Addressing Relapse in Cognitive Behavioral Therapy for Panic Disorder: Methods for Optimizing Long-Term Treatment Outcomes

Joanna J. Arch, University of Colorado at Boulder
Michelle G. Craske, University of California, Los Angeles

In this paper, we present a client with panic disorder and agoraphobia who relapses following a full course of cognitive behavioral therapy (CBT). To frame the client's treatment, the major components of CBT for panic disorder with or without agoraphobia (PD/A) are reviewed. Likely reasons for the treatment's failure and strategies for improving treatment are explored from the perspective of basic research on learning and memory. Treatment recommendations primarily focus on enhancing the exposure component of PD/A treatment but include suggestions for enhancing other CBT components as well.

Based on advances made in the late 1980s, the prevailing CBT model for panic disorder with or without agoraphobia (PD/A) emphasizes the concept of an acquired fear of bodily sensations, particularly sensations associated with autonomic arousal (e.g., Barlow, 1988; Clark, 1986). Psychological and biological predispositions enhance the vulnerability to acquire such fear, whereas fear conditioning, avoidant responding, and cognitive biases perpetuate such fear (see Barlow, 1988, 2002; Craske, 1999). It is the perpetuating factors that are targeted in CBT. In the following section, the treatment components that comprise CBT treatment for PD/A are described briefly.

CBT for PD/A

Based on this conceptualization, CBT for PD/A focuses on fears of bodily sensations and corresponding (subtle and overt) avoidance behaviors, and includes psychoeducation, self-monitoring, breathing retraining, cognitive restructuring, and exposure. Our approach is based on the Mastery of Anxiety and Panic protocol (MAP; Craske & Barlow, 2007), which shares similarities with other cognitive approaches to the treatment of panic disorder (e.g., Clark, 1986). Treatment begins with psychoeducation about the nature and symptoms of panic disorder and aims to correct misconceptions about their harmfulness. For example, the adaptive value of autonomic physiological discharge (heightened autonomic arousal, including sweating, shortness of breath, and racing heart) in conditions of real danger is described as a means to educate patients about the nature of fear responding. Following psychoeducation, self-monitoring is introduced as a way to enhance objective self-awareness. Clients are encouraged to record panic attacks as they occur as well as daily anxiety and depression episodes. Cognitive restructuring directly targets misappraisals of bodily sensations. Misappraisals are identified and subjected to logical empiricism through the evaluation of evidence from previous experiences with anxiety and panic. Behavioral experimentation provides additional evidence for the evaluation of misappraisals. Throughout the process of cognitive restructuring, therapists use Socratic questioning to help clients make guided discoveries and develop alternative appraisals that are more evidence-based rather than fear- or schema-based (i.e., based on the client's own references and conceptualizations).

The exposure component of CBT promotes the cognitive goal of providing data that disconfirms misappraisals and the behavioral goal of extinguishing conditioned emotional responses to panic-related bodily sensations (interoceptive exposure) and to situational contexts in which panic is anticipated (in-vivo exposure). Exposure therapy has developed over time, originating with the graduated and counterconditioning through relaxation approach developed by Wolpe (1959). Next, emotional processing theory emphasized habituation of fear responding within an exposure trial as a necessary precursor to habituation across treatment sessions, with the aim of long-term corrective learning (Fo& Kozak, 1986; Fo& McNally, 1996). More recently, we have emphasized optimizing inhibitory learning with an...
approach that is not necessarily dependent on reductions in fear throughout trials of exposure (Craske et al., 2008); we discuss this approach in a subsequent section.

Efficacy of CBT for PD/A

Typically, CBT treatment studies involving most or all of the components described above yield panic-free rates in the range of 70% to 80% and high end-state rates (i.e., within normative ranges of functioning) in the range of 50% to 70% (Barlow, Craske, Cerny, & Klosko, 1989; Clark et al., 1994). Although agoraphobic avoidance is sometimes associated with less positive response (e.g.,Bow et al., 2007), the overall within-group effect size from pre- to posttreatment is very large (e.g., ES=1.53; Norton & Price, 2007). When CBT is compared to wait-list conditions, the between-group effect size remains substantial (e.g., ES=.64; Haby, Donnelly, Corry, & Vos, 2006). However, more research is needed comparing CBT to alternative active treatment conditions.

CBT effects generally are sustained over time and meta-analyses show little change from posttreatment to follow-up (i.e., treatment gains are maintained) (ES=.12; Haby et al., 2006; Norton & Price, 2007). For example, Fava and colleagues (1995) found that only 18.5% of their panic-free clients relapsed over a period 5 to 7 years after exposure-based treatment for agoraphobia. Further, from their review of meta-analyses, Butler and colleagues (2006) found that the relapse rate following CBT is nearly 50% lower than the relapse rate following pharmacotherapy.

Efficacy data from research settings are now being complemented by effectiveness data from real-world, primary care settings. In an open trial, Martinsen and colleagues (1998) reported good results when group CBT for PD/A was led by physicians without formal training in CBT. In our randomized controlled trial in primary care settings with novice therapists (Roy-Byrne et al., 2005), we established that CBT for PD/A combined with expert recommendations for medication regimens was more effective than treatment as usual by primary care physicians. The effects were primarily due to CBT (Craske et al., 2005), and outcomes were positively related to the number of CBT sessions and follow-up booster calls completed (Craske, Roy-Byrne, et al., 2006).

Even though CBT for PD/A is efficacious and effective in real-world settings, not all clients achieve panic-free or high end-state status. For example, one study estimated that over a 2-year follow-up period, 30% of PD/A patients in a university CBT clinic continued to function poorly and only 48% reached high end-state status without seeking additional treatment (Brown & Barlow, 1995). The rosier view of CBT for PD/A that results from cross-sectional relative to longitudinal analysis of treatment outcome likely accounts for these sobering longitudinal findings (see Brown & Barlow, 1995). In a large landmark study (Barlow, Gorman, Shear, & Woods, 2000), only 32% of PD patients assigned to CBT alone demonstrated strong treatment response 12 months after acute treatment, a substantially smaller percentage than had been found in previous, smaller studies. This relatively low response rate may stem from the intent-to-treat nature of the analyses coupled with a high dropout rate; the 1-year follow-up response rate for patients who completed and responded well to treatment was 85% for CBT alone. Nonetheless, the combined findings suggest that CBT for PD/A has room for improvement. Finally, of those who do start treatment, the mean dropout rate from CBT for PD/A is 19%, with a range of 0% to 54% (Haby et al., 2006).

To illustrate the application of CBT to panic disorder and remaining challenges therein, we next present a case study (“John”) based on a client treated by one of the authors. In subsequent sections, we examine what went wrong with the client’s treatment. Based on lessons learned from John’s case and on relevant developments in basic learning and memory research, we present revised aims and methods of CBT for panic disorder.

Case Study: John

John was a 29-year-old male who presented with severe anxiety about panic attacks and agoraphobic avoidance. In particular, he reported anxiety about leaving a 5-mile radius around his house due to concerns that he might experience a panic attack. His fear developed during adolescence, on a family vacation. During the outward-bound air flight, the conditions were very turbulent and John experienced an unexpected panic attack. He believed he was dying. He recalled banging his head against the window as he tried to get rid of the feelings of panic, and he recalled the subsequent 7-day vacation as being tortuous, with repeated panic attacks each day.

Since that time, his panic attacks predominantly involved sensations of shortness of breath, a racing heart, difficulty breathing, and perceptions of unreality. John was concerned that if he panicked, he would die. He recalled doing something to try to get rid of the feelings of panic that in and of itself would be physically harmful, such as banging his head against the wall or forcing himself to vomit, or at the very least draw unwanted attention to himself and be seen as “being crazy.” Consequently, he rarely traveled more than 5 miles away from home and avoided public areas with large numbers of people. When he did, it was with great preparation and only in the company of others. That is, John relied upon the safety of

---

1 Details about the case have been modified to protect the identity of the client.
knowing the details of locations of medical centers, ways to return home quickly, and the presence of other people who could “take over” in the event that he experienced a panic attack. In addition, whenever he noticed uncomfortable sensations, particularly a sense of unreality, he would return home thinking, “I’m about to have a panic attack!” Through such avoidance and safety behaviors, he had managed to prevent panic attacks for the most part. Nonetheless, there had been occasions when his return home had been blocked (such as road closures due to natural disasters) or when the sensations became more intense, resulting in panic attacks. Those occasions served to only strengthen his subsequent avoidance behaviors. Overall, he maintained high levels of apprehension about the possibility of panicking and had suffered a gradual decrease in his mobility over the years. He thought: “If only I could get rid of my anxiety and panic.” He sought treatment from the urging of his family members and his fiancée to get help.

Treatment, which followed a derivation of the MAP protocol (Craske & Barlow, 2007), began with psychoeducation about the physiology of fear/panic, the role of avoidance behavior in maintaining fear and anxiety in the long term, and the catastrophic misinterpretation of panic attack symptoms as likely contributors to the onset of panic and continued anxiety about panic. John was greatly relieved by the educational information, particularly when learning about the harmlessness of the symptoms of panic attacks, which helped to counteract his beliefs that if he would die if he were to have a full-fledged panic attack. He was given a written summary of the educational material, which he read over multiple times; it was always on hand. Next, breathing retraining (slow and diaphragmatic breathing) was taught as a tool for helping John to calm his physiology in preparation for conducting exposure therapy practices. Initially, John felt anxious as he practiced the breathing exercises, because his attention was drawn to sensations of breathing and his heart rate; sensations that had been associated with his panic attacks in the past. He worried, “my fear will get worse.” However, with therapist encouragement to continue the breathing practices, along with direction to focus his attention on counting as he inhaled and exhaled, John’s discomfort declined. Thereafter, John practiced the breathing skills twice daily and felt greatly reassured that the breathing would be a tool for offsetting the chances of spiraling into a full-blown panic attack. He understood the value of relying on breathing skills in place of other people or other safety objects, so that he could learn to cope with his anxiety and panic attacks on his own.

The cognitive restructuring skills addressed John’s misappaisal that he would die from panic by examining the evidence for and against this hypothesis. The therapist encouraged John to consider the number of times that he had panicked and the end result of each one, as well as his medical condition (which was healthy) and other information pertaining to the pathophysiology of panic attacks (i.e., educational information regarding elevations in heart rate in the absence of evidence for cardiac irregularity or abnormality). John quickly understood that his catastrophic appraisals of panic-related sensations, particularly his racing heart and perceptions of unreality, were not based on factual evidence. He was able to generate alternative hypotheses for what was producing those sensations (e.g., anxiety) and what the sensations meant about his medical status (e.g., panic attacks produce a series of physiological changes that are harmless). He practiced the cognitive skills as he imagined being in panic-related situations and experiencing the physiological symptoms. Cognitive restructuring targeted John’s beliefs that panic sensations might lead him to do something that would eventually cause harm or unwanted attention, as well as the belief that sensations of unreality would lead to his going crazy. Through logical discussion with the therapist, John came to realize that the behaviors of knocking his head against the wall or forcing himself to vomit were voluntary behaviors designed to get rid of the sensations. Once he understood that the sensations themselves were not harmful, he felt he would not be driven to engage in such behaviors.

Interoceptive exposure was initiated, and John practiced deliberately inducing panic-related sensations. Some exercises were less relevant than others. For example, running in place was less relevant since John had maintained an active physical exercise schedule over the years, such that a racing heart during exercise were not fear provoking. Deliberate hyperventilation and breathing through a straw did evoke sensations that were uncomfortable, as both induced a sense of unreality. However, with the use of cognitive skills and breathing skills, and the guidance of the therapist, John was able to repeat these exercises a sufficient number of times so that his anxiety decreased to very mild levels. John was very compliant in practicing the repeated hyperventilation and straw breathing exercises in the safety of his home.

In-vivo exposure was initiated at around Session 5, using a graduated exposure format of having John move further and further beyond his 5-mile radius while weaning from his safety behaviors and signals of knowing exact locations of medical facilities and having other people accompany him. The focus of the exposure practices was to employ John’s cognitive restructuring and breathing retraining skills to manage his anxiety and to repeat each in-vivo exposure the number of times necessary until he was no longer afraid of entering the situation. Progress was relatively slow but steady. Upon returning home from each excursion, John would feel proud of his accomplishments but also relieved. On
several occasions, he experienced more anxiety than he had anticipated and expressed concerns to his therapist about whether he was “pushing” himself too much or had “gone too far,” and worried that his “fear would never go away.” However, the therapist successfully encouraged John to continue the particular in-vivo exposure practice the number of times needed until he was able to enter and stay in the situation without any anxiety at all. He shared his success enthusiastically: “I didn’t get afraid at any point in the exposure!” With this very gradual and systematic approach, John was successful in eventually expanding from a 5-mile radius to a 100-mile radius of driving from his home. John coached himself through difficult exposures by reassuring himself: “I’ll be okay because I know my fear will go away by the end.” Throughout this period, his family and fiancée were very supportive, and continuously encouraged the approach that “the more you practice, the easier it will get” and “the more you practice the less anxious you will be.”

The continued expansion of his boundary occurred in a stepwise fashion and without obvious generalization from prior situations to new or unfamiliar situations. That is, John began every new situation with elevated anxiety, although with continued practice his anxiety would subside. At 6 months into the treatment, John felt ready to tackle the highest item on his hierarchy: taking an air flight to another city in another state. He prepared himself for this journey using his cognitive skills, reassuring himself that he could manage the anxiety and that he was not going to die as a result of the panic. He prayed that he would not be overly anxious, and carried his educational information with him as reading material to cope with any anxiety that might emerge on the flight. John experienced a full-fledged panic attack at 30 minutes after takeoff; he experienced high levels of distress for the remainder of the flight. Upon reaching his destination, he remained panic stricken about the return flight, and only with great coaching from his fiancée and multiple phone calls with the therapist, along with sleeping medication, was he able to make the flight back under considerable duress. John felt defeated and retreated to his home environment, unwilling to run the risk of experiencing another panic attack. He felt he had failed and that there was little point in continuing.

Factors Accounting for Treatment Failure

John’s relapse can be explored from multiple perspectives. Due to the exposure focus of John’s treatment and relapse, we viewed John’s case primarily through the lens of learning theory and research. The exposure components of John’s therapy followed emotional processing theory (Foa, Huppert, & Cahill, 2006; Foa & Kozak, 1986; Foa & McNally, 1996). That is, exposure sessions emphasized initial fear arousal followed by immediate fear reduction. If John experienced a reduction in fear from beginning to end of an exposure trial (within-session habituation or WSH), and from exposures conducted in one therapy session to the next (between-session habituation or BSH), the therapist assumed that John had improved—i.e., that new learning about the nonharmful nature of panic sensations and contexts had taken hold. Prior to conducting the exposure on the plane, John reached the point of experiencing little to no fear during interoceptive and in-vivo exposures. He was panic-free and functioning highly. His treatment success appeared complete.

To understand why John relapsed, it is helpful to examine emotional processing theory, the basis of his exposure therapy, from the perspective of basic learning and memory research. In reviewing the evidence for causal links between WSH, BSH, and treatment outcome, we (Craske et al., 2008) found that WSH frequently occurs, but does not predict treatment outcome. For example, if WSH is a reliable index of learning, then performance during exposure should correspond to learning. As reviewed in Bjork and Bjork’s New Theory of Disuse (1992; 2006), however, performance during training is a poor or inconsistent index of learning during training. Translating this and other findings to exposure therapy, a discordance exists between “fear expression during learning” and actual “fear learning” (Craske et al., p. 11). Similarly, fear decline between treatment sessions (BSH) sometimes predicts but is not necessary for improvement to occur; improvement following exposure occurs in the absence of BSH. Furthermore, no good evidence demonstrates that WSH is needed for BSH. In summary, the evidence that BSH and particularly WSH result in long-term corrective learning—the core of emotional processing theory—is weak (Craske et al.). Rather, reliance on short-term fear habituation as the index of treatment success likely set the stage for John’s relapse. The fact that John experienced little to no anxiety during exposures just prior to flying did not predict the strength or generalization of his learning during the flight. To the contrary, when he experienced a panic attack during the flight, he experienced an immediate relapse in panic-related fear and avoidance. The strong emphasis on fear reduction during exposure led John to view the unexpected experience of fear/panic as a problem to be avoided. Hence, he interpreted his experience of a full-blown panic attack in the plane as overwhelming and a sign of failure.

Within learning theory, the panic attack on the plane functioned as a reinstatement (see Bouton, 1995) of

---

2 In particular, evidence suggests that when BSH is assessed physiologically, by heart rate and skin conductance, the lack of BSH does not indicate a lack of improvement (see Craske et al., 2008).
John’s fear of panic. Reinstatement in this case indicates that John was reexposed to the unconditioned stimulus (a panic attack) after going through exposure (or extinction), which reignited his fear of panic and caused him to become more fearful of panic-related situations and bodily sensations. If treatment had facilitated broader generalization of exposure and greater fear tolerance, then reinstatement could have been mitigated.

The emphasis on short-term fear reduction likely reinforced the belief that John experienced upon returning home from each in-vivo excursion. After all, the treatment goal was to minimize anxiety and fear and he experienced the lowest levels of anxiety and fear at home. Such relief, in turn, reinforced his perceived danger of being away from home and, in particular, of experiencing panic attacks away from home.

In addition, John only practiced interoceptive exposures in the safety of his home. He did not vary the environment in which he conducted them or combine interoceptive exposures with in-vivo exposures (conducted outside of his home). If John had conducted interoceptive exposures in feared environments, his learning would have generalized more broadly. Instead, his tolerance for experiencing the bodily sensations of panic did not generalize to real-life situations. Relatedly, the slow pace of treatment may have contributed to the treatment’s failure by implicitly communicating a need to establish safety and comfort. During exposures—for example, the plane exposure—it would have been more effective to push the client to experience all of the bodily sensations, thoughts, and feelings that he could in the plane. The therapy failed in part because the client was not encouraged to confront the feared sensations to the maximal extent that he could.

Cognitive restructuring, breathing retraining, and psychoeducation for John erred in a similar manner. John’s core fears were fear of dying and fear of going crazy. The exposures were designed around the situations in which these fears were perceived as most likely to come true, and in this regard, the exposures were matched to the patient’s core fears. Based on John’s core fears, cognitive restructuring emphasized the likelihood of dying or going crazy from a panic attack. Emphasizing the likelihood of surviving a panic attack may have been more effective. Furthermore, John tended to use cognitive restructuring for immediate and short-term relief of fear and anxiety, rather than as a path to normalize and better tolerate fear and anxiety. Similarly, John used psychoeducation to reassure himself that panic was not harmful in a manner that reinforced immediate relief of distress rather than the belief that panic was normal and tolerable. In carrying the psychoeducation materials with him during exposures, they became a safety signal that interfered with his learning. Breathing retraining also developed into a safety behavior, reassuring John that he could control and reduce the symptoms of panic at will, rather than develop toleration for symptoms. In summary, the strong emphasis on immediate and short-term fear reduction and the controllability of panic symptoms may have contributed to the treatment’s failure to result in long-term learning. Care should be taken with coping-oriented CBT strategies (e.g., cognitive restructuring, psychoeducation, and breathing retraining) to ensure that they do not become safety cues or behaviors. Indeed, breathing retraining may be particularly likely to be used by clients as a safety behavior. If this is a risk, breathing retraining can be excluded or at least modified (Craske & Barlow, 2007).

Reformulating the Pathway to Long-Term Success

The failure of John’s treatment to produce long-term, broadly generalized, panic-related learning stemmed in part from a reliance on emotional processing theory to guide exposure therapy. This reliance failed to maximize inhibitory learning or to teach John how to tolerate anxiety and fear. Basic learning research suggests that inhibitory learning lies at the core of extinction (e.g., Bouton, 1993), at least for acquired fears that cannot be reversed immediately following acquisition—as is the case in panic disorder and other anxiety disorders. In inhibitory learning, the original threat-based association between the conditioned and unconditioned stimulus remains intact while alternative, non-threat associations between the conditioned and unconditioned stimulus are formed. The goal of an inhibitory learning approach to the treatment of PD/A and other anxiety disorders (Craske et al., 2008) is to maximize the likelihood that non-threat associations (e.g., shifts in heart rate=normal and safe) inhibit access and retrieval of threat associations (e.g., shifts in heart rate=a dangerous panic attack is imminent). The degree to which threat-based versus non-threat associations are expressed at retest depends on the strength of inhibitory learning across time and context, rather than, as purported by emotional processing theory, fear expression during exposure (Craske et al.). Therefore, the most important test of learning occurs at posttreatment and follow-up retest, when the strength of inhibitory learning determines which among competing associations is expressed. The discrepancy in John’s fear levels at the end of treatment (prior to flying) versus at retest (the flight) can be explained by insufficient strength of inhibitory learning.

In addition to the importance of inhibitory learning, recent developments emphasize the role of experiential avoidance in the etiology and maintenance of anxiety disorders (Forsyth, Eifert, & Barrios, 2006) and other forms of psychopathology (Hayes et al., 2004; Hayes, Strosahl, & Wilson, 1999). Experiential avoidance involves the avoidance of uncomfortable internal experiences...
such as fear-related thoughts, feelings, and physical sensations. Forsyth and colleagues (2006) argue that anxiety disorders are caused by attempts to avoid the internal experience of anxiety and fear rather than by the presence of anxiety and fear itself. If this is true, the treatment of anxiety disorders should aim to enhance fear and anxiety toleration rather than to eliminate fear and anxiety altogether. The goal of increasing fear toleration complements the goal of increasing inhibitory learning. To the degree that fear is tolerated, inhibitory associations (i.e., fear is not dangerous) can be maximally acquired.

In summary, basic learning research and theory indicate that fear toleration and performance during retest provide more reliable indices of learning than immediate and short-term fear reduction (Craske et al., 2008). The shift from fear habituation to fear toleration and long-term performance as indices of treatment success requires reframing the aims and methods of CBT. To follow, we discuss the practical implications of this reframing, with the aim of maximizing the effectiveness of exposure and minimizing treatment failure within CBT treatment for panic disorder. Realizing this aim involves two primary steps: generating non-threat associations, and enhancing the accessibility and retrievability of non-threat associations.

**Reframing CBT for Panic Disorder**

**Generating Non-Threat Associations**

During John’s treatment, the therapist attempted to generate non-threat associations to conditioned panic cues through psychoeducation, cognitive restructuring, and exposures aimed at immediate and short-term fear reduction. Generating non-threat associations for conditioned stimuli is the first step in inhibitory learning, and thus, the first step towards extinction (in PD/A and otherwise). Producing more durable inhibitory learning requires shifting to more widely generalizable methods for generating non-threat associations. To maximize the strength of non-threat associations and minimize the risk of relapse, CBT therapists can mismatch expectancies, weaken safety signals and behaviors, integrate multiple excitors, and use cognitive enhancers (Craske et al., 2008). Current CBT for PD/A protocols use several of these techniques; we sharpen their focus and place them in the context of basic science on learning and memory.

One method for generating non-threat associations is mismatching expectancies—in other words, violating the expectation that the conditioned stimulus predicts the unconditioned stimulus (see Craske et al., 2008). Although translating from the basic science to clinical application of learning theory can be challenging, the (apex of the) panic attack can be conceptualized as the unconditioned stimulus (US) and the accompanying bodily sensations and the external agoraphobic situations can be conceptualized as the conditional stimuli (CS) (see Bouton, Mineka, & Barlow, 2001). Although most exposures focus on the conditioned stimuli, there may also be value in conducting exposures directly to the US (i.e. to panic attacks themselves). The aim of exposure to the US would be to eventually devalue the significance of panic, thereby initiating habituation to the US. In summary, the translation from basic science to clinical application is complex, but there is value to doing exposure to the US as well as the CS.

To illustrate expectancy violation, when the presence of the CS (e.g., being more than 5 miles from home) does not result in a feared outcome (e.g., panic-induced heart attack), an alternative, nonthreatening meaning for the conditioned stimuli (CS) (see Bouton, Mineka, & Barlow, 2001). Although most exposures focus on the conditioned stimuli, there may also be value in conducting exposures directly to the US (i.e. to panic attacks themselves). The aim of exposure to the US would be to eventually devalue the significance of panic, thereby initiating habituation to the US. In summary, the translation from basic science to clinical application is complex, but there is value to doing exposure to the US as well as the CS.

In summary, basic learning research and theory indicate that fear toleration and performance during retest provide more reliable indices of learning than immediate and short-term fear reduction (Craske et al., 2008). The shift from fear habituation to fear toleration and long-term performance as indices of treatment success requires reframing the aims and methods of CBT. To follow, we discuss the practical implications of this reframing, with the aim of maximizing the effectiveness of exposure and minimizing treatment failure within CBT treatment for panic disorder. Realizing this aim involves two primary steps: generating non-threat associations, and enhancing the accessibility and retrievability of non-threat associations.

**Reframing CBT for Panic Disorder**

**Generating Non-Threat Associations**

During John’s treatment, the therapist attempted to generate non-threat associations to conditioned panic cues through psychoeducation, cognitive restructuring, and exposures aimed at immediate and short-term fear reduction. Generating non-threat associations for conditioned stimuli is the first step in inhibitory learning, and thus, the first step towards extinction (in PD/A and otherwise). Producing more durable inhibitory learning requires shifting to more widely generalizable methods for generating non-threat associations. To maximize the strength of non-threat associations and minimize the risk of relapse, CBT therapists can mismatch expectancies, weaken safety signals and behaviors, integrate multiple excitors, and use cognitive enhancers (Craske et al., 2008). Current CBT for PD/A protocols use several of these techniques; we sharpen their focus and place them in the context of basic science on learning and memory.

One method for generating non-threat associations is mismatching expectancies—in other words, violating the expectation that the conditioned stimulus predicts the unconditioned stimulus (see Craske et al., 2008). Although translating from the basic science to clinical application of learning theory can be challenging, the (apex of the) panic attack can be conceptualized as the unconditioned stimulus (US) and the accompanying bodily sensations and the external agoraphobic situations can be conceptualized as the conditional stimuli (CS) (see Bouton, Mineka, & Barlow, 2001). Although most exposures focus on the conditioned stimuli, there may also be value in conducting exposures directly to the US (i.e. to panic attacks themselves). The aim of exposure to the US would be to eventually devalue the significance of panic, thereby initiating habituation to the US. In summary, the translation from basic science to clinical application is complex, but there is value to doing exposure to the US as well as the CS.

To illustrate expectancy violation, when the presence of the CS (e.g., being more than 5 miles from home) does not result in a feared outcome (e.g., panic-induced heart attack), an alternative, nonthreatening meaning for the conditioned stimuli (CS) (see Bouton, Mineka, & Barlow, 2001). Although most exposures focus on the conditioned stimuli, there may also be value in conducting exposures directly to the US (i.e. to panic attacks themselves). The aim of exposure to the US would be to eventually devalue the significance of panic, thereby initiating habituation to the US. In summary, the translation from basic science to clinical application is complex, but there is value to doing exposure to the US as well as the CS.
the safe people, objects, and places sought during safety behaviors are known as safety signals. An extensive animal literature (see Hermans, Craske, Mineka, & Lovibond, 2006) and a more methodologically limited human literature (Powers, Smits, & Telch, 2004; Sloan & Telch, 2002) shows that the use or presence of safety signals interferes with extinction. Though the mechanisms of interference are debated, one possibility is that the presence of safety signals encourages clients to attribute the lack of aversive outcomes to the safety signals rather than to develop new, non-threat associations between the conditioned and unconditioned stimulus. Instructing clients to refrain from safety behaviors has been shown to improve exposure outcomes in PD/A (Salkovskis et al., 1999) and provides a simple method for therapists to discourage safety behaviors during exposure. The presence of the therapist often serves as a safety signal, highlighting the importance of also having clients perform exposures on their own, in the absence of the therapist. Encouraging John to travel more than 5 miles from home without checking medical center locations, quick return home routes, or having a “safe” person present, are methods of eliminating safety signals and behaviors during exposure. Although these methods were used in John’s treatment, their effectiveness likely was weakened by the emphasis on immediate and short-term fear reduction in the rest of therapy.

Another method for enhancing non-threat associations derives from the combined use of multiple excitatory conditioners during exposure (see Craske et al., 2008). According to the Rescorla-Wagner model of extinction (1972), if a predicted aversive outcome does not occur, then the presence of several conditioned predictors relative to one conditioned predictor results in greater inhibitory learning. Based on this principal, Rescorla (2006) termed “deepened extinction,” in which two or more individual conditional stimuli are extinguished separately before combining them for further extinction trials. In nonprimates, deepened extinction resulted in lower spontaneous recovery, less reinstatement, and slower reacquisition of the conditioned fear response than the noncombined approach. In a clinical context, conducting exposures to feared stimuli individually and then combining them represents an application of the deepened conditioning model. For example, John could be exposed separately to interoceptive panic sensations and to traveling more than 5 blocks from home and then combine them, inducing interoceptive sensations of panic and traveling more than 5 blocks from home at the same time.

Another potential approach for enhancing the generation of non-threat associations involves cognitive inhibitory regulation. Basic science research (e.g., Hariri, Bookheimer, & Mazziotta, 2000; Hariri, Mattay, Tessitore, Weinberger, & Fera, 2003; Lieberman et al., 2007) has shown that areas of the brain associated with verbal processing play a role in mitigating amygdala activity. This finding raises the possibility that cognitive strategies, when used appropriately, may be effective for moderating anxiety during exposure. However, no studies to date have evaluated the degree to which cognitive skills are acquired, the degree to which they are applied when confronted with feared situations or sensations, or the effect of such acquisition and application on exposure therapy. That is, ongoing measurement of cognitive skills acquisition and/or application is absent from the extant literature. The types of tasks or stimuli that best activate the prefrontal cortex and/or enhance inhibitory learning during exposure also require further research. Care must be taken, however, to ensure that verbal processing tasks during exposure do not result in distraction or develop into a safety behavior.

### Enhancing the Accessibility and Retrievability of Non-Threat Associations

Once non-threat associations to panic cues are generated and strengthened, the associations must be readily retrievable. Contextual and temporal factors determine whether the non-threat associations will be recalled when panic cues are reencountered. As John’s case illustrates, the acquisition of non-threat associations towards panic cues does not guarantee that these associations will be retrieved at retest in a novel context. Methods for enhancing the retrieval of non-threat associations at reencounter/retest include maximizing variability during exposure, scheduling consolidation and booster sessions, and aiding in context retrieval (Craske et al., 2008). Each of these methods is applicable to CBT for PD/A.

According to Bjork and Bjork’s New Theory of Disuse (1992; 2006), variation during learning makes short-term learning more difficult but increases long-term retention. Learning in variable contexts generates a greater number of retrieval cues, thereby increasing the likelihood of accessing a retrieval cue at retest. Two studies in our laboratory (Lang & Craske, 2000; Rowe & Craske, 1998) provide initial evidence that conducting exposures according to a variable or random schedule results in less fear at retest than conducting exposures according to a constant or stepped schedule, at least for specific phobia patients. This approach can be translated to the treatment of John’s panic disorder. For example, rather than conduct in-vivo exposures in a stepped method according to a graded fear hierarchy, John and the therapist could generate a fear hierarchy but conduct exposures according to a random schedule. They could begin with an
exposure from the middle of the fear hierarchy (travel 10 miles from home alone), then conduct one from the upper end of the fear hierarchy (ride a bus to a city 30 miles away alone), and then one from the lower end (travel 6 miles from home alone), and so forth, in order to vary the amount of fear generated from one exposure to the next. In contrast to John’s original CBT treatment, which involved repeating interoceptive exposures again and again until his anxiety neared zero, the interoceptive exposure exercises could be varied as well. In some exposures, John could be asked to stare for long periods of time at a single object to invoke feelings of unreality, whereas in others, he would be asked to hyperventilate. Of course, the issue of patient acceptability must be considered. The rationale for conducting difficult and randomly ordered exposures could be framed as an effort to maximize long-term learning by varying the fear levels, context, and content of exposure.

According to Bjork’s work on “expanding retrieval practice” (e.g., Bjork, 1988; Landauer & Bjork, 1978), spacing learning trials at increasingly larger intervals results in better long-term retention than massed or regularly spaced learning trials, at least for nonemotional material. Bjork theorizes that spaced learning intervals allow for between-session forgetting and repeated opportunities for relearning, thus strengthening long-term memory retention and ease of retrieval. The evidence in support of spaced versus massed exposure in animals and humans is mixed, perhaps due to methodological inconsistencies and an absence of theoretical grounding (see Craske et al., 2008). Nonetheless, the evidence for expanding retrieval practice across numerous learning and memory studies translates into scheduling CBT consolidation and booster sessions at increasingly larger intervals. Once John finishes intensive treatment, the therapist could schedule booster sessions once every 2 weeks, then once per month, then once per 2 months, and so forth, in order to consolidate long-term learning.

A final method for enhancing the accessibility and retrievability of non-threat associations focuses on offsetting context renewal effects. Original fear learning is not erased during extinction; reencountering the CS (e.g., shifts in heart rate) in a context that is different than the extinction context (e.g., the flight) may result in reinstatement of the original fear (e.g., fear of heart attack; Mineka, Mystkowski, Hladek, & Rodriguez, 1999; Mystkowski, Craske, & Echiverri, 2002). One implication of this finding is to conduct exposures in as many different contexts as possible. Although few studies have tested this idea in humans, one study (Vansteenwegen et al., 2007) randomized spider phobics to view videos of a spider located in different rooms versus a single room of a house. Exposure to viewing the spider in different locations resulted in lower skin conductance at retest (e.g., viewing a spider in a novel location) than the single location exposure. For the treatment of PD/A, exposures could be conducted in as many different contexts as possible. A second treatment implication of context renewal is to help clients “bridge” the original extinction context and the novel retest context (Bouton, Woods, Moody, Sumsay, & Garcia-Gutierrez, 2006) via mental rehearsal of the original extinction context. We (Mystkowski, Craske, Echiverri, & Labus, 2006) treated spider phobics and then retested them in a different context than the treatment context. Prior to retest, half of the participants were instructed to mentally rehearse the treatment context and what they learned during treatment, whereas the other half were instructed to recall a neutral scenario. At retest in a different context, participants who rehearsed the original treatment context showed less return of fear than those who did not rehearse. Translating this method to CBT for panic disorder involves having John mentally rehearse the treatment context and what he learned in therapy prior to entering novel panic-related contexts such as flying. Finally, bridging the gap between treatment and real-world contexts could be enhanced by conducting exposures in the real-world contexts in which panic cues are most likely to be present (see Bouton et al., 2006). Emphasizing in-vivo exposures in real-world contexts over imaginal exposures or exposures conducting solely in the therapy room realizes this aim.

Psychoeducation

In translating this shift in treatment aims to psychoeducation for PD/A, the CBT therapist would move away from an immediate fear reduction agenda and instead emphasize the value of fear tolerance for enhancing long-term learning. John would be asked to learn to experience fear in order to learn how not to be afraid of fear. Rather than framing panic attacks as a sign that the treatment approach is not working, panic attacks would be framed as normal and desirable opportunities to learn greater fear tolerance and enhance long-term extinction by practicing the retrieval of non-threat associations. Panic attacks also would be viewed as opportunities to learn how not to invoke avoidance behaviors such as safety behaviors to cope with the sensations of panic, thus enhancing learning and extinction.

Cognitive Restructuring

Currently, cognitive restructuring in CBT for PD/A is used to demonstrate to the patient that a feared event is unlikely to occur (e.g., a panic attack leading to heart attack). This approach may overemphasize short-term fear relief. The above-outlined suggestions for enhancing exposure therapy provide a template for enhancing
cognitive restructuring. Cognitive restructuring could emphasize the likelihood of surviving feared events (rather than the likelihood of avoiding feared events), exposure to distressing and avoided thoughts, assessment of expectancy violations, and engagement in effortful thinking during exposure that engages the prefrontal cortex.

**Conclusion**

From the perspective of basic learning and memory research, we interpreted John’s treatment failure following CBT for PD/A. This perspective guided suggestions for improving psychoeducation, cognitive restructuring, and, in particular, exposure therapy for panic disorder. Although founded on basic learning and memory research, many of these treatment developments await direct empirical testing. Several such investigations are currently underway; we look forward to continuing to refine panic disorder treatment based on future research outcomes.

**References**


Address correspondence to Joanna J. Arch, Ph.D., Department of Psychology and Neuroscience, 345 UCB Muenzinger, Boulder, CO 80309-0345; e-mail: Joanna.Arch@Colorado.edu.

Received: August 4, 2009
Accepted: May 14, 2010
Available online 18 January 2011