform) was used as our avoidance measure. We calculated percent suppression of bar pressing for each tone as previously described (17): (pretone rate − tone rate) / (pretone rate + tone rate) × (100). A value of 0 indicates no suppression, whereas a value of 100% indicates complete suppression. To calculate pretone rates, we used the 60 seconds before tone onset. Avoidance, freezing, and suppression of bar pressing to the tone were expressed as a percentage of the 30-second tone presentation. Statistical significance was determined with Student two-tailed t tests, Wilcoxon matched pairs test, one-way analysis of variance (ANOVA), or repeated-measures ANOVA, followed by Tukey post hoc analysis, when appropriate (STATISTICA; StatSoft, Inc., Tulsa, OK).
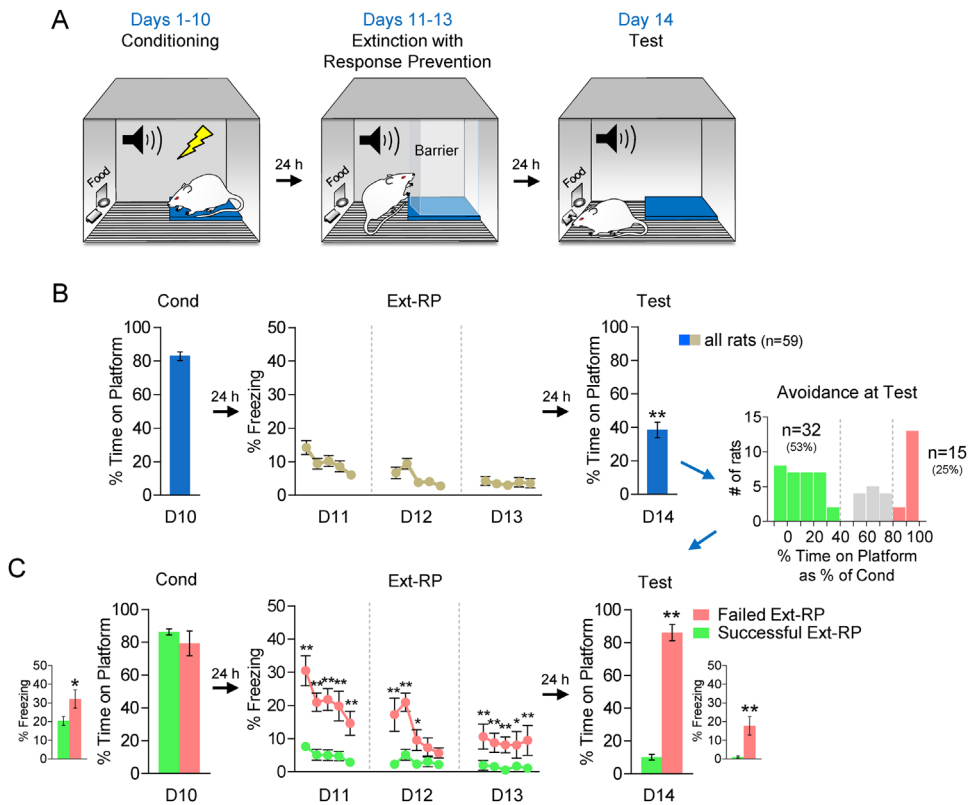
A Days 1-10 Conditioning | Days 11-13 Extinction with Response Prevention | Day 14 Test

Figure 1. Extinction with response prevention (Ext-RP) reduced avoidance in many, but not all, rats. **(A)** Schematic of the behavioral protocol for Ext-RP. Rats were trained to avoid a tone-signaled footshock by stepping onto a platform over 10 days. After conditioning, rats underwent 3 days of Ext-RP with platform access blocked by a Plexiglas barrier. A post Ext-RP test assessed the extent to which Ext-RP reduced the percent time avoiding. **(B)** Group data ($n = 59$) showed that Ext-RP reduces the percent time avoiding. Inset: Whereas 53% of rats reduced avoidance (successful Ext-RP, $n = 32$), 25% did not (failed Ext-RP, $n = 15$). **(C)** Rats that failed Ext-RP showed elevated freezing throughout the task. Insets show freezing levels. Data during Ext-RP shown in blocks of three trials. All data are shown as mean ± SEM. $*p < .05$, $**p < .01$. Cond, conditioning; D, day.

RESULTS

Extinction With Response Prevention Training Reduces Avoidance and Freezing

The Ext-RP task (Figure 1A) was a modification of the platform-mediated avoidance, in which rats avoid a tone-signaled shock by stepping onto a nearby platform (17). Following 10 days of avoidance training, access to the platform was blocked with a transparent Plexiglas barrier, and rats were given 3 days of extinction (tone, no shock). The following day (day 14), the barrier to the platform was removed and rats were tested for avoidance. The time spent avoiding at test (percent tone on platform) was significantly reduced compared with the last day of conditioning (day 10: 83% vs. day 14: 38%, Wilcoxon matched pairs test; $t_{58} = 98.5$, $p < .01$; Figure 1B). Freezing to the tone was also reduced from day 10 to day 14 (day 10: 25% vs. day 14: 6%, Wilcoxon matched pairs test; $t_{58} = 47$, $p < .01$). Thus, based on group averages, Ext-RP training successfully reduced both avoidance and freezing.

A Subset of Rats Exhibited Persistent Avoidance Following Ext-RP Training

As can be observed in Figure 1B, the percent reduction in avoidance behavior from day 10 to day 14 is not normally distributed. We therefore divided rats into different subgroups, based on the percent reduction in avoidance from day 10 to day 14 (Figure 1B inset). We found that 53% of rats ($n = 32/59$) showed a large reduction in avoidance ($< 40\%$ of

conditioned), whereas 22% of rats ($n = 12/59$) showed a partial reduction (40% to 80% of conditioned), and 25% of rats ($n = 15/59$) showed almost no reduction ($> 80\%$ of conditioned). Rats showing partial reductions were eliminated from further analysis to compare successful Ext-RP ($< 40\%$ of conditioned) versus failed Ext-RP ($> 80\%$ of conditioned) subgroups. At the end of conditioning on day 10, successful and failed subgroups showed equivalent levels of avoidance (failed Ext-RP: 79%, successful Ext-RP: 86%, Student t test; $t_{45} = -0.98$, $p = .33$), but the failed Ext-RP subgroup showed slightly higher freezing levels (Student t test; $t_{45} = 2.46$, $p = .02$; Figure 1C). The failed subgroup continued to show higher freezing in all three sessions of Ext-RP (repeated-measures ANOVA; all ps $< .01$), as well as in the test session following Ext-RP (Student t test; $t_{45} = 4.82$, $p < .01$; Figure 1C). Thus, failed rats showed excessive fear to the tone throughout.

Further characterization of these two subgroups showed that the failed subgroup had higher bar-press suppression during the three sessions of Ext-RP (repeated-measures ANOVA; all ps $< .01$) but not during the end of conditioning or the test session following Ext-RP (Student t test; all ps $> .31$; Supplemental Figure S1A). Subgroup differences in bar-press suppression do not reflect preexisting differences in motivation to press for food because no differences were observed in pretone press rates before avoidance training or during the beginning of each Ext-RP session (Student t test; all ps $> .30$; Supplemental Figure S1B). At the test session, both groups showed a reduction in rates of pressing prior to tone onset (Supplemental Figure S1B), suggesting that removal of

the barrier may have been interpreted as a return of shock. However, the failed group was pressing significantly less than the successful group (Student t test; $t_{45} = -3.91$, $p < .01$; Supplemental Figure S1B), which likely reflects the increased fear at test. Interestingly, we also found that rats that failed Ext-RP spent significantly more time looking in the direction of the blocked platform during the first minute of sessions 1 and 2 of Ext-RP (Student t test; $ps < .05$), but this behavior extinguished fully by session 3 (Student t test; $t_{45} = -0.12$, $p = .92$; Supplemental Figure S1C).

Persistent Avoidance Can Be Reduced by Inactivation of lOFC

OCD is associated with a hyperactive OFC [for reviews, see (9–11)], suggesting that persistent avoidance may be due to an overactive OFC. To test this hypothesis, we ran another group of rats through Ext-RP and subdivided them into two subgroups: those showing high freezing levels during Ext-RP (presumed failure rats) and those showing low freezing levels during Ext-RP (presumed success rats). Rats showing high freezing levels were infused with either saline or MUS to pharmacologically inactivate lOFC prior to test (day 14; Figure 2A, B). We found that lOFC inactivation reduced avoidance at test (SAL: 64%, MUS: 8%, Student t test; $t_{10} = 5.22$, $p < .01$), without decreasing freezing levels (SAL: 40%, MUS: 38%, Student t test; $t_{10} = 0.09$, $p = .93$; Figure 2C) or bar-press suppression (SAL: 40%, MUS: 53%, Student t test; $t_{10} = -0.40$, $p = .69$). Therefore, inhibition of lOFC reduces persistent avoidance in rats that would have otherwise shown Ext-RP failure.

We also inactivated lOFC in rats showing low freezing levels during Ext-RP (presumed success rats; Figure 2A, B). In

contrast to high-freezing rats, lOFC inactivation in low-freezing rats *increased* avoidance at test (SAL: 13%, MUS: 52%, Student t test; $t_{18} = -3.09$, $p < .01$), without increasing freezing levels (SAL: 9%, MUS: 8%, Student t test; $t_{18} = 0.16$, $p = .89$; Figure 2D) or bar-press suppression (SAL: 27%, MUS: 8%, Student t test; $t_{18} = 0.75$, $p = .46$). Therefore, inhibition of lOFC induces persistent avoidance in rats that would have otherwise shown Ext-RP success.

Persistent Avoidance Can Be Reduced by DBS-like Stimulation of VS

One of the eligibility requirements for DBS in OCD is failing to respond to ERP therapy (7,23). Interestingly, such OCD patients start responding to ERP when it is given together with DBS of the VC/VS (7,8). We therefore assessed if DBS of the dorsal portion of VS (homologous to VC/VS) (22,24,25), given in combination with Ext-RP, would reduce avoidance in rats that previously failed Ext-RP (from Figure 1). Rats showing Ext-RP failure at test were subsequently implanted with bipolar stimulating electrodes in the dorsal VS (Figure 3A). One week later, they were given DBS-like high-frequency stimulation for 3 hours during an additional Ext-RP session on day 20. A sham control group was implanted with electrodes but never stimulated. Both groups were matched for avoidance and freezing levels before surgery (all $ps > .25$; Figure 3B). DBS of dorsal VS did not reduce freezing levels (repeated-measures ANOVA; $F_{1,10} = 0.57$, $p = .47$; Figure 3B), bar-press suppression (repeated-measures ANOVA; $F_{1,10} = 0.11$, $p = .75$), pretone bar pressing (sham: 11%, DBS: 17%, Student t test; $t_{10} = -1.04$, $p = .32$), or the time rats spent looking at the platform (sham: 4%, DBS: 4%, Student t test; $t_{10} = -0.42$, $p = .68$) during Ext-RP. However, the following day (day 21), in
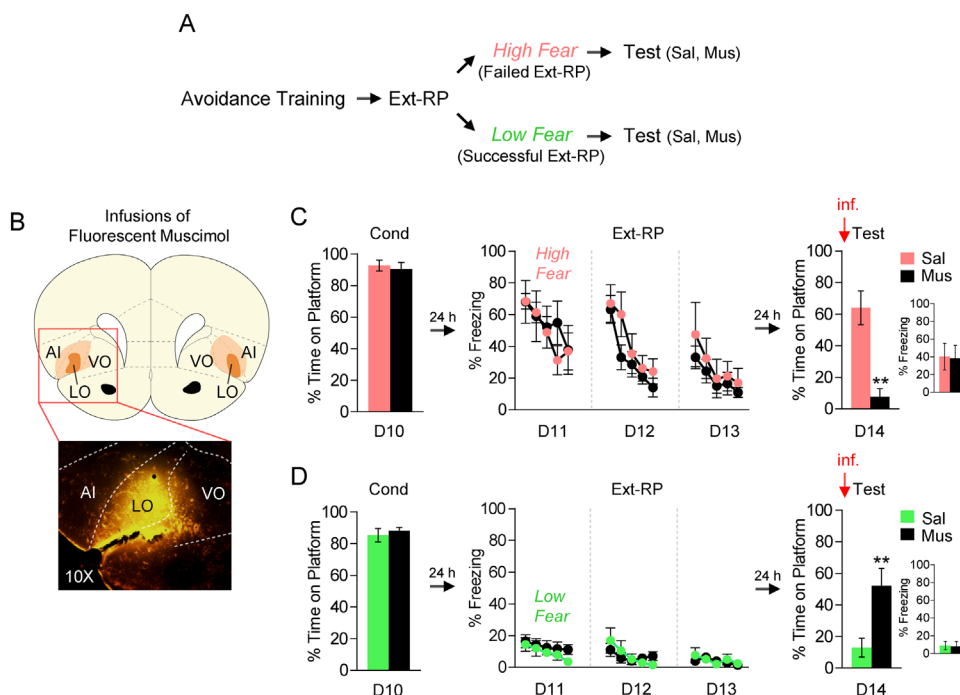

Figure 2. Pharmacologic inactivation of lateral orbitofrontal cortex (lOFC) bidirectionally modulated the expression of avoidance at test. **(A)** Experimental protocol separating rats based on freezing levels at the start of extinction with response prevention (Ext-RP). **(B)** Top: Infusions of fluorescent muscimol (Mus) into lOFC. Orange areas represent the minimum (dark) and the maximum (light) spread of Mus. Bottom: Representative micrograph showing a Mus infusion into lOFC. **(C)** In high-freezing rats (likely to fail Ext-RP), inactivation of lOFC reduced persistent avoidance without reducing freezing levels (Sal, $n = 5$; Mus, $n = 7$). **(D)** In low-freezing rats (likely to succeed in Ext-RP), inactivation of lOFC induced persistent avoidance without increasing freezing levels (Sal, $n = 10$; Mus, $n = 10$). Ext-RP data shown in blocks of three trials. All data are shown as mean ± SEM. **$p < .01$. AI, anterior insular; Cond, conditioning; D, day; inf., infusion; LO, lateral orbitofrontal; Sal, saline; VO, ventral orbitofrontal.
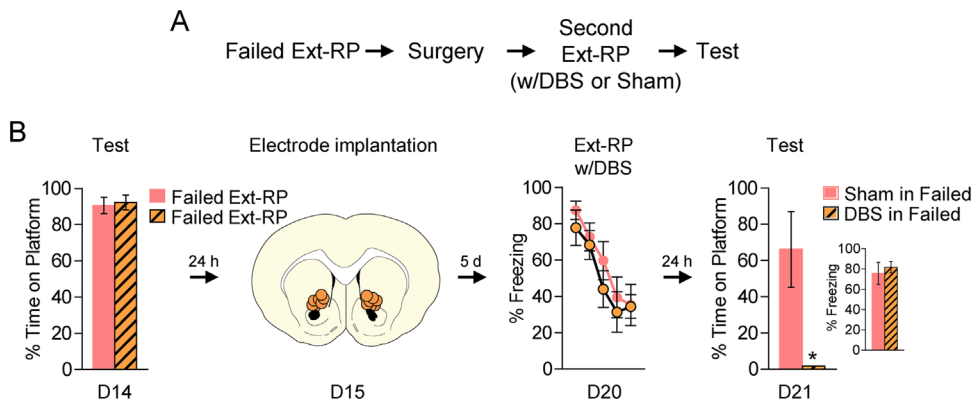
Figure 3. Deep brain stimulation (DBS) of dorsal ventral striatum eliminates persistent avoidance. **(A)** Experimental protocol for delivery of DBS to rats that failed extinction with response prevention (Ext-RP) (from Figure 1). **(B)** Compared with sham-operated control rats, DBS of dorsal ventral striatum delivered during a second Ext-RP session had no effect on freezing but eliminated persistent avoidance during test (Sham failed, $n = 6$; DBS failed, $n = 6$). Ext-RP data shown in blocks of three trials. All data are shown as mean ± SEM. *$p < .05$. D, day.

the absence of DBS, persistent avoidance was abolished (sham: 66%, DBS: 0%, Student t test; $t_{10} = 3.16$, $p = .01$), with no reduction in freezing (sham: 76%, DBS: 82%, Student t test; $t_{10} = -0.50$, $p = .63$; Figure 3B) or bar-press suppression (sham: 73%, DBS: 87%, Student t test; $t_{10} = -0.45$, $p = .66$). Therefore, similar to inactivation of lOFC, DBS of dorsal VS eliminated persistent avoidance in rats that had previously failed Ext-RP.

DISCUSSION

We developed an avoidance-based rodent model of ERP therapy in which signaled avoidance behaviors are reduced following extinction of tone-shock associations. Ext-RP training reduced avoidance in the majority of rats; however, 25% persisted in their avoidance following Ext-RP. Persistent avoidance could be eliminated by inactivating lOFC or by delivering DBS to the VS.

It is estimated that 26% of OCD patients suffer from the harm-avoidant type of OCD, because they believe that their compulsions protect them from danger (26). Many compulsions, therefore, constitute persistent avoidance responses that can be investigated with animal models of avoidance. Following Ext-RP training, the 25% of rats that exhibited persistent avoidance also expressed heightened freezing throughout Ext-RP, suggesting that excessive fear predicts Ext-RP failure. Interestingly, the majority of OCD patients who fail ERP therapy also show excessive fear to compulsive triggers (26,27). While fear may be predictive, it is not clear if it is also a cause of Ext-RP failure. If so, reducing fear with pharmacologic adjuncts such as the beta-blocker propranolol (28,29) might reduce ERP failure. However, it is possible to observe persistent avoidance in the absence of elevated fear in animals (30), healthy humans (31), and OCD patients (32), suggesting that factors other than elevated fear can elicit persistent avoidance.

A prominent hypothesis of OCD is that it is due, in part, to a hyperactive OFC (9–11). Specifically, the lOFC plays a key role in assigning value to a given action (33–35). The inability of ERP therapy to decrease the value of avoidance in some individuals may result from heightened fear combined with excessive activity in lOFC. Consistent with this idea, rats showing persistent avoidance exhibited both elevated fear and heightened value as evidenced by the time spent looking toward the platform. While the latter fully extinguished by the end of Ext-RP, the former did not, suggesting that persistent avoidance may be driven by increased fear. In contrast, nonavoiders showed low freezing and spent little time looking toward the platform. Inactivation of lOFC had opposite effects in these groups, consistent with lOFC assignment of value to actions (33–35), depending on fear levels.

In a recent report, OCD patients with a hyperactive medial OFC (mOFC) were unable to devalue avoidance responses (32). We previously showed that the mOFC in rodents is important for fear expression (22). Thus, failure to respond to ERP may stem from an interaction between elevated fear (mOFC) and deficient devaluation of avoidance (lOFC). Furthermore, our findings show that inactivation of lOFC can either induce or reduce persistent avoidance, suggesting that different neuronal populations within lOFC are responsible for driving or inhibiting persistent avoidance. Perhaps these distinct subpopulations receive inputs from different regions involved in fear regulation (e.g., infralimbic cortex, prelimbic cortex, amygdala, thalamus) (36), but this, of course, remains to be tested.

DBS of VC/VS reduces OCD symptoms in treatment-resistant patients (6) and facilitates their response to ERP therapy (7,8). While the mechanisms of DBS action are unclear, reduced OFC activity by DBS has been reported (13–15). In the present study, we found that DBS-like stimulation of the dorsal VS (a rodent homologue of VC/VS) eliminated persistent avoidance when DBS was conducted during Ext-RP. Recent reports show that pathways from both mOFC and lOFC to VS regulate perseverative grooming behavior (37,38), which has been used to model OCD. Furthermore, DBS at this VS site has been reported to reduce lOFC firing rate (16) and increase lOFC plasticity (20), suggesting that DBS may be acting by diminishing lOFC activity. It is important to note that DBS did not reduce heightened freezing, either during Ext–RP or at test the following day. This is similar to lOFC inactivation, which reduced persistent avoidance but not elevated freezing levels. This suggests that persistent avoidance stems from a hyperactive lOFC that is downstream of fear circuits.

We previously showed that DBS of the VS reduced freezing during the extinction of conditioned fear (20), which may be due to inhibition of mOFC (22). In the present study, DBS of the same VS region reduced persistent avoidance, and this reduction may be due to inhibition of the lOFC. The benefits of

DBS in VS may be due to an overall inhibition of cortical regions that project through this site, which include both mOFC and lOFC together with the prelimbic cortex (22). It is interesting to note that DBS in the present study did not reduce freezing, suggesting that prelimbic cortex and mOFC do not mediate freezing in our avoidance task, as previously observed for prelimbic cortex (17).

Our findings suggest that the effectiveness of clinical DBS may be due to enhancement of the extinction process occurring in ERP therapy. It is important to note, however, that clinical DBS electrodes are activated continuously after surgery, whereas the facilitation of Ext-RP that we observed was during a DBS-off phase. While our findings suggest that DBS during extinction is key for its beneficial effect, it remains to be determined if avoidance would still be reduced with DBS on at test. A recent behavioral task in humans mimics the experimental conditions of our rodent Ext-RP task (31). Future preclinical studies should model specific features of clinical ERP therapy in both humans and rodents, with the long–term goal of identifying markers predictive of OCD–like behavior and novel approaches for treatment.

ARTICLE INFORMATION

From the Departments of Psychiatry and Anatomy and Neurobiology (JR-R, GJQ), University of Puerto Rico School of Medicine, San Juan, Puerto Rico; and Department of Psychiatry and Human Behavior (BDG, SAR), Alpert Medical School of Brown University; and Butler Hospital and the Providence VA Medical Center (BDG), Providence, Rhode Island.

Address correspondence to Gregory J. Quirk, Ph.D., University of Puerto Rico School of Medicine, Department of Psychiatry, PO Box 365067, San Juan 00936-5067, Puerto Rico; E-mail: gregoryjquirk@gmail.com.

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