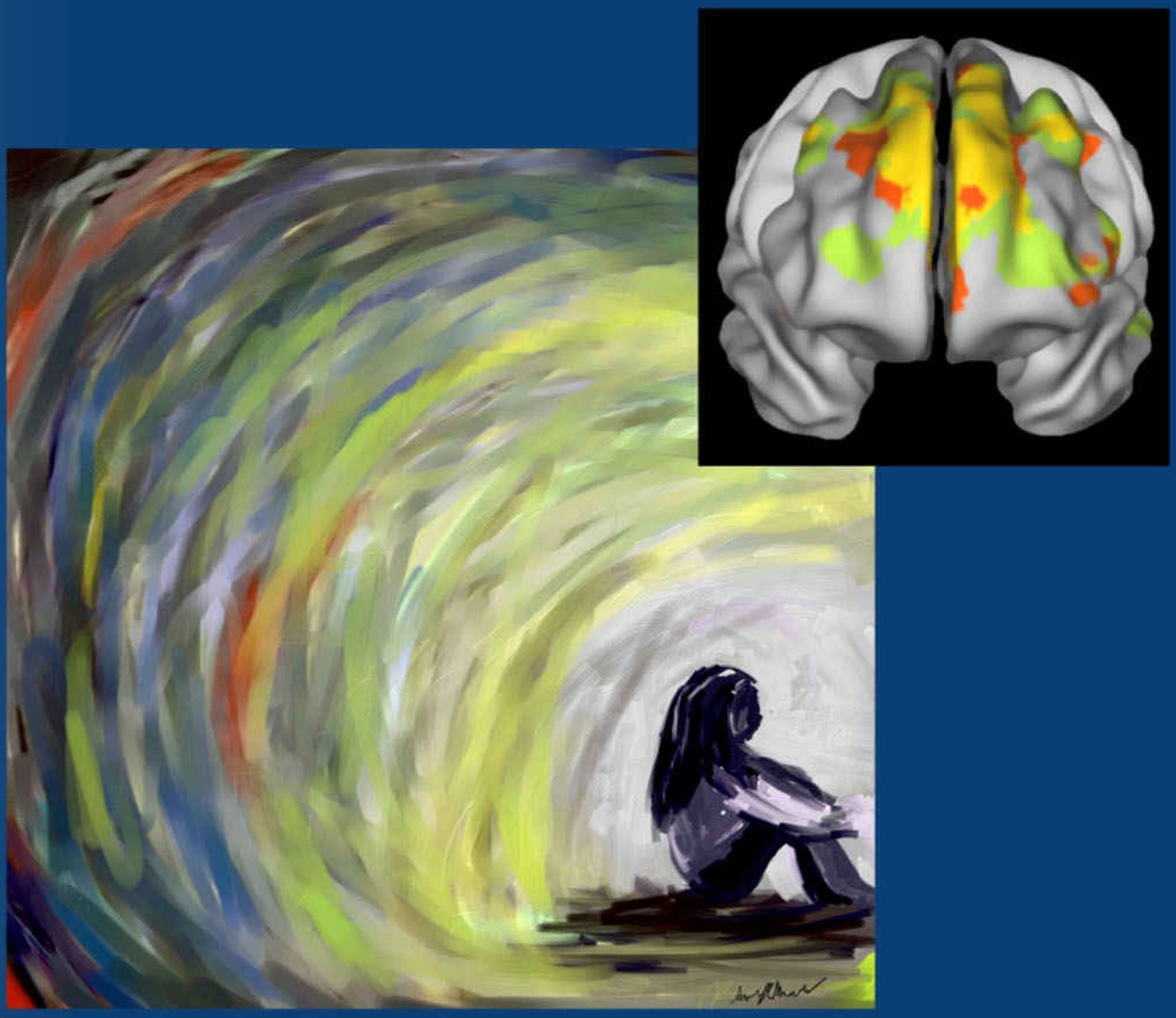
Obsessive-Compulsive Disorder

Phenomenology, Pathophysiology, and Treatment



Edited by

Christopher Pittenger

OXFORD

30.

EXTINCTION OF CONDITIONED FEAR AND AVOIDANCE: RELEVANCE FOR OCD

Jose Rodriguez-Romaguera, PhD and Gregory J. Quirk, PhD

OCD affects an estimated three million individuals in the United States (Kessler et al., 2005; Rasmussen & Eisen, 1994), underscoring the need to model this brain disorder in animals and develop novel treatments. OCD is characterized by intrusive thoughts causing uneasiness, anxiety, and worry (obsessions), as well as repetitive acts aimed at reducing the associated anxiety of the obsessions (compulsions) (Rasmussen & Eisen, 1992). Many of the compulsive behaviors of OCD (e.g., hand washing or checking of door locks) can be viewed as protective against perceived threats (e.g., infection or intruders; Franklin & Foa, 2011). Elevated fear and compulsive avoidance behaviors persist despite the absence of actual aversive events, suggesting a deficit in extinction of fear and avoidance.

Standard treatment for OCD involves a combination of pharmacology and extinction-based therapies. The primary therapy for OCD is "exposure with response prevention (ERP)," in which patients are repeatedly exposed to triggers of their compulsions, but are prevented from expressing them (see chapter 37) (Rachman et al., 1971). The goal of ERP is to extinguish compulsive behaviors (Franklin & Foa, 2011). ERP is an effective therapy, but approximately 40% of patients fail ERP or drop out (Foa et al., 2005; Simpson et al., 2008). Little is known about how ERP reduces persistent compulsions, or why it fails in some individuals. One possibility is that extinction circuits are deficient in OCD, which reduces the response to extinction-based therapies.

Extinction has been extensively studied in rodents using a fear conditioning model, in which a neutral tone (the conditioned stimulus) is paired with an aversive shock (the unconditioned stimulus; Figure 30.1). After such pairing, animals develop a long-lasting fear of the tone, which is typically quantified by measuring their freezing (a species-specific response to fear when escape is

impossible, consisting of the cessation of all movement except for breathing). Fear can be attenuated by repeatedly presenting the tone in the absence of the shock—that is, by extinction. This paradigm has proved to capture key mechanisms of fear learning and of extinction that generalize to humans.

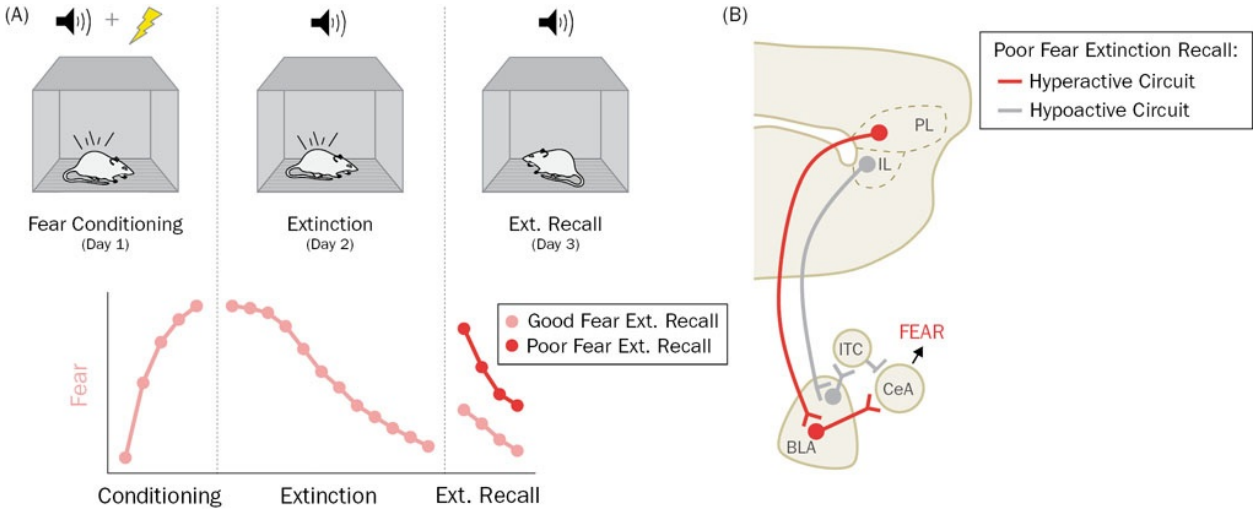


Figure 30.1 EXTINCTION OF CONDITIONED FEAR IN RODENTS. **A.** Schematic representation of the behavioral protocol commonly used to study fear extinction in rodents. On day 1, repeated presentations of a tone that co-terminates with foot-shock increase fear responses (freezing behavior). On day 2, rats are exposed to tone-alone presentations and freezing is extinguished over multiple trials. On Day 3, extinction recall is assessed by giving additional tone-alone presentations. **B.** Rodents that show poor extinction recall have a hyperactive PL together with a hypoactive IL. Ext. = extinction; PL = prelimbic; IL = infralimbic; BLA = basolateral amygdala; ITC = intercalated cells; CeA = central nucleus of the amygdala. (see color plate)

CIRCUITS OF FEAR EXTINCTION

There is remarkable homology between rodents and humans in the medial prefrontal cortex (mPFC) network that regulates fear expression (Ongur & Price, 2000; Vogt & Paxinos, 2014) (Figure 30.2). Indeed, early findings from rodents describing the role of the ventral medial PFC (vmPFC) in fear extinction (Milad & Quirk, 2002; Morgan et al., 1993; Quirk et al., 2000) motivated subsequent investigations in humans (Kalisch et al., 2006; Milad et al., 2007b; Phelps et al., 2004). Converging data from lesion, pharmacological inactivation, brain stimulation, unit-recording, and optogenetic studies have implicated the infralimbic (IL) mPFC in extinction memory (Do-Monte et al., 2015b; Laurent & Westbrook, 2009; Milad & Quirk, 2002; Mueller, 2008; Myers & Davis, 2007; Quirk & Quirk et al., 2000; Rhodes & Killcross, 2004; Sierra-Mercado et al., 2011; Sotres-Bayon et al., 2004; Thompson et al., 2010; Vidal-Gonzalez et al., 2006), and the prelimbic (PL) mPFC in the expression of learned fears (Blum

et al., 2006; Burgos-Robles et al., 2009; Corcoran & Quirk, 2007; Do-Monte et al., 2015a; Kim et al., 2013; Laurent & Westbrook, 2009; Vidal-Gonzalez et al., 2006). Fear conditioning studies have suggested that the rodent IL is functionally homologous to the human vmPFC, and the rodent PL is functionally homologous to the human dorsal anterior cingulate cortex (dACC) (see Figure 30.2) (Delgado et al., 2006; Milad & Quirk, 2012; Pitman et al., 2012; Rauch et al., 2006).

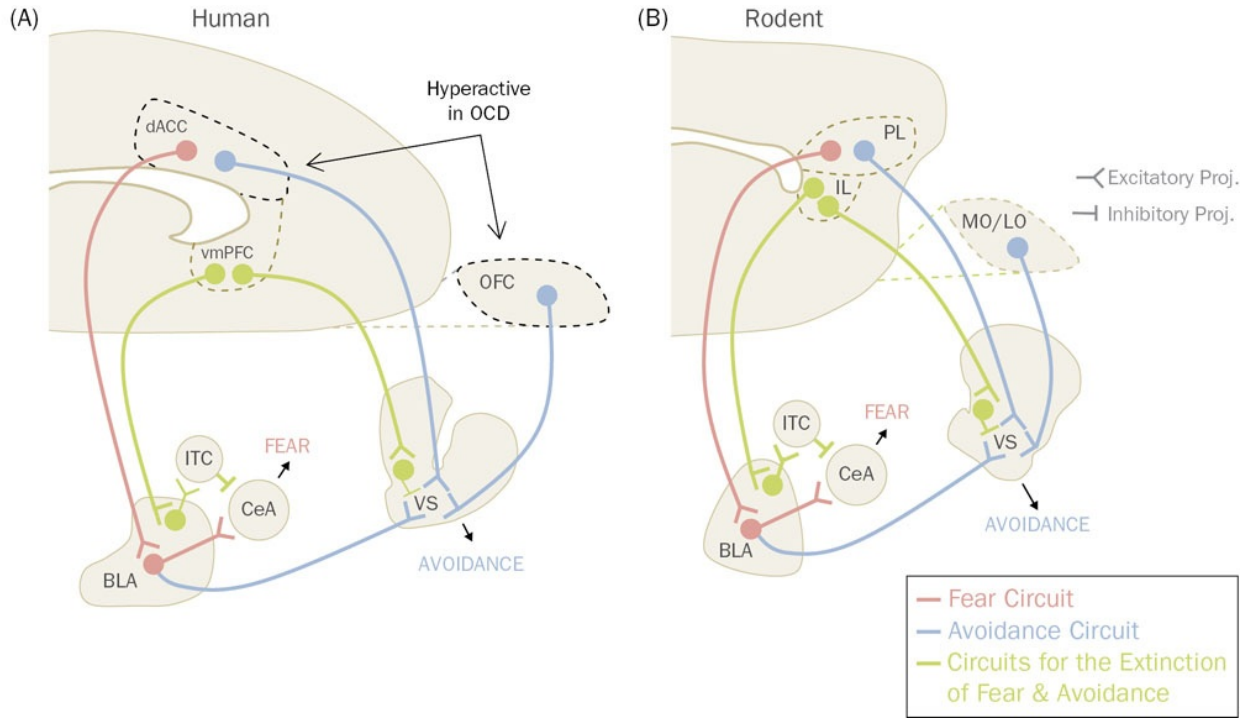


Figure 30.2 POSSIBLE HUMAN–RODENT HOMOLOGIES IN THE CIRCUITS MEDIATING CONDITIONED FEAR, AVOIDANCE, AND EXTINCTION. **A.** Human: dACC = dorsal anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; OFC = orbitofrontal cortex; BLA = basolateral amygdala; ITC = intercalated cells; CeA = central nucleus of the amygdala; VS = ventral striatum. **B.** Rodent: PL = prelimbic; IL = infralimbic; MO/LO = medial & lateral orbitofrontal cortex; BLA = basolateral amygdala; ITC = intercalated cells; CeA = central nucleus of the amygdala; VS = ventral striatum. (see color plate)

IL and PL (and their respective homologues in humans) mediate opposite effects on fear expression via their projections to different targets within the basal amygdala (Berendse et al., 1992; McDonald et al., 1996; Milad & Quirk, 2012; Pitman et al., 2012; Sotres-Bayon & Quirk, 2010; Vertes, 2004). PL targets the basal nucleus of the amygdala (BLA; Berendse et al., 1992; McDonald et al., 1996; Vertes, 2004), which is critical for expression of learned fear (Anglada-Figueroa & Quirk, 2005; LeDoux et al., 1990) and projects to the central nucleus of the amygdala (CeA) to trigger a fear response (Herry &

Johansen, 2014). IL also targets the BLA, but its cellular targets regulate inhibitory intercalated (ITC) cells (Berendse et al., 1992; McDonald et al., 1996; Pinard et al., 2012; but see Strobel et al., 2015; Vertes, 2004), which can inhibit amygdala output via inhibition of the central nucleus of the amygdala (Ehrlich et al., 2009; Pare et al., 2004). A failure of extinction can result from hyperactivity in PL or hypoactivity in IL (see Figure 30.1). These circuits are highly conserved between rodents and humans (see Figure 30.2) (Milad & Quirk, 2012).

USING RODENTS TO STUDY PHARMACOLOGICAL ADJUNCTS FOR EXTINCTION-BASED THERAPIES

Rodent models of fear extinction have facilitated the development of potential pharmacological adjuncts to extinction-based therapies (Bowers & Ressler, 2015; Singewald et al., 2015) (Figure 30.3). In rodents, pharmacological adjuncts to extinction can reduce fear expression, enhance extinction memory, or both. For example, the beta-adrenergic blocker propranolol has been shown to reduce fear expression without impairing extinction learning (Rodriguez-Romaguera et al., 2009). Adjuncts that enhance extinction memory, such as serotonin reuptake inhibitors and the NMDA partial agonist D-Cycloserine, have been shown to enhance extinction in both rodents and humans (Davis et al., 2006). More recently, deep brain stimulation (DBS) of the ventral striatum (VS) and systemic infusions of BDNF have been shown to both reduce fear expression and enhance extinction memory (Peters et al., 2010; Rodriguez-Romaguera et al., 2012). For a full list of other potential pharmacological adjuncts to reduce fear and enhance extinction memory, the reader is referred to recent comprehensive reviews (Bowers & Ressler, 2015; Fitzgerald et al., 2014; Graham et al., 2011; Singewald et al., 2015). Although the pharmacological augmentation of therapy has not yet entered broad clinical use, it represents an exciting area in which our growing understanding of the neurobiology of extinction may lead to changes in clinical practice and to improved patient outcomes.

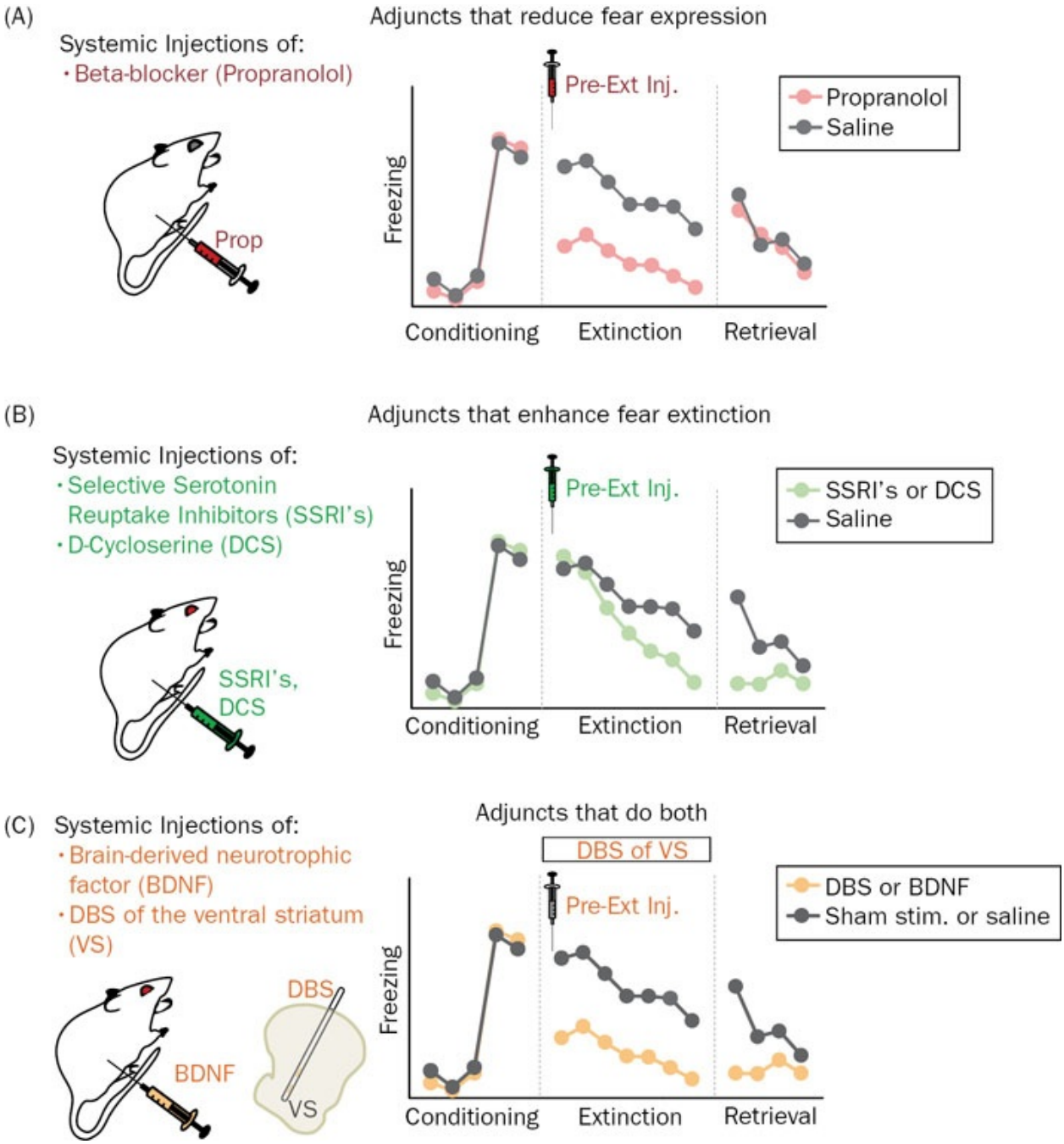


Figure 30.3 RODENT STUDIES OF PHARMACOLOGICAL ADJUNCTS TO FACILITATE EXTINCTION. **A.** In rodents, systemic injection of propranolol reduces fear expression during extinction training but does not enhance extinction learning. **B.** In both rodents and humans, systemic administration of SSRIs and DCS enhance fear extinction. **C.** In rodents, systemic administration of BDNF agonists, and deep brain stimulation (DBS) of VS, reduce fear expression and enhance extinction learning. Pre-Ext Inj. = pre-extinction injections. (Modified from: Davis et al., 2006; Peters et al., 2010; Rodriguez-Romaguera et al., 2009, 2016.) (see color plate)

CIRCUITS OF ACTIVE AVOIDANCE

Avoidance behaviors are often pervasive in OCD and may be even more clinically impairing than compulsions. “Active avoidance” refers to an experimental paradigm in which an animal learns to perform an action in response to a cue in order to avoid a feared negative outcome (such as a shock). This differs from freezing in the fear conditioning paradigm described in that the animal undertakes an active, learned behavioral response to avoid an impending aversive consequence. Active avoidance may be particularly relevant to patients with primarily harm-avoidant OCD symptomatology (McGuire et al., 2012).

There is a long history of research on active avoidance in rodents (Kamin et al., 1963; Mowrer & Lamoreaux, 1946). In signaled active avoidance, execution of a behavior during a conditioned tone prevents delivery of a shock. The first step in avoidance learning is the formation of a Pavlovian association between the tone and shock (the same association as is formed during cued fear conditioning). This is followed by the acquisition of the avoidance behavior. Lesion and inactivation of the BLA (but not the CeA) reduces avoidance expression (Bravo-Rivera et al., 2014; Choi et al., 2010). The involvement of the striatum in active avoidance was suggested by an early lesion study (Hart et al., 1978) and has been confirmed by more recent inactivation studies (Bravo-Rivera et al., 2014; Ramirez et al., 2015). Using a platform-mediated avoidance task (Figure 30.4), it was recently shown that PL is also important for avoidance expression (Bravo-Rivera et al., 2014). Taken together, this suggests that avoidance expression requires an amygdalo-cortico-striatal network (see Figure 30.2).

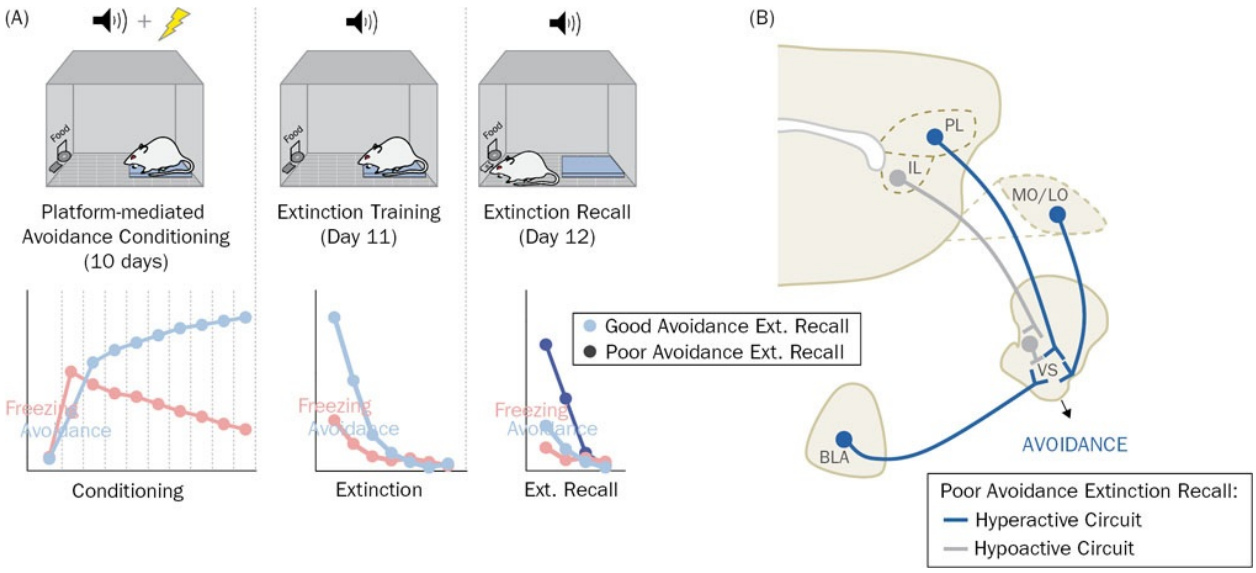


Figure 30.4 EXTINCTION OF AVOIDANCE IN RODENTS. **A.** Schematic representation of the platform-mediated model of avoidance extinction in rodents. For 10 days rats are trained to avoid a tone paired with

foot-shock by stepping onto a nearby safe platform. Initially rats freeze to the tone, but with subsequent training learn to reduce freezing and avoid the foot-shock. On day 11, the avoidance response is extinguished over multiple trials, with the fear responses remaining low. On Day 12, extinction recall is assessed with additional tone-alone presentations. **B.** Rodents showing poor extinction recall have a hyperactive PL, MO/LO & BLA together with a hypoactive IL. Ext. = extinction; PL = prelimbic; IL = infralimbic; MO/LO = medial & lateral orbitofrontal cortex; BLA = basolateral amygdala; VS = ventral striatum. (Modified from: Bravo-Rivera et al., 2014, 2015.) (see color plate)

In the platform-mediated avoidance task, inactivation of the BLA, PL, and VS all reduce avoidance (Bravo-Rivera et al., 2014). However, inactivation of these areas has different effects on freezing. Inactivation of the BLA reduced both avoidance and freezing, suggesting that the BLA is the main site for the tone-shock association (Bravo-Rivera et al., 2014). In contrast, inactivation of the VS increased freezing, suggesting that rats reverted to freezing behavior in the absence of avoidance (Bravo-Rivera et al., 2014). These findings suggest that the BLA may be the start point and the VS the end point of an avoidance response to a cue. Interestingly, inactivation of PL reduced avoidance but did not change freezing levels (Bravo-Rivera et al., 2014), suggesting that PL lies somewhere between fear and the action to avoid (see Figure 30.2). PL may serve as a decision node receiving tone-shock information from the BLA, together with other inputs, to activate the VS and consequently drive the avoidance response. Prior studies in rodents have shown that PL is important for decision-making, specifically, the orchestration of goal-directed behaviors to seek reward (see Balleine & O'Doherty, 2010 for review). In this framework, avoidance can be viewed as a goal-directed behavior motivated by the desire to avoid shock.

At first glance, extinction of avoidance appears similar to extinction of fear, but there are potentially important differences. Pharmacological inactivation of IL impairs extinction of avoidance learning (Bravo-Rivera et al., 2014), as it does for extinction of conditioned fear (Quirk & Mueller, 2008). However, it has been suggested that the circuit mechanisms mediating these two forms of extinction may differ: extinction of avoidance may involve projections from IL to the ventral striatum to inhibit avoidance responses (see Figure 30.4) (Bravo-Rivera et al., 2015). The VS is not necessary for fear extinction (Rodriguez-Romaguera et al., 2012), suggesting that this pathway may be specific for extinction of avoidance. Furthermore, the lateral orbitofrontal cortex is recruited during the extinction of avoidance, but not during the extinction of fear (Bravo-Rivera et al., 2015; Morgan & LeDoux, 1999; Rodriguez-Romaguera et al., 2016). Finally, fear extinction triggers BDNF expression in the BLA, but avoidance extinction triggers BDNF in the mediodorsal thalamus (Rosas-Vidal et al., 2015).

INTERACTIONS BETWEEN FEAR AND AVOIDANCE CIRCUITS: ROLE OF THE ORBITOFRONTAL CORTEX

The rodent mPFC and OFC systems show distinct patterns of projections to subcortical targets (McDonald et al., 1996; Ongur & Price, 2000). The mPFC system projects strongly to visceromotor areas including the striatum, amygdala, hypothalamus, and midbrain. The mPFC consists of the ventral mPFC (PL & IL) and the dorsal mPFC (cingulate area 1 & 2) (Gabbott et al., 2005). The OFC system arises from the ventral surface of the prefrontal cortex, extending from the medial OFC (MO) to ventral and lateral OFC (LO), including parts of the anterior insular cortex. The OFC network receives polymodal inputs and projects to the striatum and distinct parts of the mediodorsal thalamus (Hoover & Vertes, 2011). It was recently shown that optogenetic activation of MO projections to striatum induces persistent repetitive grooming in rodents (Ahmari et al., 2013); on the assumption that elevated grooming is isomorphic to compulsions, this may resemble the hyperactivity observed in the medial orbitofrontal cortex (mOFC) of OCD patients during symptom provocation (Adler et al., 2000; Breiter et al., 1996; Mataix-Cols et al., 2002; Rauch et al., 2007) (see chapter 21). The mOFC in rodents (MO) is necessary for expression of conditioned freezing (Rodriguez-Romaguera et al., 2015), suggesting that mOFC may integrate fear inputs that drive compulsive behaviors in OCD.

OVERLAP OF EXTINCTION AND AVOIDANCE CIRCUITS IN OCD

The corresponding portions of the prefrontal cortex in humans can be similarly divided into two distinct networks: a “medial prefrontal” network (mPFC) and an “orbitofrontal” network (OFC), each with different connectivity and functions (see Chapter 20). The mPFC network consists of the vmPFC and the dACC. Like the mPFC in rodents, this network projects to visceromotor areas including the striatum, amygdala, hypothalamus, and midbrain; it is thought to regulate emotional expression. The OFC network consists of the mOFC and lateral OFC (lOFC). The OFC network receives polymodal inputs and, as in rodents, projects to striatum and distinct parts of the mediodorsal thalamus. The OFC system is thought to be involved primarily in regulating goal directed behavior (reward seeking in particular), behavioral flexibility, and ritualistic and avoidance behaviors.

A prominent hypothesis is that OCD arises in part from a dysfunctional OFC (for reviews see Baxter et al., 1996; Menzies et al., 2008; Milad & Rauch, 2012) (see chapter 20). Functional brain imaging studies indicate that OFC is

hyperactive in OCD, both at rest (Baxter et al., 1988; Busatto et al., 2000) and during symptom provocation (Adler et al., 2000; Breiter et al., 1996; Mataix-Cols et al., 2002; Rauch et al., 2007) (see chapter 21). This has led to the hypothesis that hyperactivity in OFC drives compulsions in OCD by constantly activating its striatal targets (see also chapter 31). However, OCD patients have also shown impaired recruitment of OFC during tasks designed to dissociate specific cognitive processes, such as reversal learning and devaluation (Chamberlain et al., 2008; Gu et al., 2008; Remijnse et al., 2006; Woolley et al., 2008). Therefore, OCD could involve either hyperactivity or relative hypoactivity in OFC, depending on the process in which the patient is engaged.

OCD is also characterized by abnormal activity within the mPFC system, similar to other anxiety disorders such as PTSD, panic, and phobias (Milad & Rauch, 2012) (see chapter 21, 22). This suggests that deficits in emotional regulation play a role in OCD symptoms, particularly with respect to fear and anxiety. As in the animal studies of fear learning and extinction summarized above, the mPFC system in humans is implicated in the expression and extinction of learned fear. Using a Pavlovian fear conditioning paradigm in humans, it has been shown that the function and thickness of the dACC are correlated with conditioned fear expression (Gabbott et al., 2005; Linnman et al., 2012; Milad et al., 2007a; Vogt, 2005). Similar findings link the vmPFC with the extinction of conditioned fear (Ahs et al., 2015; Kalisch et al., 2006; Linnman et al., 2012; Milad et al., 2007b, 2009; Phelps et al., 2004). Lesions of dACC, known as anterior cingulotomy, have been used to treat OCD (see Greenberg et al., 2010a for a review) (see chapter 45). Furthermore, OCD patients show deficits in extinction of conditioned fear, and associated hypoactivity in vmPFC (Milad et al., 2013). These findings suggest that OCD symptoms may be due, in part, to impaired extinction of fear, stemming from a dysfunctional mPFC network.

CAN WE MODEL EXPOSURE THERAPY IN RODENTS?

OCD is a complex human disorder that includes a range of symptoms; some of these can plausibly be recapitulated in a rodent, while others cannot (see chapter 29). Rodents therefore cannot be used to model OCD in its entirety, but can potentially be used to model certain aspects of OCD-like behavior, and associated brain circuitry abnormalities.

As previously mentioned, the standard treatment for OCD is ERP therapy, in which patients are repeatedly exposed to triggers of their compulsions but are prevented from expressing them and thus, over time, undergo extinction

(Franklin & Foa, 2011; Rachman et al., 1971) (see chapter 37). Recently, the authors developed an avoidance-based rodent model of ERP therapy (extinction with response prevention, Ext-RP) (Rodriguez-Romaguera et al., 2016). Rats are trained in active avoidance, using the platform avoidance paradigm described (see Figure 30.4). After acquiring the active avoidance behavior, they undergo extinction of the tone-shock association while access to an avoidance platform is blocked (Figure 30.5). Ext-RP training reduces avoidance in the majority of rats. However, 25% persisted in their avoidance, resembling ERP failure.

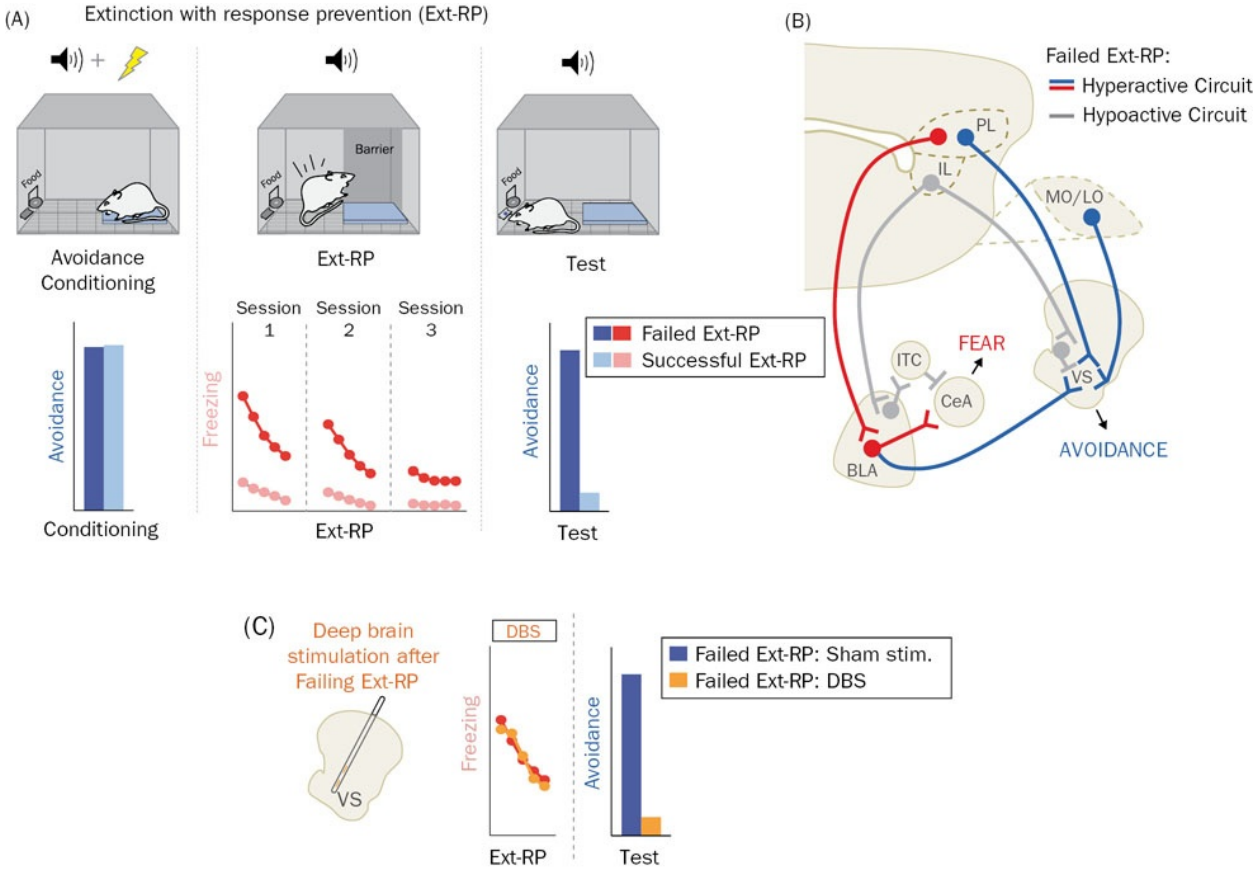


Figure 30.5 MODELING EXTINCTION WITH RESPONSE PREVENTION IN RODENTS. **A.** Schematic representation of the behavioral protocol used to study extinction with response prevention (Ext-RP) in rodents. Using platform-mediated avoidance, rats are conditioned to avoid a tone paired with foot-shock. Subsequently rats are extinguished while preventing access to the platform with a transparent Plexiglas barrier (Ext-RP), over three sessions. Rats are then tested for avoidance with the barrier removed. A subgroup of rats fail Ext-RP, persisting to avoid at test. **B.** Rodents failing Ext-RP have a hyperactive PL, MO/LO & BLA together with a hypoactive IL. **C.** DBS of the Dorsal-VS administered during an additional Ext-RP session restores Ext-RP learning in rats that previously failed Ext-RP. Ext. = extinction; PL = prelimbic; IL = infralimbic; MO/LO = medial & lateral orbitofrontal cortex; BLA = basolateral amygdala; VS = ventral striatum. (Modified from: Bravo-Rivera et al., 2015, 2016.) (see color plate)

Using this Ext-RP model, the authors recently found that rats exhibiting

persistent avoidance also expressed heightened freezing throughout Ext-RP, suggesting that excessive fear predicts Ext-RP failure (Rodriguez-Romaguera et al., 2016). Interestingly, the majority of OCD patients who fail ERP therapy also show excessive fear to compulsive triggers (Foa, 1979; McGuire et al., 2012). Although fear may be predictive, it is not clear if it is also a cause of Ext-RP failure. If so, reducing fear with pharmacological adjuncts such as the beta-blocker propranolol (Brunet et al., 2008; Rodriguez-Romaguera et al., 2009) might reduce ERP failure. However, it is possible to observe persistent avoidance in the absence of elevated fear in animals (Bravo-Rivera et al., 2015), healthy humans (Vervliet & Indekeu, 2015), and OCD patients (Gillan et al., 2015), suggesting that factors other than elevated fear can elicit persistent avoidance. In agreement with this latter hypothesis, persistent avoidance could be eliminated by inactivating the LO; however, this LO inactivation did not reduce freezing (Rodriguez-Romaguera et al., 2016). This suggests that the LO (like PL) lies somewhere between the tone-shock association (e.g., BLA) and the avoidance response (e.g., VS); and can drive persistent avoidance independent of fear. One possibility is that LO projects to the VS to regulate avoidance behavior, together with inputs from PL (see Figure 30.5).

In summary, avoidance behaviors may involve an interaction between the mPFC and OFC networks. However, this oversimplified model (see Figure 30.5B) remains to be tested. Future studies using optogenetic techniques could test the directionality of the proposed model. For example, using the same behavioral tasks, optogenetic studies could target projection neurons from the LO to the VS and test the necessity of this projection for persistent avoidance in rats exhibiting high levels of fear.

RODENT MODELS OF DEEP BRAIN STIMULATION FOR REFRACTORY OCD

In humans, OCD symptoms are reduced by chronic DBS of the VC/VS site (Greenberg et al., 2010b) (see chapter 46), which stimulates axons from the mPFC and OFC that project through this site (Cosyns et al., 2003; Haber et al., 2006; Kopell et al., 2004). The maximum benefits of DBS occur after 1 to 3 months of continuous stimulation, suggesting that DBS induces long-lasting plasticity in stimulated circuits. Similar to the human VC/VS, the rat VS is heavily innervated with myelinated fiber bundles from mPFC and OFC (Berendse et al., 1992; Hoover & Vertes, 2012; Mailly et al., 2013; McGeorge & Faull, 1989; Rodriguez-Romaguera et al., 2015; Schilman et al., 2008; Sesack et al., 1989; Vertes, 2004). DBS-like stimulation of the VS in anesthetized rats

modulates activity in both the mPFC and OFC networks (McCracken & Grace, 2007, 2009). DBS of the VS over multiple days in rats induces an overall rewiring of mPFC and OFC networks (Ewing & Grace, 2013), suggesting that DBS may recalibrate faulty brain circuits in OCD (Insel, 2010).

Previously, it was shown that DBS of the VS reduces fear expression and facilitates fear extinction (see Figure 30.3) (Rodriguez-Romaguera et al., 2012). The specific region that was found to facilitate fear extinction (dorsal-VS, just above the anterior commissure) receives strong projections from MO and PL, but not IL (Mailly et al., 2013; Rodriguez-Romaguera et al., 2015). Pharmacological inactivation of either MO or PL reduces freezing (Rodriguez-Romaguera et al., 2015; Sierra-Mercado et al., 2011), suggesting that DBS may act through these areas to reduce fear. DBS of the dorsal-VS also increases plasticity in the IL projection to amygdala ITC cells (Do-Monte et al., 2013; Rodriguez-Romaguera et al., 2012). DBS of the dorsal-VS may enhance extinction both by inhibiting MO and PL, as well as indirectly potentiating the pathway from IL to ITC cells. In the Ext-RP task, DBS of the dorsal-VS facilitates Ext-RP in rats that had previously failed it (see Figure 30.5) (Rodriguez-Romaguera et al., 2016), perhaps by reducing activity in LO.

CONCLUSION

The premise of this chapter is that OCD patients have deficiencies in extinction of fear and avoidance. Rodent models of fear and avoidance can shed light on the circuitry that is malfunctioning in OCD. Research tools that are available in rodents allow us to probe the interactions between the mPFC and OFC systems that are dysfunctional in OCD. Rodent models can also be used to study how pharmacological adjuncts can reduce fear/avoidance, as well as enhance extinction memory in order to discover novel therapeutic techniques to treat OCD.

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