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Invited Essay

Optimizing inhibitory learning during exposure therapy

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Abstract

Prevailing models of exposure therapy for phobias and anxiety disorders construe level of fear throughout exposure trials as an index of corrective learning. However, the evidence, reviewed herein, indicates that neither the degree by which fear reduces nor the ending fear level predict therapeutic outcome. Developments in the theory and science of fear extinction, and learning and memory, indicate that 'performance during training' is not commensurate with learning at the process level. Inhibitory learning is recognized as being central to extinction and access to secondary inhibitory associations is subject to influences such as context and time, rather than fear during extinction training. Strategies for enhancing inhibitory learning, and its retrieval over time and context, are reviewed along with their clinical implications for exposure therapy and directions for future research.
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Keywords: Fears; Phobias; Exposure; Extinction; Habituation; Inhibitory learning

Introduction

The primary goal of this paper is to address the gap between advances in the basic science of extinction learning and memory on the one hand, and models and methods of exposure therapy for phobias and anxiety disorders on the other hand. The argument to be made is that the customary reductions in reported fear and physiological arousal throughout exposure therapy are not evidence for corrective learning. Therapeutic efforts are better directed towards toleration of distress within a structure that enhances the consolidation and retrievability of exposure-based inhibitory learning over context and time. The goal is not to question the necessity of exposure therapy for phobias and anxiety disorders; it is already well established that phobias and anxiety disorders respond positively to approaches such as cognitive therapy (e.g., Norton & Price, 2007) and medications (e.g., Roy-Byrne & Cowley, 2002) as well as exposure-based therapies. Rather, the goal is to update conceptualizations of the mechanisms underlying exposure therapy.

The first of two lines of basic science research from which we draw is extinction learning, since the extinction of conditioned fear can be viewed as a laboratory analogue for exposure therapy (Bouton, Mineka, & Barlow,

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2001; Davey, 1997; Eelen, Hermans & Baeyens, 2001; Mineka, 1985).[1] Knowledge of the mechanisms underlying extinction learning, and the resultant conditions that facilitate or hamper extinction learning, may help to sharpen exposure treatments and maximize outcomes in both the short and long run (i.e., relapse prevention). Indeed, extinction learning has served as the explicit model of behavior therapy for phobias for many years (see Eelen & Vervliet, 2006), and extinction-like processes continue to be emphasized, albeit in ways that lag behind recent advances.

The second line of basic science research pertains to learning and memory, since what is learned throughout exposure therapy is intended to be remembered in different places and at later points in time once exposure therapy is over. The evidence pertaining to the retrieval strength of learning, presented cogently in the 'new theory of disuse' (Bjork & Bjork, 1992, 2006), has relevance to the long-term outcomes from exposure therapy. Naturally, this line of research overlaps with the science of extinction learning.

Before discussing these advances, we overview the prevailing model of exposure therapy for phobias and anxiety disorders, which purports that fear levels throughout exposure therapy are reflective of learning and are critical to overall therapeutic outcome.

Emotional processing theory

The concept of habituation (e.g., Groves & Thompson, 1970) was combined with the concept of 'corrective learning' to explain the effects of exposure therapy in the widely known 'emotional processing' theory (EPT), initiated by Rachman (1980), extensively expanded by Foa and Kozak (1986) and subsequently revised to take into account developments in context specificity of extinction (Foa & McNally, 1996). EPT purports that the effects of exposure therapy derive from activation of a 'fear structure' and integration of information that is incompatible with it, resulting in the development of a non-fear structure that replaces (Foa & Kozak, 1986) or competes with (Foa & McNally, 1996) the original one. A 'fear structure', as first put forth by Lang (1971), is a set of propositions about a stimulus (e.g., spider), response (e.g., racing heart) and their meaning (e.g., 'I will be poisoned') that are stored in memory. The fear structure is posited to be activated by inputs that match part of the structure (such as a spider, a racing heart or a thought about poisoning), which generalizes to activate other parts of the structure. The index of activation is fear, measured subjectively and physiologically.

Once activated, corrective learning occurs through integration of information that is incompatible with the structure. Incompatible information derives from two primary sources. The first is within-session habituation (WSH) of the physiological and/or verbalized fear response, that disassociates the stimulus from response propositions (i.e., the stimulus is no longer connected with fear responding). WSH is considered a necessary pre-requisite for the second piece of incompatible information, which derives from between-session habituation (BSH) over repeated occasions of exposure. BSH is purported to form the basis for long-term learning, and to be mediated by changes in the meaning proposition, in the form of lowered probability of harm (i.e., risk) and lessened negativity (i.e., valence) of the stimulus.

Hence, successful learning is indexed by initial fear activation (IFA), WSH and BSH habituation of the fear response. EPT clearly guided the focus of exposure therapy upon initial elevation followed by within- and between-session reductions in reported fear and physiological arousal, as continuation of those responses was presumed to represent erroneous evaluation of the probability of risk and negative valence. The evidence for these premises is reviewed in the following section.

Fear activation, within-session and between-session habituation as indices of learning?

IFA is operationalized as the peak response during the first exposure trial, or the first part thereof, where peak is defined as maximum fear levels (self-report or physiology) minus baseline levels (e.g., Kozak, Foa, & Steketee, 1988).[2] WSH is measured as the difference between the peak response and the end response of an exposure trial. BSH is measured either as the difference in peak responses from the first to the last exposure

[1] Note, however, this is not to imply that extinction is the only mechanism accountable for the effects of exposure therapy.

[2] Subtraction of baseline values, however, may result in underestimation of peak fear, and whether peak responding is best defined by the highest value at the start of exposure or throughout the exposure trial is unclear.

trial (e.g., Kozak et al., 1988; Pitman, Orr, Altman, & Longpre, 1996a, 1996b) or the difference between the end response of a former exposure trial and the beginning response of the next exposure trial, although this latter method confounds WSH with BSH (Kozak et al., 1988).

Evaluation of the role of IFA, WSH and BSH requires continuous measurement of self-reported fear and physiology throughout exposure trials that are conducted on at least two separate occasions, spaced apart enough to capture long-term learning (i.e., BSH). Moreover, to avoid tautology, outcome should be assessed independently of the indices of emotional processing, such as by standardized clinical scales or behavioral avoidance tests of the same stimuli that were targeted in exposure therapy but at a later time or in a different context, or stimuli from the same category but that differ from the precise stimuli used throughout exposure. Repetition of independent assessments after exposure therapy is essential as well, whether that be an interval of 1 h, 1 day, several days (as is typical of post-treatment assessments) or weeks or months (as is typical of follow-up assessments).

As seen below, only a handful of studies adequately assess IFA, WSH and BSH, and comparison across them is limited by methodological variations, such as graduated versus constant exposure, number and length of exposure trials and of intervals between them, imaginal versus in vivo exposure, and between-session exposure assignments.

Initial fear activation (IFA)

Several studies report a positive relationship between IFA as measured by heart rate and independently assessed outcome. Lang, Melamed, and Hart (1970) found that heart rate during initial trials of an 11-session imaginal systematic desensitization treatment correlated with the amount of fear reduction from pre- to post-treatment. However, this relationship did not extend to other psychophysiological measures of skin conductance or respiration. Kozak et al. (1988) found that peak heart rate response in the first session of imaginal and in vivo exposure for obsessive compulsive disorder correlated with four out of six independent outcome change scores, although again the effect did not extend to measures of skin conductance, nor to reported anxiety. Foa, Riggs, Massie, and Yarczower (1995) and Pitman et al. (1996a) reported significant correlations between peak heart rate response during initial imaginal flooding therapy to trauma scenes and reductions in number of trauma memory intrusions from pre- to post-treatment. Again, the results did not extend to other psychophysiological measures of skin conductance or electromyogram. Finally, in a study of flying phobias by Beckham, Vrana, May, Gustafson, and Smith (1990), participants who subsequently flew in the 8 weeks following a test flight showed higher heart rate during the test flight than participants who did not subsequently fly. However, number of subsequent flights is likely to represent factors other than treatment effects (e.g., financial), thereby reducing the value of these findings.

Others fail to find a role for IFA in predicting outcome. Foa et al. (1983) reported a negative relationship between reported fear at initial imaginal/in vivo exposure and changes by post-assessment and no relationship by follow-up, within an obsessive compulsive disorder sample; although there were no physiological measurements. Pitman et al. (1996b) found no relationship between peak physiological response and outcome from eye movement desensitization for trauma exposure. However, eye movement desensitization involves brief, multiple imaginal exposures followed by instructions to 'blank out the image', which is substantially different than exposure therapy in its usual form. In studies of in vivo exposure to a claustrophobia situation, Kamphuis and Telch (2000) and Telch et al. (2004) reported no relationship and a negative relationship between IFA and overall outcomes. However, various methodological issues limit the value of these findings as well. For example, the (non-significant) finding that higher IFA of reported fear during the first 5 min of exposure related to *higher* fear at post-assessment did not extend to the 2-week follow-up assessment in the Kamphuis and Telch (2000) study. Furthermore, IFA was confounded by averaging initial, peak and ending fear levels of the first 5 min. In their second study, Telch et al. (2004) reported that neither self-reported fear nor heart rate in the first 5 min block of exposure related to fear reduction from pre- to post-assessment. However, the index of IFA had the same limitations as in the study by Kamphuis and Telch (2000), and the post-assessment was not sufficiently independent since it was conducted immediately following exposure with the same exact stimulus as used during exposure. Rauch, Foa, Furr, and Filip (2004), who evaluated 6 weekly sessions of imaginal exposure, found that maximum reported anxiety during the first treatment session did not

relate to post-treatment severity of post-traumatic stress disorder symptoms (although corresponding values during the 3rd, 4th, 5th and 6th sessions did). However, they did not measure physiological indices and did not evaluate the relationship between IFA and *change* in post-traumatic stress disorder severity.

Several other studies report similar patterns of IFA across groups that eventually show differential outcomes. However, none directly evaluate the relationship between IFA and change from pre- to post-/follow-up assessment. For example, we (Tsao & Craske, 2000) evaluated four, 7 min in vivo exposure trials to a public-speaking task, in a massed format on the same day, or over uniform or expanding spaced schedules across 4 days. There were no group differences in IFA of heart rate, and yet the massed exposure group showed more return of fear at 1-month follow-up than the other groups. Sloan and Telch (2002) evaluated in vivo exposure to a claustrophobic situation, accompanied by safety behaviors, threat appraisal or nothing. Even though initial reported distress and heart rate during the first 5 min block of the 30 min of exposure did not differ among the groups, the group that incorporated safety behaviors did more poorly at follow-up. Van Minnen and Hagenaars (2002) conducted nine, 60 min imaginal exposure sessions for post-traumatic stress disorder, combined with daily exposure practice between sessions. Mean and peak distress ratings recorded every 10 min during the first session did not differ between participants who were classified (via an independent symptom scale) as improvers or non-improvers at post-assessment.

In summary, four studies find support for IFA, although the effects were limited to heart rate and do not extend to other physiological indices or self-reported distress. This is significant because heart rate is influenced by a myriad of factors *other* than sympathetic fear-based arousal, for which skin conductance is a more sensitive measure (e.g., Berntson, Cacioppo, & Quigley, 1991). Five more studies find no support for IFA, but are methodologically limited and/or do not evaluate the relationship between IFA and *changes* from pre- to post-/follow-up assessment. Several other studies report that outcomes differ across those who show the same patterns of IFA, but failed to directly assess the relationship between IFA and outcomes. Thus, the extant evidence neither consistently supports nor refutes IFA effects.

Within-session habituation

Although reported and physiological indices of expressed fear most often decline from the beginning to the end of an exposure trial (e.g., Grayson, Foa, & Steketee, 1982; Grey, Rachman, & Sartory, 1981; Grey, Sartory, & Rachman, 1979; Watson, Gaind, & Marks, 1972), there is very little evidence that WSH relates to superior outcomes overall. Pitman et al. (1996a) reported a positive *trend* for WSH of heart rate during prolonged imaginal exposure to correlate ($r = .51$) with overall improvements for post-traumatic stress disorder. Foa et al. (1983) reported that WSH of reported fear correlated with overall improvement at post-treatment and follow-up in their obsessive compulsive disorder sample, although physiological measures were not included. In their study of flying phobias, Beckham et al. (1990) found that relative to those who did not, those who flew during an 8 week interval following a test flight showed more WSH in heart rate from the beginning to the end of the test flight. However, as noted before, factors other than treatment effects likely influenced whether a subsequent flight was taken.

Other studies do not find support for WSH as a predictor of outcome. Kozak et al. (1988) reported that WSH of heart rate and skin conductance during imaginal and in vivo exposure did not correlate with outcome for obsessive compulsive disorder. Riley et al. (1995) also found that WSH of reported distress during interoceptive exposure, towards the beginning, middle or end of an 8-week treatment program for panic disorder with agoraphobia, did not relate to outcome. However, exposure was confounded by the addition of mild to moderate doses of alprazolam. Pitman and colleagues found no relationship between WSH of physiological (Pitman et al., 1996b) or verbal (Pitman et al., 1996a) indices and independent outcomes from imaginal exposure for post-traumatic stress disorder, although the second study involved eye movement desensitization (Pitman et al., 1996b).

Several studies report that groups showing the most overall improvement also show the greatest WSH, but do not directly investigate the habituation–outcome relationship. For example, Borkovec and Sides (1979) found that systematic desensitization was not only associated with greater WSH in heart rate compared to exposure with non-contiguous relaxation, and exposure only, but also showed the most improvement overall. Oliver and Page (2003) compared three, 10 min exposures to slides of blood and injury, each separated by

1 week, under conditions of distracted exposure focused exposure, or exposure alone. The distracted exposure groups, in which more WSH of reported fear occurred, also improved most by follow-up.

Other studies report that despite lack of group differences in rates of WSH, groups differ in independently assessed outcomes, or despite lack of WSH, overall improvement takes place. Although, none directly evaluate the degree to which WSH predicts overall improvement. For example, in our study (Tsao & Craske, 2000), heart rate did not decrease significantly within four in vivo exposure trials, and yet participants improved by follow-up. Furthermore, although our three groups (massed, spaced and uniformly spaced trials) did not differ in rates of WSH for heart rate or reported fear, there were group differences in overall outcome. In another study of acrophobia, we found that 'random' in vivo exposure conditions under which heart rate remained elevated for the full hour of exposure was as effective at follow-up assessment as constant exposure conditions under which heart rate declined over the hour of exposure (Lang & Craske, 2000). Also, even though WSH did not differ among four groups of in vivo exposure for claustrophobia (combined with guided threat reappraisal, a cognitive load distractor, both or neither), Kamphuis and Telch (2000) reported group differences in overall outcome. The same pattern was found by Sloan and Telch (2002) in their comparison of in vivo exposure to a claustrophobic situation combined with safety behaviors, threat appraisal or nothing. Finally, there were no differences in WSH of reported fear for participants who were categorized as improvers versus non-improvers at completion of prolonged imaginal exposure for post-traumatic stress disorder (van Minnen & Hagenaars, 2002).

In direct contrast to EPT, several studies indicated that exposure therapy was effective when each exposure trial was terminated at the point of elevated or unduly high anxiety, albeit always followed by further exposure trials (e.g., Emmelkamp & Mersch, 1982; Rachman, Craske, Tallman, & Solyom, 1986). Even more compelling are results from experimental manipulations, which indicate that lower fear at completion of exposure does not predict better outcomes overall. Rachman, Robinson, and Lopatka (1987) found that those who continued a single exposure trial until fear reduced by 100% from baseline showed more return of fear 4 weeks later than those whose exposure discontinued when 50% reductions from baseline had been achieved. Rachman and Lopatka (1988) evaluated a third overlearning condition in which an additional 15 min of non-fearful modeling was provided after reported fear had reduced to zero. Overlearning did not lessen return of fear 4 weeks later relative to the other conditions. In another study, Farchione (2002) conducted 3 min exposure trials to spiders for the number of times necessary until fear reached a criterion of 10 or less on a 0–100 point scale (mean = 4.3 trials). Participants were then randomized to either 200% more trials than the number taken to reach the criterion ('overlearning' group), versus a control group who stopped exposure at the point at which the criterion was reached. Behavioral tests at baseline and 3 weeks later involved a spider different than the one used during exposure. There were no group differences at follow-up. The second and third studies indicate that repetition of exposure trials in the presence of low levels of expressed fear, which, according to EPT would provide particularly incompatible information for disassociating stimulus and response propositions, had no effect on outcome. It is conceivable that these effects are limited to one exposure occasion and that different findings would emerge over repeated occasions of exposure. Yet, extinction research with non-primates similarly indicates that additional non-reinforced exposures beyond those needed to eliminate fear responding have no observable effect upon fear at re-test (Rauhut, Thomas, & Ayres, 2001).

In summary, support for the role of WSH is limited to three studies, one in which the effect was non-significant, one which did not include physiological measures, and the other limited by methodological problems. Four other studies do not support the role of WSH, although at least two of these studies are limited methodologically. A number of studies indicate that groups showing the most overall improvement also show the most WSH, whereas other studies show the opposite, but in neither case is the relationship between WSH and degree of improvement from pre- to post-/follow-up directly evaluated. Finally, ending exposure at the point of elevated anxiety has been shown to be effective, and two studies in humans and at least one in rodents indicate that continuation of exposure/extinction beyond the point at which fear has declined does not affect the amount of fear upon re-test nor thwart the renewal of fear. Thus, whereas reported fear and physiological arousal generally decline within an exposure trial (although not always), there is no good evidence to indicate that such declines are indicative of learning or of long-lasting improvement.

Between-session habituation

Several studies find support for the role of BSH in outcomes. Lang et al. (1970) found a strong correlation ($r = .91$) between BSH of heart rate over 11 sessions of systematic desensitization, and overall outcome. These effects, however, did not extend to measures of skin conductance. Foa et al. (1983) reported that BSH of reported fear in their obsessive compulsive disorder sample correlated with overall improvement at post-assessment although not at follow-up, and in the absence of physiological measures. In their study of imaginal and in vivo exposure for obsessive compulsive disorder, Kozak et al. (1988) found that BSH of heart rate correlated significantly ($r = .44$–$.52$) with overall improvements. However, the effect did not extend to skin conductance and trends for reported anxiety were not statistically significant. Pitman et al. (1996a) reported a non-significant trend for BSH in heart rate (but not skin conductance) during imaginal exposure to correlate ($r = .46$) with overall improvements in post-traumatic stress disorder. More recently, Rauch et al. (2004) found that BSH of reported distress over six sessions of imaginal exposure for post-traumatic stress disorder was predictive of greater reductions in symptoms from pre- to post-assessment. However, physiological indices were not measured. Conversely, Pitman et al. (1996b) found no relationship between physiological and verbal indices of BSH and overall improvement for post-traumatic stress disorder; however, this finding was based on eye movement desensitization.

Several other studies report greater improvements in groups that show more BSH, although these studies do not directly evaluate the habituation–outcome relationship. Jaycox, Foa, and Morral (1998) observed three patterns of verbal responding within individuals undergoing trauma memory exposures: IFA followed by BSH; IFA without BSH; and limited IFA without BSH. Rates of overall improvement were considerably better in the first group. Van Minnen and Hagenaars (2002) reported that 'improvers' following prolonged imaginal exposure for post-traumatic stress disorder reported greater reductions in mean and peak fear from the first to the second exposure session of a nine-session treatment, but they did not evaluate rates of BSH beyond the second session, nor measured physiological indices. In Oliver and Page (2003), distracted compared to focused and exposure alone groups achieved more BSH of reported fear by the third and final exposure session, and greater overall improvement by follow-up. Finally, Ressler et al. (2004) evaluated virtual reality exposure combined with D-cycloserine (DCS; an agonist at the glycine binding site of the NMDA receptor; see below) or placebo, over two, 35-min graduated exposure trials, for acrophobia. The DCS group not only reported less fear during the first part of the second exposure session (1–2 weeks apart) but improved more by follow-up. However, the absence of an independent assessment in vivo limits the value of these findings.

Despite the significant correlation between BSH of heart rate and outcomes in the study by Kozak et al. (1988), they also observed that neither heart rate nor skin conductance significantly reduced across sessions and yet participants showed overall improvement. We have similarly found that improvements take place even though heart rate does not decline across occasions of exposure, in individuals fearful of spiders (Rowe & Craske, 1998b), heights (Lang & Craske, 2000) and public speaking (Tsao & Craske, 2000). Reported fear did decrease across exposures in the first two studies. These studies suggest that significant declines in heart rate and skin conductance across exposure occasions are not necessary for overall improvement.[3]

In summary, five studies find support for the role of BSH in terms of heart rate and/or reported anxiety, although, as stated earlier, reliance upon heart rate as a measure of fear arousal is problematic. Other studies indicate more BSH of reported fear in groups who achieve more improvement overall. However, these studies did not directly evaluate the habituation–outcome relationship, and other studies show that improvement occurs despite lack of significant reductions in heart rate or skin conductance over occasions of exposure. Thus, like the other indices of EPT, the evidence for BSH is limited.

[3]Additionally, these studies highlight the desynchrony between verbal and physiological indices of fear responding, something that is not well addressed by EPT. A similar desynchrony is seen in laboratory studies, where skin conductance responses remain stable throughout extinction training after the point at which differential stated expectancies for shocks have dissipated (Dawson, Schell, & Bannis, 1986; Schell, Dawson, & Marinkovic, 1991).

Summary

The premises of EPT are only weakly supported. There is no good, consistent evidence to support or refute the role of IFA. Fear often declines from the beginning to the end of an exposure trial (WSH), but the amount by which it declines or the level of fear on which a given exposure trial ends does not predict overall improvement; WSH appears to be mediated by mechanisms that are different than the mechanisms responsible for long-term outcomes. There is some evidence that the amount by which fear declines across occasions of exposure (BSH) predicts outcomes, although sustained heart rate and skin conductance responding across days of exposure does not preclude improvement following exposure therapy. Finally, we found no evidence for the premise that WSH is a necessary precursor to BSH; in the only study addressing this relationship, group differences in WSH of reported fear did not predict group differences in BSH (Jaycox et al., 1998).

New directions for optimizing learning

Fear expression versus fear learning

The emphasis upon fear reduction within an exposure trial (i.e., 'remain in the context until fear has declined') assumes that performance during training is commensurate with learning. That is, EPT purports that continued fear by the end of exposure represents continued erroneous evaluation of the probability of danger or negative valence of the stimulus (Foa & Kozak, 1986; Foa & McNally, 1996). Whereas downshifting of the probability of danger or the negative valence of target stimuli may indeed be critical to the success of exposure therapy,[4] the preceding review suggests that ongoing levels of reported or physiological fear throughout exposure are not good indices of such cognitive shifts.

The notion that fear expressed throughout exposure is an index of learning contradicts memory research which shows that performance during instruction is an unreliable index of learning (Bjork & Bjork, 2006). That is, latent learning experiments in animals and motor learning experiments in humans show that learning happens over intervals in which there are no changes in performance, and that little or no learning can happen across intervals in which there are substantial changes in performance (Adams & Reynolds, 1954; Christina & Bjork, 1991; Schmidt & Bjork, 1992; Tolman & Honzik, 1930; see Bjork & Bjork, 2006). The evidence pertaining to WSH and BSH mirrors these effects.

Discordance between fear expression versus learning is found in the basic science of conditioning and extinction learning as well. At the neurobiological level, different brain structures appear to be involved in the expression versus the memory for fear: the amygdala is central to learning and memory of emotionally arousing stimuli, but is not critical to the expression of emotion (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000). Also, in rodent samples, behavioral and/or physiological fear during extinction training is not representative of learning at the process level and does not predict performance upon re-test, when the strength of new learning is assessed (e.g., Bouton, Garcia-Gutierrez, Zilski, & Moody, 2006; Rescorla, 2006). The discrepancy between fear during extinction training versus at subsequent re-test is understandable within the context of the mechanisms of extinction learning.

It is now thought that inhibitory learning is central to extinction (Bouton, 1993; Miller & Matzel, 1988). Although there may be additional mechanisms at play during extinction learning (Myers & Davis, 2007), it is the inhibitory mechanisms which explain the discrepancies between extinction training and post-extinction fear levels. Inhibitory pathways are also recognized in the neurobiology of fear extinction (see Sotres-Bayon, Cain, & LeDoux, 2006). Within a Pavlovian conditioning approach, inhibitory learning means that the original CS–US association learned during fear conditioning is not erased during extinction, but rather is left intact as a new, secondary learning about the CS–US develops (e.g., Bouton, 1993; Bouton & King, 1983). More specifically, Bouton and colleagues propose that after extinction, the CS possesses two meanings; its

[4]Several theoreticians propose that cognitive shifts mediate the efficacy of exposure therapy, and some provide supportive empirical evidence, such as the match–mismatch theory (Taylor & Rachman, 1994) and cognitive reappraisal models (e.g., Clark et al., 1994; Hofmann, 2004).

original excitatory meaning (CS–US) as well as an additional inhibitory meaning (CS–noUS). Therefore, even though fear subsides with enough trials of the CS in the absence of the UCS, retention of at least part of the original association can be uncovered by various procedures, including changing the test context (renewal; Bouton, 1993), presenting unsignaled unconditional stimuli (re-instatement; Rescorla & Heth, 1975), re-acquisition of original associations (Ricker & Bouton, 1996), or simply allowing time to pass (spontaneous recovery; Baum, 1988).[5] Thus, the inhibitory association acquired as a result of extinction is not always expressed at re-test, either because it is fragile or it is gated by context (Myers & Davis, 2007). In sum, inhibitory associations may be acquired independently of fear levels expressed throughout extinction, and the degree to which inhibitory associations shape fear responding at re-test (the index of strength and stability of new 'learning'), is similarly independent of fear levels expressed throughout extinction and instead is dependent on factors such as context and time.

These mechanisms of extinction imply that the most informative and critical test of exposure therapy is post- or follow-up assessment, when the inhibitory learning acquired during exposure will shape the expression of fear, regardless of the level of fear that was expressed during exposure therapy. However, the inhibitory learning itself is vulnerable to time and context, such that return of fear (i.e., weakened access to inhibitory associations) may occur after the passage of time (as would occur when failing to remain in contact with the previously feared stimulus after treatment is over), if the stimulus is encountered in a context that is distinctly different from the treatment context, or if traumatization occurs (see Craske & Mystkowski, 2006; Hermans, Craske, Mineka, & Lovibond, 2006). Again, these post-exposure effects are independent of the level of fear expressed during or at completion of exposure therapy.

Fear reduction versus fear toleration

Emphasis upon fear reduction throughout exposure runs counter to the notion of 'fear toleration'. 'Toleration' is central to the concept of emotion regulation, operationalized as the actions designed to influence which emotions are present, and how they are experienced or expressed (Gross, 2002). Emotion regulation is considered to be dysfunctional when applied rigidly to downregulate emotions through suppression, control, avoidance or escape. Persistent attempts to downregulate aversive states are hypothesized to be critical to the onset of phobias and anxiety disorders (e.g., Forsyth, Eifert, & Barrios, 2006), although the evidence is rather limited to date. Nonetheless, rigid downregulation, also termed 'experiential avoidance', predicts severity of fear responding to a novel task of carbon dioxide inhalation (Karekla, Forsyth, & Kelly, 2004) whereas acceptance of emotions lessens distress to the same novel task (Eifert & Heffner, 2003). Thus, toleration of fear may be more critical to exposure therapy than the reduction of fear.

Somewhat related to this issue is the experimental evidence showing that procedures which sustain fear responding throughout extinction enhance extinction learning. Specifically, pharmacological inhibition of beta-adrenergic neurotransmission negatively influences extinction (Berman & Dudai, 2001), whereas yohimbine, an alpha-2 adrenergic antagonist that potentiates beta-adrenergic transmission, facilitates extinction in non-primates (Cain, Blouin, & Barad, 2004). In comparison, propranalol and a placebo-type control do not have this enhancing effect, especially for spaced extinction trials. Cain et al. (2004) posit that enhanced adrenergic transmission facilitates the formation of fear extinction memories. These findings suggest that greater adrenalin release may actually *enhance* learning during exposure therapy, a suggestion that is clearly counter to the emphasis upon reducing fear throughout exposure therapy.[6]

[5]Recent evidence raises the possibility that complete erasure of original learning may occur if extinction happens shortly after acquisition in contrast to the inhibitory nature of extinction that takes place following the consolidation of fear learning (Cain, Godsil, Shekib, & Barad, 2005; Lin et al., 2003; Myers, Ressler, & Davis, 2006; Nader, Foa, & Coles, 2000). However, the evidence is mixed (e.g., Bouton, 2007) and phobias and anxiety disorders rarely if ever are treated immediately following acquisition; thus, the inhibitory nature of extinction is a more relevant model for the exposure treatment of these disorders.

[6]Importantly, this is not to suggest that expressed fear during extinction is an index of learning, but rather suggests that methods that secondarily evoke fear enhance extinction learning via their impact upon beta adrenergic transmission.

Self-efficacy versus illusion of competency

In contrast to EPT, self-efficacy theory de-emphasizes fear and anxiety throughout exposure and instead emphasizes skill and mastery performance ('guided mastery therapy'; Williams, 1990). Performance is emphasized because it is considered to be the most potent agent for raising self-efficacy, or, the 'conviction that one can successfully execute the behavior required to produce an outcome' (Bandura, 1977, p. 193), which in turn is considered to be the critical agent of therapeutic change (Bandura, 1977). In accord, several studies report that self-efficacy predicts treatment outcome (e.g., Williams, Dooseman & Kleifield, 1984; Williams, Kinney & Falbo, 1989; Williams, Turner & Peer, 1985). However, in each case, the predictive relationship is between self-efficacy and behavior measured at a single point in time, whether at post-treatment or follow-up. The only study to evaluate whether changes in self-efficacy throughout exposure therapy predict subsequent performance did not find statistically significant effects (Borden, Clum, & Salmon, 1991).

Furthermore, there is now evidence to suggest that judgments of one's own competency throughout training are not good predictors of performance at re-test (i.e., learning) (see Bjork, 2004). Learners appear to misinterpret objective and subjective indices of their performance and become fooled by their own successes during training (Bjork, 2004; Jacoby, Bjork, & Kelley, 1994). Interestingly, certain training conditions enhance the illusion of competency, such as massed practice, constancy of training conditions, and provision of continuous feedback, because these conditions result in relatively sharp improvements in performance but have more limited effects on long-term learning than conditions that introduce more difficulties for the learner ('desirable difficulties') (Bjork, 2004). Notably, the former conditions match aspects of the typical approach to exposure therapy (e.g., constancy and continuous feedback); by producing relatively immediate reductions in fear, they are likely to enhance the perception of self-efficacy. However, this perception may remain an illusion since fear reduction throughout exposure therapy is not a good predictor of long-term effects from exposure therapy. As discussed in further detail below, conditions that introduce difficulties, such as variable practice, while possibly slowing the rate at which fear declines and self-efficacy increases throughout exposure therapy, may enhance learning in the long term. The 'desirable difficulty' approach to exposure therapy also resonates with the value of fear toleration rather than fear reduction during exposure therapy.

New directions

In the next section, we justify moving away from initial activation followed by fear reduction as the guiding principle of exposure therapy, and instead recommend an inhibitory learning based approach for developing new, non-threat associations, and enhancing the accessibility and retrievability of the newly learned associations over time and context. The proposed methods for developing non-threat associations are derived from basic science of extinction learning and memory, and include structuring exposure trials to optimize mismatches with expectancies, inclusion of multiple conditioned excitors, elimination of safety signals and safety behaviors, use of cognitive enhancers, and enhancement of inhibitory regulation. The proposed methods for enhancing accessibility and retrievability of newly learned associations include variability, spaced scheduling of exposure trials, and retrieval cues for offsetting the renewal of fear.

Development of non-threat associations

Mismatch with expectancies

Expectancies for the likelihood of aversive events are central to human fear conditioning. For example, contingency awareness (i.e., knowledge that a specific CS predicts a specific US), although of debatable *necessity* for conditioned responding (e.g., Lovibond and Shanks (2002) versus Ohman and Mineka (2001)) is a strong *correlate* of conditioned responding (e.g., Purkis & Lipp, 2001). In turn, extinction is posited to follow from a mismatch between the expectancy of an aversive event and the absence of its occurrence (Rescorla & Wagner, 1972), or from the perception of a negative change in the rate at which aversive events are associated with the CS (Gallistel & Gibbon, 2000). In other words, expectancies for the US are violated during extinction.

In terms of inhibitory mechanisms, violation of expectancies for the US would lead to new, secondary learning that the CS does not predict the US. In human samples, such shifts in associative expectancies may occur at both automatic and propositional levels (Beaver, Mogg & Bradley, 2005; Clark & Squire, 1998; Lovibond, 2003, 2004; Ohman & Mineka, 2001).

There probably are a number of ways of violating expectancies for the US, and in human samples this may extend to means other than direct exposure to the CS, such as by information about the CS or US (Davey, 1992). This, of course, pertains to cognitive therapy approaches, which aim to shift expectancies for aversive events through discussion and logical empiricism rather than necessarily through direct experience (e.g., Clark & Fairburn, 1997). Shifts in expectancies clearly are the focus when cognitive therapy is applied within the context of exposure therapy. However, the current discussion centers upon ways of structuring the *experience* of exposure therapy to maximally optimize new learning, at both automatic and propositional levels.

Durations or frequencies of unreinforced exposure to the CS that surpass the rate at which aversive events are expected to occur would provide potent mismatches to form the basis of new learning. Surprisingly, studies of this topic are sparse. In rodent samples, one study found that massed CS presentations during extinction, interpreted to represent one continuous CS presentation that exceeded the length of CS during acquisition, was more effective than spaced CS trials throughout extinction (Cain, Blouin, & Barad, 2003). Also, Drew, Yang, Ohyama, and Balsam (2004) demonstrated that extinction learning, assessed at re-test, was greatest when the CS duration during extinction was similar to rather than shorter than its duration during acquisition. However, durations that were substantially longer during extinction also led to poorer extinction learning at re-test. Conceivably, the substantially shorter and longer extinction durations resulted in a distinctly different CS during acquisition versus extinction. Clearly, further basic research on CS durations and frequencies is warranted.

Laboratory conditioning studies in humans have not yet evaluated the length or frequency of CSs during extinction relative to acquisition. There is evidence that expectancies for risk and valence of the CS at the conclusion of extinction training predict how much fear is expressed at re-test (Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2004; Hermans et al., 2005). However, the degree to which changes in those expectancies predict improvement from pre-test to post-extinction re-test have not been evaluated.

In phobic samples, there is some evidence for a single massed exposure to be more effective than a series of short exposures of the same total duration (Chaplin and Levine, 1981; Marshall, 1985; Rabavilas, Boulougouris, & Stefanis, 1976; Stern and Marks, 1973; Watson & Marks, 1971). For example, one 60 min duration was more effective than three, 20 min durations of exposure (e.g., Marshall, 1985). Conceivably, lengthier (massed) exposure is more effective by virtue of providing sufficient time to learn that aversive outcomes do not occur (i.e., to violate negative expectancies). However, none of these studies directly manipulated the duration of exposure trials relative to violation of fear-based expectancies.

Potentially relevant are studies of distraction during exposure since distraction in essence represents disrupted (i.e., 'unmassed') exposure. However, as with the reports above, studies of distraction have not been designed in order to test violation of expectancies (i.e., does the distractor directly impede violation of fear-based expectancies?). Moreover, results from 'distracted exposure' have been contradictory (Kamphuis & Telch, 2000; Oliver & Page, 2003; Rodriguez & Craske, 1995; Rose & McGlynn, 1997; Telch et al., 2004). The equivocal nature of the findings may derive from lack of an operational definition of distraction, from confounds with the affective quality of the distractor, and from the unknown amount of distraction that actually takes place (Rodriguez & Craske, 1993).

Direct comparisons are needed of durations (or numbers) of exposure trials that discontinue before versus after the point (or number of occasions) at which an aversive event is fully expected to occur, regardless of the level of fear expressed. Hypothetically, the appraisal of fainting as a likely event upon driving five or more miles from home would be more effectively violated by driving six miles from home than driving two miles from home, regardless of the level of fear experienced. If the aversive event is fear itself, as is often the case in anxiety disorders (Barlow, 1988), then exposure trials would be designed to last longer versus shorter than the interval of time (or number of repetitions) at which fear is judged to become intolerable.

Experimental investigation of this topic, however, will prove challenging. For example, in addition to matching groups on total duration of exposure, the number of times the phobic stimulus is 'approached' will

be a potential confound, given the potency of early session cues in extinction learning (e.g., Brooks & Bouton, 1993). Also, stated expectancies for aversive outcomes may shift throughout the course of exposure, such that on-line expectancy ratings are needed to continuously guide the length or number of exposure trials. Changes in expectancies may not even shift until some time after the completion of exposure therapy and before re-test. There is also the possibility that whereas violation of outcome expectancies may be critical to learning throughout exposure therapy, the verbal statement of expectancies before or during exposure trials may simply reflect another index of 'performance during training' versus new inhibitory learning.

Multiple conditioned excitors

Another method for developing new, non-threat associations, and one that does not depend upon stated expectancies, derives from the facilitative effect of multiple excitatory conditioned stimuli during extinction training (Rescorla, 2000, 2001; Thomas & Ayres, 2004). These effects have been attributed to associative mechanisms outlined in the Rescorla–Wagner error correction model (1972), wherein the amount of extinction is determined by the discrepancy between the total associative strength of all stimuli present, their respective saliences, and non-reinforcement of the US. That is, greater associative (inhibitory) learning derives from the absence of the aversive stimulus in the presence of multiple compared to single original predictors of the aversive stimulus.

Most recently, Rescorla (2006) extended this research to study 'deepened extinction', in which two or more CSs are extinguished separately before combining them for additional extinction trials. This approach was superior to non-compound extinction, resulting in less spontaneous recovery, less re-instatement and slowed re-acquisition. The compound approach produced more fear responding during extinction training, but level of responding did not account for the effects (Rescorla, 2006, study 5), again pointing to the discord between level of fear expressed during training and learning at the process level.

Two laboratory studies in humans failed to find enhancement of extinction through multiple conditioned excitors (Lovibond, Davis, & O'Flaherty, 2000; Vervliet, Vansteenwegen, Hermans, & Eelen, 2007). However, these findings may be attributable to simultaneous versus sequential extinction of two excitatory stimuli. That is, Rescorla (2006) suggested that concurrent CSs may present difficulties when the salience of one overshadows the other. Alternatively, the negative findings may be due to ethical constraints on the magnitude of the US in human studies that impede the normal process of additivity that underlies the Rescorla–Wagner model (Mitchell & Lovibond, 2002).

There have been no direct investigations of multiple feared stimuli in human phobic samples. However, the concept of 'deepened extinction' is easily translated into exposure therapy, and is indeed the method employed in the treatment for panic disorder and agoraphobia when interoceptive exposure to feared physiological sensations (e.g., elevated heart rate) and in vivo exposure to feared situations (e.g., walking through a shopping mall) are subsequently combined (e.g., drinking caffeinated substances while walking through a shopping mall) (Barlow & Craske, 1988). Given the important clinical implications, direct investigation of deepened extinction in human phobic samples is needed.

Wean safety signals and safety behaviors

Safety signals are conditioned inhibitors, or predictors of the absence of the US. Common safety signals for anxiety disorder patients are the presence of another person, therapists, medications, food or drink (Barlow, 1988). In the experimental literature, conditioned inhibitors alleviate CRs in the short term, but the excitatory stimulus continues to elicit a CR when subsequently tested without the conditional inhibitory stimulus (Siddle & Bond, 1988). These effects have been explained by associative and attributional mechanisms. The former model (e.g., Rescorla–Wagner) assumes that the negative associative strength of the inhibitory stimulus cancels the positive associative strength of the excitatory stimulus, so that there is no change from what is predicted by all cues (Lovibond et al., 2000). The attributional model implies that when the absence of an expected aversive outcome is attributed to an inhibitory stimulus, there is no reason to change the causal status of the excitatory stimulus. Associative and attributional models converge on the idea that safety signals interfere with the development of new, non-threat associations.

For this reason, inclusion of conditioned inhibitors during extinction training may interfere with extinction learning. Surprisingly, the animal literature on conditioned inhibition during extinction is mixed (Lovibond et al., 2000), and the only human laboratory study yielded results that were difficult to interpret. That is, Lovibond et al. (2000) demonstrated that extinction was blocked by an inhibitory stimulus, as hypothesized. However, a conditioned excitor performed in the same way as the inhibitor. The results were attributed to context specificity, given that re-testing of the excitatory stimulus alone served as a sufficiently different context than what occurred during the extinction trials when the excitatory stimulus was accompanied by either another excitatory stimulus or an inhibitory stimulus (more description of context specificity is presented below).

Several studies have evaluated safety signals in human phobic samples. For example, in a study already described, Sloan and Telch (2002) reported that claustrophobic participants who were encouraged to use safety signals during exposure (e.g., opening a window, checking that the door-lock unlocks) reported more fear at post-test and follow-up than those encouraged to focus on their fear during exposure. In a subsequent study, Powers, Smits, and Telch (2004) found that the perception of safety (i.e., availability of the same types of safety signals regardless of whether they were used) had the same detrimental effects on outcome as the actual use of safety signals. However, in both studies, the effects of safety signal encouragement may have been attributable to distraction. Furthermore, some of the safety signals constituted behaviors that in essence degraded the CS (i.e., opening a window) and thus more closely represented safety-seeking avoidance responses than safety signals.

On the other hand, avoidance responses may share some functional properties with Pavlovian safety signals (Lovibond & Shanks, 2002), and other data indicate that safety seeking avoidance behavior also negatively influences exposure therapy. That is, Salkovskis (1991) and Wells et al. (1995) showed that requesting anxious clients to refrain from 'within situation safety behaviors' led to greater improvement after an exposure session than no instructions regarding safety behaviors, although how well clients refrained from those behaviors was not directly assessed. More investigation is needed on the effects of safety signals and safety behaviors during exposure, especially given the very direct implications for clinical practice. It is notable that effective safety signals and behaviors should lessen fear responding throughout exposure while at the same time interfere with inhibitory learning, thereby again highlighting the discord between fear reduction and new learning.

Cognitive enhancers: D-cycloserine

Fear extinction is dependent on NMDA-type glutamate receptors (NMDAr) (reviewed in Walker & Davis, 2002). NMDAr inhibitors block extinction when given systemically or infused directly into the amygdala during extinction training (Baker & Azorlosa, 1996; Falls, Miserendino, & Davis, 1992). Furthermore, systemic or intra-amygdala treatments with DCS, an agonist at the glycine binding site of the NMDA receptor, facilitate extinction in rodents (Walker & Davis, 2002). However, the facilitative effects are not complete: while DCS reduces spontaneous recovery and re-instatement effects, it does not offset context renewal or rapid re-acquisition effects (Vervliet, in press; Woods & Bouton, 2006). Notably, DCS is a cognitive enhancer that does not influence expression of the CR during extinction, which is yet another illustration of the discord between expression of fear and learning.

Interestingly, the only study of DCS in a human laboratory conditioning study did not find a facilitative effect upon extinction (Guastella, Lovibond, Dadds, Mitchell, & Richardson, 2007). Moreover, results with human phobic samples are mixed. Ressler et al. (2004) found that participants who received DCS before two sessions of virtual reality glass elevator exposures had greater improvements 3 months later, on self-report, physiological and behavioral measures, than those given a placebo drug. In line with non-primate research, the benefits of DCS were not associated with changes in levels of anxiety during exposure relative to placebo. Hofmann, Pollack, and Otto (2006) found that participants who received DCS prior to each of four sessions of exposure therapy for social anxiety had greater improvements at post-treatment and 1 month later than those who ingested a placebo drug, although the measures were limited to reported anxiety. Conversely, Guastella, Dadds, Lovibond, Mitchell, and Richardson (2007) found no difference between DCS and placebo for sub-clinical spider phobia. This well controlled study included physiological and behavioral measures and evaluation in contexts that were the same and different than the exposure treatment context. Thus, despite

some initial promising results, further evaluation of the practical effects and theoretical explanation of DCS is needed.

Enhancing inhibitory regulation

The majority of neurobiological research on fear learning and extinction has focused on three general structures: the amygdala, the prefrontal cortex (PFC), and the hippocampus (see Sotres-Bayon et al., 2006 for a review). The amygdala has long been implicated as playing a key role in fear learning (for a review see Fendt & Fanselow, 1999) and seems to be involved in extinction learning as well, albeit perhaps serving a less extensive function (Sotres-Bayon, Bush, & LeDoux, 2004). The PFC and hippocampus seem to be vital to extinction learning and may offer an additional window into possibilities for the enhancement of extinction learning.

The hippocampus, which is important for encoding contextual information (Fanselow, 2000), has been shown to be involved in the context-sensitive aspect of extinction and fear renewal. For example, Ji and Maren (2005) demonstrated that lesions to the dorsal hippocampus either before or after extinction training offset fear renewal following extinction, although an earlier study failed to find this effect (Frohardt, Guarraci, & Bouton, 2000). If the hippocampus is central to post-extinction effects, such as renewal of fear, then non-invasive hippocampal manipulations may be promising for exposure therapies. However, what those manipulations might entail is not clear at this point.

The PFC has long been implicated in executive control and decision making (see Stuss & Knight, 2002). Recent work has revealed that certain parts of the PFC (i.e., ventral medial) are also responsible for emotional regulation, and, in particular, the ability to interpret emotional stimuli and change behavior accordingly (see Sotres-Bayon et al., 2006). Given this role, the ventral medial PFC potentially serves as a prime candidate for a fear extinction structure. In support, extinction in non-primates is associated with neuronal activity primarily within the medial PFC (Phelps, 2004; Quirk, Garcia, & Gonzalez-Lima, 2006; Rauch, Shin, & Phelps, 2006). Research with humans similarly shows that changes in the medial PFC occur during extinction (Gottfried & Dolan, 2004; Knight, Smith, Cheng, Stein, & Helmstetter, 2004; Phelps, 2004). There is also evidence for greater cortical thickness in the ventromedial PFC in participants with improved extinction performance at re-test (Milad et al., 2005), further pointing to the involvement of the PFC in extinction learning.

While research has yet to pinpoint its specific role in fear extinction and post-extinction phenomena (e.g., renewal), one possibility is that during extinction and re-test the PFC exerts inhibitory control over the amygdala (see Maren and Quirk, 2004; Sotres-Bayon et al., 2004). That is, the PFC serves as the neurobiological basis for inhibitory learning. In support, studies using functional magnetic resonance imaging have shown that as activity in the ventrolateral PFC increases, activity in the amygdala decreases (Hariri, Bookheimer, & Mazziotta, 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Lieberman et al., 2007; Lieberman, Hariri, Jarcho, Eisenberger, & Bookheimer, 2005; Ochsner, Bunge, Gross, & Gabrieli, 2002). The question of *how* this inhibitory control is exerted has been met with mixed results (see for a review Sotres-Bayon et al., 2006). Still, enhanced activation of the PFC may be one of the most promising ways to inhibit or 'cover' the original fear learned during extinction, thereby reducing risk for return of fear.

Pharmacological and neuronal methods targeting the PFC, such as high-frequency stimulation prior to extinction training in mice (Herry & Garcia, 2002) and metabolic enhancers in rats (Gonzalez-Lima & Bruchey, 2004) have been shown to enhance extinction learning. Consistent with the previous discussion of performance during training versus learning, the results are not apparent in terms of the rate of extinction learning but rather performance upon re-test. However, the effects of brain stimulation upon exposure therapy in humans have not been evaluated.

Behavioral methods for enhancing PFC throughout exposure therapy may prove to be a useful direction for future research. Conceivably, when cognitive restructuring enhances the benefits of exposure therapy alone, it may be doing so by activation of the PFC. In a recent analog investigation, we studied the effect of repeated exposure to aversive pictures that were first presented alone before being combined with affective labels compared to non-affective labels or no labels (Tabibnia, Lieberman, & Craske, in press). In Experiment 1, healthy individuals were exposed to repeated pictures of disturbing scenes paired with a fixation cross,

non-affective labels, or negative relevant or irrelevant labels. The pictures were tested 1 week later without the fixation cross or labels. Experiment 2 was similar in design except that participants were spider-fearful and were exposed to pictures of spiders and only negative irrelevant (e.g., bomb) and neutral labels were used. In both studies, sympathetic responding (skin conductance) decreased from Day 1 to Day 8, but significantly more in the negative irrelevant label condition. In other words, exposure plus negative irrelevant labels, but not negative relevant or neutral labels, led to more attenuation than exposure alone. Conceivably, the negative irrelevant labels, by virtue of their mismatch with the content of the aversive pictures, more effectively activated the PFC. However, without direct evidence via fMRI scanning during exposure sessions this remains speculative. Further investigation is also warranted given the contrast between negative irrelevant linguistic processing and typical cognitive restructuring: it would be of interest to establish the role of PFC activation in each case and the connection of such activation to the development of new, inhibitory associations and expectancies.

Enhancing accessibility and retrievability of exposure-based learning

Variability throughout exposure

In general, retention of learned non-emotional material is enhanced by random and variable practice (Magill & Hall, 1990). Even though variation increases difficulty throughout learning, Bjork and Bjork (1992, 2006) proposed that variation enhances long-term outcome. According to their model, variation increases the storage strength of information to be learned by making retrieval of past learning easier via the availability of cues that were present during prior learning. In addition, drawing from stimulus fluctuation theory (Estes, 1955), variation results in pairing the information to be learned with more retrieval cues, thus enhancing retrievability because the cues associated with new learning are more likely to be present in a situation where retrieval is required (Bjork, 1988). Furthermore, variation is posited to result in generation and application of a rule that captures the invariance among tasks (Schmidt & Bjork, 1992). That is, despite dissimilarities, the basic principles are the same across tasks and can be applied regardless of situational dissimilarities. In other words, variation leads to superior generalization. The benefit of varying the to-be-learned material has been demonstrated with motor and verbal learning tasks (Schmidt & Bjork, 1992).

There have been no studies of variable and random extinction training in either rodents or in human laboratory conditioning studies. Studies in phobic samples have shown that exposure to varied phobic stimuli (i.e., multiple spiders) led to better maintenance of treatment gains at follow-up than did exposure to a constant stimulus (i.e., a single spider) (Rowe & Craske, 1998b). In addition, we found benefits to random and variable, compared to blocked and constant, exposure for height phobias (Lang & Craske, 2000). In the random/variable condition, participants practiced exposure to heights in random order, such as 8th floor, 2nd floor, 10th floor and 3rd floor balconies in more than one situation (e.g., inside versus outside stairwell) and approached the precipice in different ways (e.g., looking out versus down). This was compared to blocked exposure to the same balconies repeatedly before moving to the next floor, with the same manner of approaching the height during each exposure trial. The random/variable practice resulted in less general anxiety 1 month later despite higher peak levels of anxiety (including heart rate) throughout exposure. Clearly, the topic of variation needs further investigation.

Spacing of exposure trials

Temporally spaced training trials often result in stronger acquisition-type learning than temporally massed trials (e.g., Fanselow, DeCola, & Young, 1993; Josselyn et al., 2001; Kogan et al., 1997; Scharf et al., 2002). Studies in human memory for non-emotional material similarly support the value of spaced or distributed learning trials, at least when the retention interval is lengthy (Bjork & Bjork, 1992). This effect has been attributed to the greater storage strength of memory that is gained by partial forgetting between learning episodes, which in turn is presumed to slow the loss of the retrievability of a memory over time (Bjork & Bjork, 1992).

However, the effects of spacing during extinction training have been inconsistent in rodent samples (e.g., Bouton & Garcia-Gutierrez, 2006; Martasian, Smith, Neill, & Rieg, 1992; Moody, Sunsay, & Bouton, 2006;

Terry & Anthony, 1980). According to Cain, Blouin, and Barad (2003), one possible explanation for the discrepancies is that studies have not consistently presented the CS during extinction training for durations that exceed the CS duration during acquisition. In other words, Cain et al. (2003) propose that spacing results in greater consolidation of learning than does non-spacing, but only when spacing occurs for blocks of CS presentations that are sufficiently massed to violate expectancies of the US. Additionally, discrepancies may derive from the way in which massed versus spaced are operationalized. For example, whereas Cain et al. (2003) used a 6 s ITI for massed extinction and a 600 s ITI for spaced extinction, Li and Westbrook (as reported in Bouton et al., 2006) used a 'few minutes' ITI for massed extinction and a 24 h ITI for spaced extinction.

There have been no human laboratory conditioning studies on this topic, and research in human phobic samples has been non-theoretically driven and has produced discrepant findings. Also, as with rodent studies, studies of spacing *between* exposure occasions have been conducted without assuring that exposure sufficiently mismatches expectancies for the aversive *within* each exposure occasion, and what is labeled as massed in one study is labeled as spaced in another. For example, Foa, Jameson, Turner, and Payne (1980) found greater decrements in anxiety and avoidance behavior in those receiving massed (daily) rather than spaced (weekly) exposure sessions for one group with agoraphobia, while massed and spaced schedules did not differ in their other group. Ramsay, Barends, Breuker, and Kruseman (1966) found spaced schedules to be superior to massed schedules for specific phobias. Their massed treatment involved 40 min of exposure on each of 2 days spaced 4 days apart, whereas spaced exposure involved 20 min of exposure on 4 consecutive days. Conceivably, the 4 day separation in the massed treatment blurred the intended distinction between conditions. In addition, neither study evaluated long-term follow-up, which is when the benefits of spaced exposure would be expected. We observed less return of fear at follow-up after an expanding spaced schedule of progressively longer intervals between exposure occasions compared to consecutive days of exposure (Rowe & Craske, 1998a; Tsao & Craske, 2000). Many other studies show no differences between massed and spaced exposure schedules (e.g., Berah, 1981; Chambless, 1990; Emmelkamp, van Linden van den Heuvell, Ruphan, & Sanderman, 1989; Ning & Liddell, 1991). A major gap in the translation from basic science to clinical practice is theoretically driven research directly comparing different schedules of exposure trials.

Offsetting context renewal and re-instatement effects

As already described, four standard effects of spontaneous recovery, context renewal, re-instatement and rapid re-acquisition demonstrate that original fear learning is not erased during extinction. The first three have particular relevance to the return of fear following exposure therapy. All have been well documented in rodents and human laboratory conditioning studies (see Hermans et al., 2006; Vervliet, in press). The context renewal phenomenon has been studied the most in human phobia samples.

Bouton and colleagues (see Bouton, 1993; Bouton & King, 1983; Bouton & Nelson, 1998) propose that the dual meaning of the CS after extinction training (excitatory and inhibitory) creates an ambiguity which is resolved only by the current context of the CS. For example, bodily sensations may mean 'sudden death' when experienced in a context that reminds the person of intense panic attacks, whereas the same sensations may mean 'unpleasant but harmless' when experienced in a context that reminds a person of their success with treatment. Specifically, Bouton proposes an 'AND' gate; a stimulus and context occurring together activate an AND gate which is the mechanism to activate inhibitory associations with the US. Without the joint presence of the stimulus and the context, the inhibitory path is not activated and the excitatory path controls the response to the US leading to context renewal. Thus, return of fear may be explained at least partly by context renewal effects.

In accord, more return of fear is found when participants are subsequently assessed in a context distinctly different from the context in which they were treated (Mineka, Mystkowski, Hladek, & Rodriguez, 1999; Mystkowski, Craske, & Echiverri, 2002; Rodriguez, Craske, Mineka, & Hladek, 1999). These effects extend to internal contexts (i.e., caffeinated versus placebo substances; Mystkowski, Mineka, Vernon, & Zinbarg, 2003). The majority of effects are statistically but not clinically significant, although larger effects were obtained when more distinctly different contexts were employed (Mystkowski et al., 2002). Conceivably, even larger effects would be obtained if re-testing occurred in the original fear acquisition context, since in the animal

literature, the contextual control is stronger when the animal is tested for renewal of fear in the context in which the fear was originally conditioned (ABA) than when tested in a new context (ABC) (Bouton & Brooks, 1993). It is also conceivable, however, that context effects apply mainly to the initial response to the CS, and that renewal subsides with continued exposure. In phobic samples, this would imply that renewal effects would be over-ridden by continued exposure to the previously feared stimulus in a new context.

Bouton (1993) suggested that the more integrated the contextual information with other features of the stored representation, the more context dependent is the retrieval. Thus, contexts which are more meaningful to a feared stimulus may be more influential. For example, proximity of a medical facility may be a particularly meaningful context during treatment for panic disorder, as might be summer weather conditions, when the roads are not wet and slippery, during exposure for fears of driving. However, these types of contextual variables relate directly to perceptions of safety, and thus their distinctiveness from safety signals is unclear. In fact, the interdependence of stimulus and context has long been argued (e.g., Rescorla, 1985).

In addition to difficulties identifying relevant contexts, other factors may moderate the potency of contextual variables. For example, a contextual variable may be less influential as a result of cue overload, due to pervasive associations with a number of previously formed memories (Eich, 1989; Watkins & Watkins, 1976). For example, in addition to serving as a context for extinction of fears of bodily sensations, medical facilities may be a context for acquisition of fears of blood, as well as a context for loss of a loved one. In addition, drawing from Thorndike's (1932) notions of causal belongingness, integrative links between contexts and encoding of events may depend on the perception that the context is causing or at least enabling these events (e.g., Eich, 1985, 1995). It remains to be determined what contexts are perceived as most causal to fear learning and fear extinction.

Nonetheless, one implication from context renewal effects is to conduct exposure therapy in multiple contexts, especially those in which the previously feared stimulus is likely to be encountered once treatment is over. Animal studies on this topic have produced inconsistent results, with only some finding that extinction in multiple relative to single contexts reduces fear renewal in a final novel context (Chelonis, Calton, Hart, & Schachtman, 1999; Gunther, Denniston, & Miller, 1998 versus Bouton et al., 2006). In a recent study of a spider fearful sample, Vansteenwegen et al. (2007) compared viewing video fragments of a spider in different locations versus a single location of a house. Electrodermal responding showed a renewal effect in a novel house location in the single and not the different context exposure group.

Another approach to offsetting contextual renewal is to provide a 'bridge' from extinction contexts to re-test contexts (Bouton et al., 2006). One such bridge is to instruct participants to recall the extinction context. When participants are instructed to recall an original learning environment just prior to free recall of a list of words in an unfamiliar environment, a release from contextual dependence is observed and performance is identical to that of participants tested in the original learning environment (Smith, 1979). Thus, we evaluated the role of mental rehearsal of context on return of fear (Mystkowski, Craske, Echiverri, & Labus, 2006). Spider phobic participants were treated and followed-up in the same context or different context. At the time of follow-up, half of the participants were instructed to mentally rehearse the treatment context and the material learned in that context before entering the test context, whereas the other half was asked to recall a neutral scenario. Participants who mentally rehearsed the treatment context, before encountering the phobic stimulus in a different context at follow-up, had less return of fear than those who did not.

Bridging from the extinction to renewal context also can be provided by objects that serve as retrieval cues (Bouton et al., 2006). In rodents, retrieval cues during extinction trials attenuate context-based renewal effects, and more so than relatively novel cues or cues that were present during conditioning rather than extinction (Brooks & Bouton, 1993). In human samples, Collins and Brandon (2002) showed that the return of alcohol cue reactivity after extinction due to a context-change could be reduced by the use of retrieval cues that were present during extinction. More investigation of retrieval cues is needed, although mental rehearsal effects may have more practical value than retrieval objects, since fear cues might be encountered at times when retrieval objects are not available (Mystkowski & Mineka, 2007), and conditioned inhibitor (i.e., safety signal) effects may arise with repeated use of an object as a retrieval cue.

Another area of investigation for phobias is to replicate the evidence from rodent samples that US-alone exposures throughout extinction training offset context-based renewal effects (Rauhut et al., 2001). This effect was attributed to habituation to the US. The clinical application would be to encourage panic attacks or other

aversive experiences throughout the course of exposure therapy, which again is at complete odds with prevailing models of exposure therapy that encourage immediate fear reduction.

Conclusions

Reliance upon fear levels throughout exposure therapy as an index of learning is not only lacking empirical support, but assumes that performance during 'instruction' is a reliable index of learning; an assumption that is not supported by learning and memory research. Inhibitory processes are now recognized as being central to extinction learning, and evocation of such processes at the time of re-exposure to a previously feared stimulus largely shapes the level of fear, regardless of how much fear was expressed during or at completion of extinction training. Evocation of inhibitory associations is instead influenced by variables such as context and time.

Furthermore, reliance upon fear reduction as an index of corrective learning is at odds with the importance of toleration of fear. Thus, in the paper, we argue for moving away from immediate fear reduction and toward fear toleration as a primary goal of exposure therapy. Also, we conceptualize exposure therapy as reshaping memory, forming new, secondary learning and involving brain regions that contribute to such learning. We posit that exposure efforts should be oriented towards facilitating inhibitory learning, or ways of developing competing, non-threat associations, at both propositional and automatic levels, and ways of enhancing the accessibility and retrievability of those associations over time and in different contexts. We have outlined methodologies for consolidation and retrievability of exposure-based learning that are derived from basic science of learning and memory, and extinction research, some of which have been investigated and some awaiting such investigation.

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