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Bridging the gap: Lessons we have learnt from the merging of psychology and psychiatry for the optimisation of treatments for emotional disorders

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ABSTRACT

In recent years the gap between psychological and psychiatric research and practice has lessened. In turn, greater attention has been paid toward how psychological and pharmacological treatments interact. Unfortunately, the majority of research has indicated no additive effect of anxiolytics and antidepressants when combined with psychological treatments, and in many cases pharmacological treatments attenuate the effectiveness of psychological treatments. However, as psychology and psychiatry have come closer together, research has started to investigate the neural and molecular mechanisms underlying psychological treatments. Such research has utilised preclinical models of psychological treatments, such as fear extinction, in both rodents and humans to determine multiple neural and molecular changes that may be responsible for the long-term cognitive and behavioural changes that psychological treatments induce. Currently, researchers are attempting to identify pharmacological agents that directly augment these neural/molecular changes, and which may be more effective adjuncts to psychological treatments than traditional anxiolytics and antidepressants. In this review we describe the research that has led to this new wave of thinking about combined psychological/pharmacological treatments. We also argue that an increased emphasis on identifying individual difference factors that predict the effectiveness of pharmacological adjuncts is critical in facilitating the translation of this preclinical research into clinical practice.

Psychology and Psychiatry have traditionally operated in parallel, with too little communication between the disciplines. In particular, the two disciplines have vastly different approaches to the treatment of mental illness, with Psychiatrists mainly utilising pharmacological/physiological interventions and Psychologists mainly utilising skills-based interventions that directly alter cognitions and behaviours. In addition, researchers within these disciplines have taken a "silo" approach, which has led to the development of very different theoretical viewpoints on the critical mechanisms underlying mental illness, with little attempt to reconcile the two. Specifically, Psychiatrists have typically emphasised the importance of neurotransmitter and neural circuitry dysfunction whereas Psychologists have focused on the role of maladaptive cognitive biases and behavioural patterns. In more recent years, however, the gap between Psychology and Psychiatry, both in terms of research and clinical practice, has started to be bridged. This has in part been brought about by a much more refined understanding of the neural and molecular basis of mental illness that has allowed specific cognitive and behavioural deficits to be mapped onto specific aberrations in neural functioning. This has also been fostered by an increased recognition that psychological treatments may directly or indirectly attenuate the molecular/neural abnormalities thought to underlie mental illness.

One consequence of the increased communication between the disciplines is that greater attention has been paid to how psychological and pharmacological treatments interact. From this, we have gained two broad insights. The first is that pharmacotherapy does not always complement psychological treatment (i.e., many studies show no additive effects) and in the worst of cases, pharmacotherapy may attenuate the efficacy of psychological treatment. The second insight is that if we can increase our understanding of how psychological treatments work at the neural and molecular levels, then this may pave the way for the development of novel pharmacological adjuncts that directly augment these neural/molecular processes, thus creating a more potent treatment for mental illness.

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In this review we first outline the transdiagnostic components of the most widely used and empirically validated psychological treatment for emotional (i.e., mood and anxiety) disorders, cognitive behavioural therapy (CBT). We then describe research from animal models and human neuroimaging studies that has identified several molecular and neural targets that likely underpin the success of CBT. Next, we describe the outcomes of research examining the efficacy of combining current pharmacotherapies with CBT, and we account for these outcomes by considering how the neural/molecular targets of pharmacotherapy complement/interfere with the putative neural/molecular underpinnings of CBT. Finally, we describe a burgeoning field of research that is attempting to bridge the gap between pharmacological and psychological approaches to treatment. This field is capitalising on our increased understanding of the neural/molecular substrates of psychological treatments, and attempting to identify potential pharmacological adjuncts that may enhance these substrates. Moreover, beyond merely developing adjuncts to enhance CBT, emerging research in this field is also attempting to identify various individual difference factors that may increase or decrease the effectiveness of such adjuncts. This type of research has the potential to increase our ability to predict treatment responsiveness, which would allow health professionals to tailor treatments at the outset to match the idiosyncrasies of the individual, thus increasing the number of people who benefit from treatment.

Cognitive behavioural therapy for emotional disorders

CBT rests on the assumption that most symptoms in emotional disorders are experienced by most people from time to time, but that, due to maladaptive response tendencies, some people become "stuck" in a cycle in which they experience these symptoms with a greater severity, intensity, and/or frequency than people in the general population (Beck, 1976). Consistent with this assumption, CBT does not attempt to address the cause of distressing symptoms; or indeed, the symptoms themselves. Rather, CBT purports to target the hypothesised cognitive and behavioural factors that maintain distressing symptoms (i.e., those factors that prevent symptoms from spontaneously remitting, as occurs in the general population; Clark, 2004). These factors include maladaptive cognitive appraisals (e.g., overestimation of the probability and cost of catastrophic outcomes in anxiety disorders, Otto, Smits, & Reese, 2004; or negative views about the self, the world, and the future in depression, Beck, 1976), unhelpful behavioural responses to strong emotions (e.g., withdrawal in depression, Jacobson, Martell, & Dimidjian, 2001), and emotional/experiential avoidance (e.g., avoidance of feared stimuli/situations in anxiety, Otto et al., 2004). CBT stands in contrast to the psychiatric approach to treatment of psychopathology with latter placing much more emphasis on direct modulation of the symptoms themselves, usually via pharmacological intervention.

CBT is predominantly skills focused; patients are taught new ways of thinking, responding, and problem solving. Initially patients rely heavily on guidance from the therapist, but as cognitive flexibility improves, patients become more independent, ultimately becoming their own "therapist". As such, CBT depends on patients being able to integrate and consolidate new information-in other words, to learn and retain new memories (Otto et al., 2004). This may account for CBT's long-lasting effects, as well as the finding that recipients of CBT often exhibit continued improvement even once treatment has officially terminated (e.g., Haug et al., 2003; Marks et al., 1993).

The initial development of CBT protocols was directed toward discrete disorders. This resulted in a plethora of manualised treatments, each purporting to target the individual features of a specific diagnosis. In the last decade, however, there has been a shift toward a transdiagnostic approach to CBT, spurred by epidemiological data highlighting strong comorbidity between different diagnoses, the finding that CBT aimed at one diagnosis often leads to symptom reduction associated with comorbid diagnoses, and the growing contention that there may be common mechanisms of dysfunction across different diagnoses (Barlow, Allen, & Choate, 2004). Currently, many researchers are attempting to extract the underlying principles of CBT that may be effective when applied transdiagnostically. Indeed, such principles may represent the critical components underlying the efficacy of earlier CBT protocols aimed at specific disorders. The most influential transdiagnostic CBT protocol has been Barlow's "Unified Protocol" (UP) for emotional disorders (Ellard, Fairholme, Boisseau, Farchione, & Barlow, 2010). UP contains a number of core modules designed to target the main factors thought to underlie and maintain emotional disorders, described above. For example, maladaptive cognitive appraisals are targeted by cognitive reappraisal training (i.e., learning to re-evaluate a situation in a more positive, or at least neutral, manner so that the emotional consequence is altered). Maladaptive emotion-driven behaviours are targeted by modules designed to train more adaptive behavioural responses to strong emotions (e.g., engagement in activities when feeling depressed), and emotional/experiential avoidance is targeted by exposure therapy modules that encourage gradual engagement with previously avoided emotions, situations, and physical sensations.

A thorough critique of the advantages versus disadvantages of transdiagnostic CBT is beyond the scope of this review; we describe UP here merely because it highlights the common components of CBT that have been empirically demonstrated to be effective in the treatment of emotional disorders. More pertinent to the purposes of this review is that transdiagnostic approaches to CBT may aid research at the preclinical level. This is because treatments that are composed of distilled common principles (and that are designed to target common underlying mechanisms of dysfunction, rather than specific symptoms characteristic of discrete disorders) are more amenable to being modelled in laboratory settings. Preclinical research in both non-human animals and healthy humans has the capacity to increase our understanding of the neural and molecular substrates of mental illness, the neural and molecular substrates underlying effective treatment, and the individual difference factors that predict treatment response (Graham, Langton, & Richardson, 2011; Holmes & Singewald, 2013). Such understanding will allow us to further refine our treatment of emotional disorders by developing pharmacological adjuncts to augment the neural/molecular processes underlying CBT, and to make more informed decisions about which treatments and adjuncts will work best for particular individuals. The methods by which emotional disorders and their treatment have been modelled preclinically, and the utility of this approach, are reviewed next.

Preclinical models of emotional disorders and their treatment

Animal models of fear learning and fear inhibition, as well as more recent neuroimaging studies examining the same processes in humans, have been instrumental in our understanding of the neural and molecular basis of CBT's long-term effectiveness. In both rodent and human studies, fear learning occurs when a subject is given multiple pairings of an initially neutral stimulus such as a light (i.e., the conditioned stimulus; CS) followed by an aversive outcome such as a loud noise or shock (i.e., the unconditioned stimulus; US). Following such pairings the subject eventually learns that the CS predicts the US and begins to show a variety of conditioned fear behaviours to that CS (e.g., increased skin conductance response (SCR) in humans and freezing in rodents). After fear

learning occurs, levels of fear to the CS can be inhibited via extinction training. During a typical fear extinction procedure the subject receives multiple presentations of the CS alone, without the reinforcing negative outcome. This training results in a context-dependent fear extinction (i.e., safety) memory which competes with the original fear memory for expression (i.e., the subject learns that the CS no longer predicts the US *in the extinction context*, and their fear responding to the CS is lessened in that context; Todd, Verbic, & Bouton, 2014).

While fear conditioning may not accurately model the cause of emotional disorders (except for those with PTSD, and in some cases, those with phobias, most anxious individuals do not report a specific conditioning event; Mineka & Zinbarg, 2006), it does produce behaviours which are consistent with the clinical presentation of those disorders (i.e., explicit fear and avoidance of cues believed to be predictive of danger, and withdrawal). Further, the process of extinguishing fear to those cues is widely believed to be an essential 'active ingredient' of CBT. Specifically, avoidance is thought to be a major maintaining factor in emotional disorders (e.g., avoidance of feared stimuli/situations/physiological symptoms in anxiety disorders, and avoidance of particular emotions in depression). As noted above, a major component of transdiagnostic CBT involves gradually exposing individuals to previously avoided stimuli, situations, physiological symptoms, and emotions to induce extinction learning (exposure therapy). Hence, by studying the neural and molecular basis of emotional learning and, more importantly, extinction, we are likely to gain a deeper understanding of the mechanisms underlying CBT's long-term effects.

Another advantage of fear extinction is that, while it is often considered a "bottom up", or automatic form of emotion regulation, it may actually activate a similar neural circuitry to that activated by "top-down", controlled strategies of emotion regulation utilised in transdiagnostic CBT, such as cognitive reappraisal. fMRI studies in both healthy and clinical populations have demonstrated that successful fear extinction and cognitive reappraisal both depend on prefrontal cortex inhibition of amygdala activity (Delgado, Nearing, LeDoux, & Phelps, 2008; Hermann et al., 2009; see below for a more detailed description of this circuitry). Thus, laboratory studies of fear extinction in rodents and humans alike may provide insight into the neural and molecular substrates of multiple components of transdiagnostic CBT, not just those involving exposure therapy but also those involving controlled cognitive modes of emotion regulation.

The neurobiology of fear learning and extinction

In the last two decades our understanding of the neurobiology of fear learning and extinction has flourished. Human neuroimaging studies and rodent studies using anatomical lesions, pharmacological inactivation, drug antagonists, and electrophysiological recordings have converged to map out a complex neural circuit which supports fear learning and fear inhibition. Specifically, in both rats and humans the lateral amygdala is considered to be involved in the formation and storage of conditioned fear associations (Davis, 1992; LeDoux, 2000; Phelps & LeDoux, 2005), while the central nucleus of the amygdala (CeA) is thought to represent the fear output centre.

While the amygdala has long been considered to be the acquisition and storage site of conditioned fear associations, more recent evidence suggests that extra-amygdala regions control the expression of amygdala-dependent fear memories. Studies in rodents have demonstrated that activity in the prelimbic (PL) region of the mPFC regulates amygdala activity and fear learning. Specifically, microstimulation of the PL enhanced conditioned fear responses and impaired extinction (Vidal-Gonzalez, Vidal-Gonzalez, Rauch, & Quirk, 2006), whereas inactivation of the PL had the opposite effect on conditioned fear behaviours (Corcoran & Quirk, 2007). Also, electrophysiological recordings demonstrated that activity in PL neurons increased during fear conditioning and decreased during fear extinction, mirroring freezing behaviour in those animals (Burgos-Robles, Vidal-Gonzalez, & Quirk, 2009). These data suggest that the PL regulates fear learning by increasing amygdala activity. Findings from preclinical human studies have largely been consistent those of rodent studies. The human homologue of the PL, the dorsal anterior cingulate cortex (dACC), is activated along with the amygdala during fear conditioning (Milad, Quirk, et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004) and thickness of the dACC is positively associated with conditioned SCRs (Milad, Quirk, et al., 2007).

In contrast to the role of the PL/dACC in fear conditioning, another division of the mPFC – the infralimbic region (IL) – appears to be important for inhibiting amygdala activity during extinction via its connections with the hippocampus. Specifically, the current dominant neural model of extinction suggests that the hippocampus provides contextual information to the IL which integrates this information with data about the CS coming from the amygdala. When the extinguished stimulus is presented in contexts which match extinction training the hippocampus activates the IL, resulting in feed-forward inhibition of amygdala output, resulting in suppression of the conditioned fear response. In contrast, when the context is different from that during extinction training the hippocampus does not activate the IL, amygdala activity is not inhibited, and a conditioned fear response emerges (Quirk & Mueller, 2008).

While the dominant model of extinction was developed from rodent data, humans appear to use remarkably similar circuitry to inhibit fear responses both during extinction learning and when recalling the extinction memory. For example, preclinical fMRI studies in humans have shown that activity in the vmPFC increases during extinction learning and at extinction recall (Gottfried & Dolan, 2004; Milad, Wright, et al., 2007), and level of extinction recall has been shown to be positively associated with vmPFC thickness (Milad et al., 2005). Recent fMRI studies have demonstrated a causal role for vmPFC control of amygdala activity in human populations (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2014). In that study, relative to non-lesion participants, neurosurgical patients with focal bilateral vmPFC damage exhibited potentiated amygdala activity, both at rest and in response to aversive images. Finally, the role of the hippocampus in contextually-gating extinction memories via the vmPFC is also supported in humans (Kalisch et al., 2006). In that study, individuals tested in the same context as extinction exhibited enhanced and positively correlated vmPFC and hippocampal activity and retrieved the extinction memory. However, when individuals were tested for extinction recall in the conditioning context the fear memory was retrieved and activity in the vmPFC and hippocampus was not positively correlated (also see Lonsdorf, Haaker, & Kalisch, 2014). Together, the evidence reviewed above is consistent with the idea that a unique neural circuit involving the amygdala, vmPFC, and hippocampus supports extinction learning in rodents, and that this neural circuitry has been conserved across evolution to support similar basic learning processes in humans. See Fig. 1 for a schematic depicting the way the described neural circuitry maps onto the behavioural expression of fear.

Understanding the molecular mechanisms underlying extinction-related plasticity within the fear circuit may help to uncover targets which could be pharmacologically manipulated to enhance extinction learning or retention. While an exhaustive review of the molecular pathways involved in extinction learning is beyond the scope of this paper (readers are referred to the

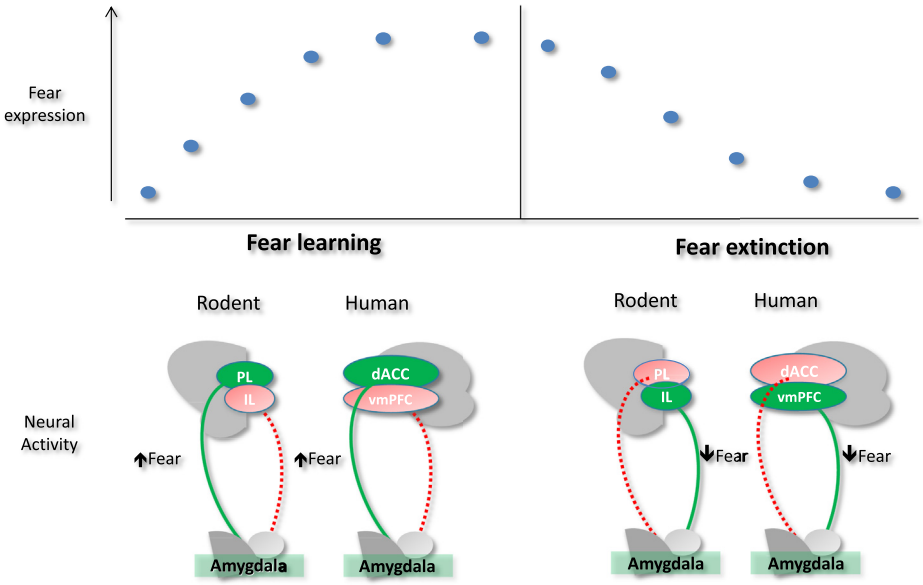

Fig. 1. The behavioural expression of fear, and the neural activity in the prefrontal cortex and amygdala, during fear acquisition and extinction training.

following excellent reviews on the topic: Myers & Davis, 2007; Quirk & Mueller, 2008), it is of benefit to highlight that the molecular signals which appear to be involved in extinction across species are also those known to be important in the consolidation of new memories. For instance, successful consolidation of extinction memories depends on a cascade of molecular events beginning with N-methyl-D-aspartate (NMDA) receptor activation (Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2007; Santini, Muller, & Quirk, 2001). Indeed, pharmacological manipulations of NMDA receptor activity, via the drug D-cycloserine (DCS), have shown promise in enhancing extinction learning and retention in rodents and humans (e.g., Ledgerwood, Richardson, & Cranney, 2003; Norberg, Krystal, & Tolin, 2008; Ressler et al., 2004; Walker, Ressler, Lu, & Davis, 2002).

Extinction learning in emotional disorders

Not only is the neural circuitry underlying extinction well-preserved across species, but abnormalities in the extinction circuitry appear to occur in individuals with mental health problems, suggesting that deficits in extinction circuitry may be the fundamental neural pathology in these illnesses. For example, when viewing fearful faces combat-exposed veterans with PTSD exhibit enhanced amygdala activity and decreased vmPFC activity relative to combat-exposed veterans without PTSD (Rauch et al., 2000; Shin et al., 2005). Also, symptom severity in PTSD patients during recall of trauma-related events was positively correlated with cerebral blood flow (CBF) in the amygdala and negatively correlated with CBF in the medial central gyrus (a region of the mPFC; Shin et al., 2004). Dysfunctional amygdala-prefrontal circuitry also appears to be a feature in individuals with spider phobia. Spider-phobic individuals exhibited increased activity in the amygdala, insula, anterior cingulate, and dorsal medial (dm)PFC when viewing imagery of spiders versus neutral imagery (i.e., mushrooms), whereas non-phobic individuals did not show stronger activation to spiders versus mushrooms in any brain region (Straube, Mentzel, & Miltner, 2006). Finally, structural integrity in the amygdala-prefrontal pathway (measured using diffusion tensor imaging) is negatively correlated with trait levels of anxiety (Kim & Whalen, 2009).

In addition to the abnormalities in extinction circuitry observed in anxious populations, there is also extensive evidence of deficits in extinction learning and/or recall in these populations. For example, individuals with PTSD exhibit deficits in extinction learning indexed by higher physiological arousal (SCR and heart rate; HR), as well as higher US expectancy and valence ratings of the CS (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000). Even when there are no differences in levels of conditioned fear or within-session extinction, individuals with PTSD exhibit poorer extinction recall (Milad et al., 2008, 2009). Deficits in extinction learning have been shown in a number of other anxiety disorders (e.g., panic disorder; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007), and a recent study demonstrated deficits in extinction learning in a clinical group comprised of individuals with PTSD, panic disorder, and major depressive disorder (Otto et al., 2014).

Some studies have examined extinction learning/recall in anxiety disordered participants within the fMRI scanner and have supported the idea that alterations in extinction neural circuitry mediate the deficits in extinction learning/recall. For instance, Milad and colleagues conditioned, extinguished, and then tested PTSD patients in an fMRI scanner across two days (Milad et al., 2009; Rougemont-Bücking et al., 2011). They showed that PTSD patients exhibited poorer recall of extinction on the second day which was associated with increased activity in the amygdala during extinction learning (on day 1), as well as decreased vmPFC and hippocampal activity during the extinction retention test (day 2). These researchers also reported increased activity in the dACC in PTSD patients on day 2, the area normally associated with conditioned fear responding. In another study, brain activity in PTSD and non-PTSD combat-exposed veterans was examined during the early phase of extinction learning (Sripada, Garfinkel, & Liberzon, 2013). It was reported that greater avoidance symptoms in PTSD patients were associated with greater activity in the amygdala, vmPFC, dmPFC, insula, and hippocampus during early extinction. These data could indicate that extinction recall deficits are mediated by dysfunctions in the neural networks governing extinction learning and consolidation. Although much of the data examining neural circuit activation during extinction is limited to the PTSD patient population, it provides compelling evidence that alterations

in extinction circuitry underlie deficits in extinction learning, which appear to be common across the anxiety disorders, and potentially, the emotional disorders more generally.

Impact of CBT on the neural circuitry underlying extinction learning

If the abnormalities in extinction neural circuitry are fundamental to pathology in emotional disorders then successful recovery following treatment should be associated with a change in that neural circuitry. Indeed, there is now substantial evidence across numerous different disorders demonstrating lasting changes in the extinction circuitry following CBT. For example, individuals given CBT for spider phobia were shown to have attenuated neural activity in the insula and anterior cingulate cortex relative to spider phobic individuals that were not given treatment (i.e., wait-list control; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006). Also, OCD patients scanned during symptom provocation (using standardised subtype-specific stimuli) exhibited reductions in activity in the OFC, nucleus caudatus, ventrolateral PFC, and supramarginal gyrus across pre-CBT to post-CBT treatment time-points (Baioui et al., 2013). In contrast, when symptom provocation stimuli were individualised to the patient's idiosyncratic obsessions post-treatment activity reductions were observed in the nucleus accumbens. Interestingly, attenuating nucleus accumbens activity through deep brain stimulation has been shown to effectively treat refractory OCD in some studies (Sturm et al., 2003), suggesting that treatment-related reductions in this region may be fundamental for symptom reduction in OCD, irrespective of whether this is achieved through psychological or physiological means. It is worth noting that brain changes observed following CBT are not limited to functional plasticity. In a recent study, preliminary evidence suggested that CBT can induce structural changes in the brain; decreased supplementary motor area and amygdala volume were observed in spider phobic patients across pre- to 6 months post-CBT, and were correlated with a reduction in symptom severity (Schienle, Wabnegger, & Scharmüller, 2014).

As mentioned earlier, CBT involves both bottom-up (exposure therapy) and top-down (cognitive reappraisal) emotion regulation strategies, and studies examining each of these therapy components separately have reported neural changes associated with treatment. For example, hyperactivity in the amygdala, insula, and dACC observed in response to phobic stimuli was reduced following one session of intensive exposure therapy in spider phobic patients (Goossens, Sunaert, Peeters, Griez, & Schruers, 2007). A similar treatment also resulted in increased OFC activity immediately after therapy, an effect which was maintained at 6 months (Schienle, Schäfer, Hermann, Rohrmann, & Vaitl, 2007). In another study, PTSD patients were scanned whilst engaging in imaginal exposure to their traumatic memory (Cisler et al., 2014). Exposure was associated with increased functional connectivity of the amygdala with the hippocampus, insula, and mPFC, and of the hippocampus with the striatum, OFC, and dCC. Importantly, PTSD symptom severity tempered those associations suggesting that higher levels of symptoms were associated with a smaller change in functional connectivity during exposure. Similarly, brain changes also occur when the cognitive component of CBT is isolated. For example, individuals with social anxiety disorder (SAD) exhibited decreased amygdala activity when given instructions to use cognitive reappraisal when attempting to down-regulate their emotional reactivity to negative self-beliefs (Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009).

While the data discussed so far demonstrate the effect of CBT on the underlying neural pathology of anxiety disorders, it should be noted that CBT also causes functional brain changes when used to treat mood disorders. For instance, a case series using PET contrasted the scans of patients with major depressive disorder (MDD) before and after 15–20 weeks of CBT (Goldapple et al., 2004). CBT was associated with significant clinical improvement in depressive symptomology as well as significant brain metabolic changes: increases in the hippocampus and dorsal cingulate cortex and decreases in the dorsal, ventral and medial frontal cortex. In another study, differences in neural activity were reported pre-post CBT (Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011). Specifically, pre- to post-treatment MDD patients exhibited increased basal vmPFC activity, increased discrimination between emotional vs neutral stimuli reflected by activity in the amygdala, caudate and hippocampus, and increased responsiveness in anterior temporal lobe to positive versus negative stimuli. More recently it was reported that CBT resulted in functional brain changes during a specific task: self-referential processing of negative words (Yoshimura et al., 2013). In that study participants were scanned while performing a task in which they were asked whether words of differing valence (positive/negative) were descriptive of themselves. Before CBT, MDD patients exhibited hyperactivity in the mPFC during self-referential processing of negative words. After CBT, however, previously depressed subjects exhibited decreased mPFC and vACC activity for self-referential processing of negative words, while activity in these regions was increased when performing self-referential processing of positive words. It is clear that some variance exists in the reported effects of CBT for mood disorders on brain activity using functional imaging techniques. These differences could be due to the tasks subjects performed while functional scans were taken, differences in the imaging technology, or a host of other protocol-specific factors. Regardless, the main point to be taken from these data is that effective CBT for depression, as for anxiety, causes functional neural changes in regions which appear dysfunctional pre-treatment. Importantly, many of those regions (specifically, the frontal cortices, hippocampus, and amygdala) are also affected by CBT in anxious populations, suggesting that similar circuits are disrupted in anxious and depressed populations and that CBT appears to target that disrupted circuitry to effect symptom reduction.

Together these data demonstrate that CBT targets core circuitry disruptions (whether these are structural or functional) that may underlie emotional disorders. These data also support the use of extinction learning in rodents and healthy humans as a preclinical transdiagnostic model for the neural underpinnings of CBT's long-term effects. In the next section we describe preclinical research and clinical trials that have compared the efficacy of CBT (or laboratory models of CBT) when administered in combination with or without antidepressant or anxiolytic medication.

Traditional pharmacotherapy interactions with CBT

Anxiolytics

Benzodiazepines

For many years, benzodiazepines were the most widely prescribed psychotropic for anxiety and depressive disorders. Whilst no longer recommended as the front-line pharmacological treatment for anxiety disorders, prescription of benzodiazepines by general practitioners and other health professionals remains prolific (Julien, 2005). Benzodiazepines facilitate gamma-aminobutyric acid (GABA) transmission, which is the major inhibitory neurotransmitter in the nervous system (Farach et al., 2012). Their anxiolytic effects result from binding to and inhibiting activity in limbic structures associated with emotion production, such as the amygdala. However, as benzodiazepines are administered systemically, they also bind to GABA receptors throughout the rest of the central nervous system, including the cerebral cortex and brain

stem. Hence, benzodiazepines are classically associated with sedative and amnestic side effects. Indeed, stronger doses of benzodiazepines than those prescribed for mental illness are used as hypnotics in the treatment of insomnia, as a component of general anaesthesia during surgical procedures, and as adjuncts in the treatment of epilepsy (Julien, 2005).

With respect to their efficacy in the treatment of mental illness, it appears that benzodiazepines merely mask symptoms via their anxiolytic and sedative effects. This contention is supported by the large proportion of people who experience symptom relapse following termination of benzodiazepine treatment (as many as 50%, as reported in a study examining the efficacy of alprazolam for Panic Disorder; Spiegel, Bruce, Gregg, & Nuzzarello, 1994).

Given that benzodiazepines are frequently used by patients with anxiety disorders, and that a large component of CBT involves exposure therapy, animal studies have examined the impact of benzodiazepines on the extinction of learned fear. Such studies have consistently demonstrated that benzodiazepines, when administered before or immediately after fear extinction, impair long-term extinction memory when the animal is tested drug free, despite causing reduced fear responses during extinction training (Bouton, Kenney, & Rosengard, 1990; Hart, Harris, & Westbrook, 2009; Pereira, Rosat, Huang, Godoy, & Izquierdo, 1989). These preclinical findings do not bode well for those using benzodiazepines whilst receiving CBT, given that between-session reductions in fear (i.e., long-term extinction memories) predict overall clinical improvement in anxiety (Berry, Rosenfield, & Smits, 2009).

Interestingly, despite the robustness of the preclinical findings in rodents, and despite the widespread use of benzodiazepines by patients undergoing psychological treatment, there have been few controlled studies examining the impact of combined CBT and benzodiazepine use on symptom reduction. The first compared the efficacy of exposure therapy versus a combination of exposure therapy and the benzodiazepine alprazolam in people with Panic Disorder (Marks et al., 1993). In the initial eight weeks, the combined treatment was as effective as exposure therapy alone in leading to improvement on a range of symptoms, including reduced avoidance of agoraphobic situations, greater work and social adjustment, reduced panic attacks, and a clinical rating of global improvement. However, following the treatment taper period, patients given exposure therapy alone continued to exhibit improvements that were not observed in patients given the combined treatment. In other words, alprazolam attenuated the long-term effectiveness of CBT without altering its initial efficacy. Similar findings were reported in a later study of the impact of CBT versus CBT plus the benzodiazepine temazepam on late-life insomnia (Morin, Colecchi, Stone, Sood, & Brink, 1999). That is, while the combined treatment led to equivalent symptom reduction as compared to CBT alone during treatment, symptoms reported at progressive follow-up assessments (until 24 months post-treatment) were more severe in those patients who received the combined treatment compared to those who received CBT alone. Put simply, patients receiving the combined treatment exhibited relapse of symptoms whereas those receiving CBT did not.

Three studies have investigated the impact of benzodiazepines on CBT in more naturalistic (uncontrolled) settings. One study reported that benzodiazepine use was not associated with significantly worse response to CBT for panic disorder, assessed at a 6 month follow-up, although this study did note that there was a significant decline in the number of patients using benzodiazepines from pre to post treatment, and to follow-up assessment (Arch & Craske, 2007). Another study reported that "as needed" use of benzodiazepines during CBT for panic with agoraphobia negatively predicted treatment response, as assessed immediately post-CBT; in contrast, regular benzodiazepine users exhibited similar treatment response to non-medicated patients (Westra, Stewart, & Conrad, 2002). Finally, a third study reported that patients who entered remission from panic disorder medication free were less likely to relapse than those who remained on medications throughout treatment and into remission (Otto, Pollack, & Sabatino, 1996).

When the mechanisms of action of each treatment are contrasted, it is not difficult to ascertain likely reasons for the observed reactions to combined CBT and benzodiazepine treatment. That is, CBT depends on learning and long-term memory formation. As described previously, learning and long term memory formation require activation of the NMDA receptor, increased neuronal excitability, and synaptic plasticity. Benzodiazepines, by activating the GABA receptor, lead to increased neuronal inhibition, creating a neural environment that is not permissive for the formation of new memories. As such the mechanisms of CBT and benzodiazepine treatment are fundamentally at odds with one another. Alternatively, or in addition, benzodiazepines may create an intereoceptive context that becomes a "cue" for extinction, and subsequently the subject will only recall the extinction memory when again experiencing that interoceptive context. Evidence for benzodiazepines inducing such state-dependent extinction learning has been reported in rodent studies (Bouton et al., 1990).

In addition to the physiological incompatibilities, there are also psychological reasons as to why benzodiazepines may reduce the effectiveness of CBT. One such reason is that patients may attribute the success of CBT to the benzodiazepine, such that the drug integrates with the pathology to become an additional "safety" behaviour (i.e., a subtle form of avoidance whereby patients will only engage in feared situations when accompanied by items or actions that are designed to prevent the feared outcome from occurring, thus making them feel safer at the outset). Safety behaviours have been demonstrated to prevent shifts in cognitions about the probability and cost of catastrophe from occurring during exposure therapy (Wells et al., 1995). For example, an individual with agoraphobia may attribute the absence of a fainting episode in a crowded shopping centre to the influence of the benzodiazepine, rather than to the low probability of the fainting episode occurring in the first instance. Alternatively, benzodiazepines may be so effective at reducing anxiety that patients lose motivation to fully engage with CBT, and so only gain the short-term anxiolytic benefit of the benzodiazepine, which is lost once the drug treatment is terminated. Whatever the exact mechanism, the existing evidence suggests that combined CBT/benzodiazepine treatment is not effective. In fact, the evidence strongly suggests that use of benzodiazepines during CBT should be contraindicated given that benzodiazepines appear to diminish the long-term effectiveness of CBT.

Propranolol

Propranolol is a beta-adrenergic receptor antagonist that dampens sympathetic nervous system activation, commonly known as the "fight or flight" response. It is currently recommended for treatment of a number of medical conditions, including hypertension, angina, myocardial infarction, and tremor. It is currently not recommended for the treatment of anxiety disorders (or is recommended for investigational use only), on the basis of there being no evidence of its efficacy (Farach et al., 2012). Despite this, it is often prescribed by medical practitioners (or acquired through other means by individuals with anxiety disorders) to reduce anxious symptoms, and so we have included a brief discussion of its interactions with CBT in this review.

Preclinical studies in rodents regarding the impact of propranolol on fear extinction have produced mixed results, with some studies reporting no impact of acute propranolol administered

systemically prior to extinction learning on long-term fear extinction retention as measured the following day, drug free (Cain, Blouin, & Barad, 2004; Rodriguez-Romaguera, Sotres-Bayon, Mueller, & Quirk, 2009). In contrast, a study involving infusion of propranolol directly into the IL subdivision of the PFC just prior to fear extinction training reported no anxiolytic effect during extinction training, but an impairment in long-term extinction retention the following day, drug free (Mueller, Porter, & Quirk, 2008). A recent preclinical study in healthy humans reported that propranolol disrupted extinction learning and retention at a cognitive level (i.e., participants treated with propranolol prior to extinction learning reported greater expectancy of the shock US during both during extinction learning when the drug was on board and during extinction retention, drug free (Bos, Beckers, & Kindt, 2012)). However, propranolol-treated participants exhibited similar reduction in arousal responses to the CS (e.g., skin conductance and startle reflex) to that exhibited by placebo-treated participants.

The one clinical trial investigating propranolol/CBT interactions in humans examined the impact of propranolol on exposure therapy for individuals with agoraphobia (Hafner & Milton, 1977). Participants received 40 mg of propranolol or placebo, in a double-blind fashion, prior to three 5 h exposure sessions across three days. During exposure, the propranolol group had significantly reduced heart rate and experienced significantly fewer panic attacks compared to those receiving the placebo. Of the panic attacks that were experienced, over the course of the three days of exposure, the severity of the attacks declined in those who received the placebo but this effect was absent in those who received propranolol. Likewise, self-reported coping with panic attacks increased across exposure sessions in placebo- but not propranolol-treated individuals. Three months-post exposure treatment, those who received the placebo reported spending significantly more time travelling alone, and significantly reduced endorsement of general symptoms on the fear-survey schedule, relative to the propranolol group.

Thus, of the studies that have reported an effect of propranolol on fear extinction/exposure therapy, the effect has been consistently negative, which supports the contention that the use of propranolol during CBT may, in many cases, actually diminish the benefits of psychological treatment. The most likely explanations for this outcome are similar to those of the effects of benzodiazepines on CBT. On a neurobiological level, propranolol inhibits adrenergic signalling, such as norepinephrine, which has been extensively implicated as a necessary component of the molecular consolidation of long-term memory (Mueller & Cahill, 2010). Thus, by preventing arousal during exposure therapy and other components of CBT, propranolol may prevent new safety memories, new ways of responding, and new strategies from being consolidated into long-term storage. It is interesting to note that yohimbine, an *enhancer* of adrenergic signalling, has been demonstrated to augment extinction in rodents and enhances exposure therapy in clinically anxious humans (Mueller & Cahill, 2010; Smits et al., 2014), potentially via up-regulating the molecular consolidation of the extinction learning. On a practical level, the fact that propranolol reduced heart rate and the incidence of panic attacks during exposure therapy (Hafner & Milton, 1997) meant that propranolol necessarily reduced the learning opportunities available during exposure therapy. That is, these patients received a smaller "dose" of exposure therapy by the very nature of the fact that they experienced less exposure to feared interoceptive cues in the absence of catastrophic outcome, hence less opportunity to form new safety memories. A similar argument could also be made regarding the detrimental effect of benzodiazepines on exposure therapy for panic disorder. Thus, aside from their disruptive impact on the molecular storage of memory, or their potential induction of a state-dependent memory, both of which would reduce the maintenance of treatment gains in the longer-term, commonly prescribed anxiolytics are incompatible with CBT (at least in the case of Panic Disorder, which requires exposure to interoceptive cues) because they may prevent patients' opportunities to make those gains at the outset. Finally, similar to benzodiazepines, propranolol may induce state-dependent extinction learning that precludes the extinction memory from being recalled unless under the same drug state, although this has not been empirically assessed. Indeed, it should be noted that any drug that produces noticeable interoceptive changes (e.g., feelings of tranquillity induced by benzodiazepines and propranolol) and that is combined with extinction may produce a state-dependent extinction memory, the expression of which is dependent on the presence of the drug. Any such drug that induces state-dependent learning would be contraindicated for use as an adjunct to CBT.

Antidepressants

Antidepressants were introduced around half a century ago, as the name suggests, for the treatment of depression. However, selective-serotonin reuptake inhibitors (SSRIs), the most commonly used form of antidepressant, are now also recommended as the first line pharmacological treatment for anxiety disorders (Farach et al., 2012). There have been many formulations of antidepressants over the last 50 years, but the therapeutic impact of most is due to increased transmission of serotonin, and increased transmission of serotonin and norepinephrine in the case of the first generation antidepressants (tricyclic antidepressants; TCAs, and monoamine oxidase inhibitors; MAOIs; Julien, 2005). The mechanism by which this occurs differs for different formulations (e.g., TCAs and SSRIs block the reuptake of serotonin, whereas MAOIs prevent the breakdown of serotonin), and the side effects caused by other physiological effects of the drug also vastly differ (e.g., TCAs block histamine, leading to sedative effects, whereas SSRI use can lead to serotonin overactivity, which is associated with anxiety and insomnia, amongst other effects; Julien, 2005). It is becoming increasingly recognised that in addition to modulating serotonin and norepinephrine, the therapeutic action of antidepressants may depend on their ability to influence a variety of messenger signals, transcription factors, and trophic factors in the brain (Duman & Aghajanian, 2012). The overall effect of this is to increase brain plasticity and regeneration.

Interestingly, many of the signals upregulated by antidepressants are common to those that have been implicated in the molecular consolidation of long-term memory (Kandel, 2001). Given that traditional anxiolytics have been purported to interfere with the benefits of CBT due to their memory impairing properties, it is possible that combining antidepressants with CBT could lead to the opposite effect (i.e., enhance CBT) by augmenting memory consolidation.

Preclinical studies in rodents that have explored this idea have produced contradictory results, which may be due to subtle differences in specific antidepressant formulations and/or their side effects. For example, a recent study reported that fluoxetine treatment, commencing immediately after fear conditioning and continuing during extinction training and testing two weeks later, led to a significantly enhanced rate of extinction learning, and significantly reduced reinstatement and renewal (i.e., common models of relapse), in mice (Karpova et al., 2011). When administered chronically after extinction training, fluoxetine has also been demonstrated to prevent stress-induced relapse in rats (Deschaux et al., 2013). In contrast to these results, one study reported that chronic fluoxetine administered in the two weeks prior to

extinction training suppressed freezing responses during extinction learning without enhancing extinction recall in females extinguished during periods of low progesterone and estradiol; fluoxetine had no effect on either extinction learning or extinction recall in male rats or females extinguished during periods of high progesterone and estradiol (Lebrón-Milad, Tsareva, Ahmed, & Milad, 2013). Another study that investigated a different SSRI, citalopram, reported that chronic (but not sub-chronic) exposure slowed extinction learning and impaired extinction recall in rats (Burghardt, Sigurdsson, Gorman, McEwen, & LeDoux, 2013). That same study also demonstrated that tianeptine, a new antidepressant that enhances serotonin reuptake yet paradoxically has been shown to be effective in the treatment of depression, also impairs extinction learning and recall in rats. The impairing effects of both antidepressants examined in that study were associated with reduced amygdala expression of the NMDA NR2B receptor.

A considerable number of clinical studies have investigated the effects of combining antidepressants with CBT for emotional disorders. Like the preclinical rodent studies, however, results have been mixed, with some studies reporting no effects, some reporting modest benefits, and some reporting detrimental effects. With respect to depression, one meta-analysis reported some evidence for a modest enhancement of combined pharmacotherapy with psychological treatment over either treatment alone (Cuijpers, van Straten, Warmerdam, & Andersson, 2009). In this meta-analysis the enhancement resulting from combined treatment was greatest when SSRIs or TCAs were used as the pharmacological treatment, and when certain populations were investigated (e.g., the elderly, and people with HIV, suggesting the importance of individual difference factors in response to pharmacological adjuncts; see the following section). The enhancement was smallest, however, when CBT was used as the comparison psychological treatment as opposed to other treatments like interpersonal therapy. In addition, no advantage of combined treatments was found at follow-up assessment. Another meta-analysis examining the treatment of adolescent depression reported no added benefit of combining CBT with pharmacotherapy versus pharmacotherapy alone (Dubicka et al., 2010). This meta-analysis did not include research that compared the efficacy of CBT without medication to CBT with medication.

Similarly inconsistent results have been obtained when examining the impact of combined antidepressant and CBT treatment for anxiety. Simpson et al. (2004) reported that patients receiving combined exposure therapy/response prevention with clomipramine (an SSRI) for OCD responded to treatment equivalently to those receiving exposure therapy/response prevention alone, as measured throughout treatment and at a 12 week follow-up. Likewise, combined CBT and fluoxetine led to equivalent reduction in social anxiety symptoms as compared to CBT alone in individuals with generalised social phobia, as assessed throughout a 14 week treatment (Davidson et al., 2004). In contrast, Haug et al. (2003) reported that social phobia patients treated with combined CBT and sertraline (an SSRI) failed to exhibit the further enhancement of treatment gains evident in those treated with CBT alone when assessed at a one year follow up, despite showing comparable gains immediately post-treatment. A study examining the naturalistic use of antidepressants reported that patients with panic disorder exhibited a delayed response to CBT, and reduced overall treatment gains, when using antidepressants throughout treatment versus remaining medication free (Arch & Craske, 2007). In further contrast to these results, a recent study examining the impact of combined paroxetine (an SSRI) and exposure therapy for the treatment of PTSD in World Trade Centre survivors reported a greater response in those receiving the combined treatment versus exposure therapy alone at the end of treatment (Schneier et al., 2012). However, when participants were measured following a 12 week period (during which they continued to receive paroxetine or placebo, without further exposure therapy), no group differences in symptom severity were apparent.

It seems that, similar to the impact of antidepressants on CBT for depression, at best, combining antidepressants with CBT for anxiety leads to modest or no improvements compared to CBT alone, and at worst, it may impede further symptom reduction often observed following CBT discontinuation. This contention is supported by a recent meta-analysis which suggested that while CBT plus pharmacotherapy was generally more effective than CBT plus placebo at post-treatment for measures of anxiety disorder severity and treatment response, this difference generally disappeared by 6-months post-treatment discontinuation (Hofmann, Sawyer, Korte, & Smits, 2009). One reason for the disparate effects of antidepressants on CBT for emotional disorders may be due to the wide variations in the molecular targets of antidepressants, some of which (e.g., increased neurotrophic expression) may enhance memory formation and thus CBT, and others (e.g., suppression of NMDA receptor expression) may be detrimental to memory formation and CBT. Depending on the precise extent and combination of up- or down-regulation of each of these targets, potential positive effects on CBT might be permitted, cancelled out, or in the worst of cases, negative effects may result. It is possible that as antidepressant treatments become more refined on the basis of a better understanding of the precise molecular targets that lead to therapeutic benefit, more consistently positive cumulative effects of antidepressants and CBT will be observed.

The “new wave” approach to combined pharmacotherapy and CBT

As described above, the available evidence quite clearly shows that combining typical pharmacological adjuncts with CBT either has no added benefit or actually reduces treatment efficacy. Because of such findings, more recent work on the potential use of pharmacological adjuncts to enhance the loss of fear following extinction or CBT has taken one of two novel approaches. One approach has focused on the concept of memory reconsolidation while the other has focused on synaptic plasticity (i.e., learning).

Memory reconsolidation is the idea that retrieving an old, well-established memory causes it to become labile and modifiable. That is, memory is thought to go through a consolidation phase shortly after a learning experience. During this time the memory is labile and can be modified, but as the memory becomes “consolidated” over time it is less and less susceptible to modification (including disruption; McGaugh, 2000). However, if an old, well-consolidated memory is reactivated (e.g., retrieved) at a later point in time it becomes de-stabilised and needs to be “re-consolidated”, during which time it is again modifiable. Although a number of early studies had clearly demonstrated the phenomenon of memory reconsolidation (e.g., Misanin, Miller, & Lewis, 1968), the concept was largely ignored until the publication by Nader, Schafe, and LeDoux (2000) showing that administration of a protein synthesis inhibitor disrupted memory reconsolidation in rats. This study led to a dramatic resurgence of interest in the idea of memory reconsolidation, including in humans (e.g., Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012). A key element of this renewed interest was the idea that disrupting reconsolidation of negative memories might be a novel way of enhancing treatment gains in clinical settings (e.g., Schwabe, Nader, & Pruessner, 2014). From this perspective, pharmacological adjuncts that facilitate the disruption of memory reconsolidation could further enhance treatment efficacy. There is clear preclinical evidence in humans that certain agents (e.g., propranolol) can disrupt reconsolidation of negative

memories in an experimental setting (e.g., Schwabe et al., 2012; Soeter & Kindt, 2010; 2011). If these findings can be translated to clinical populations and settings, then this approach could lead to improved treatment efficacy, although there are a number of potential issues that would need to be addressed (e.g., does this approach lead to "erasure" of only the original memory or are other memories also affected). The limited work to date on this issue has focused on disrupting memories associated with PTSD (e.g., Brunet et al., 2011), but an intriguing possibility here, although not discussed much if at all, is that disrupting memory reconsolidation may be a particularly effective approach to treating depression. That is, a prominent feature in many cases of depression is a high rate of rumination, which would lead to relevant memories (i.e., those associated with the source of the mood disorder, or those associated with maintaining the depressed mood) frequently being in an active state and therefore susceptible to disruptions in reconsolidation.

The idea underlying the second novel approach to developing pharmacological adjuncts to enhance CBT focuses on the notion, discussed extensively above, that this form of therapy involves new learning. Therefore, agents that enhance the biological processes underlying learning will enhance treatment efficacy. Extinction of learned fear is a widely-accepted model preparation for the safety learning that underlies CBT (e.g., Graham & Milad, 2011; Milad & Quirk, 2012). As noted above, fear extinction may not just be a relevant laboratory model for exposure therapy for anxiety disorders, but may also model the key processes involved in other strategies used in CBT, such as cognitive reappraisal, which is widely utilised in the treatment of emotional disorders transdiagnostically. There have been a number of outstanding reviews on pharmacological agents that enhance extinction of learned fear (e.g., Graham et al., 2011; Myers & Davis, 2007), with a focus on the potential translational importance of such work for enhancing treatment outcomes with CBT, so we will not go through that material here. Rather, what we will focus on is the need for an increased appreciation, and empirical examination, of various factors that influence the effectiveness of these various pharmacological adjuncts (i.e., a focus on what is referred to as the "new wave" in Fig. 2).

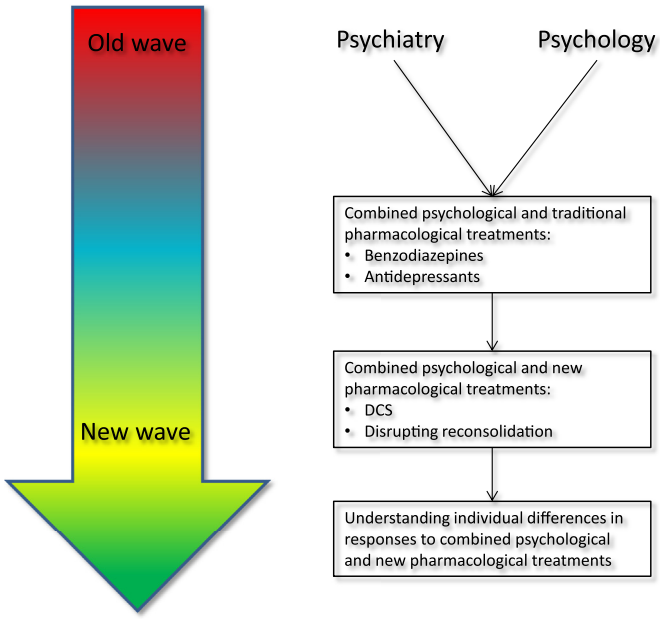

Fig. 2. Schematic depicting the various phases comprising the gradual merging of Psychiatry and Psychology.

Both of these novel approaches hold considerable promise for improving treatment outcomes in a number of ways. For example, these approaches may lead to an increased number of patients successfully completing treatment, a decrease in drop-out rates, faster treatment responses, and longer-lasting gains that are less susceptible to relapse. However, it is unlikely that either approach will lead to improved treatment outcomes for all. Benefits from pharmacological adjuncts, whether they disrupt memory reconsolidation or enhance the learning that occurs during CBT, almost certainly will be mediated by a number of individual differences, varying from genetic to early life experiences. A greater understanding of how these various factors influence the effects of pharmacological adjuncts is an important next step in this area of research. To date, there has been very limited research exploring this issue and there is a clear need for much more. Preclinical models in rodents and humans can be effectively used to identify potentially important candidate individual differences that can then be explored in clinical settings. Determining how individual difference factors influence treatment gains when using pharmacological adjuncts that either facilitate the disruption of memory reconsolidation or that enhance the learning that occurs during CBT will be useful in personalising treatment for specific patients (e.g., a particular factor may reduce the effectiveness of a pharmacological adjunct aimed at disrupting memory reconsolidation but have no effect on a pharmacological agent that is aimed at enhancing the learning occurring during CBT, or vice-versa).

Most of the work that has been done in this area to date has involved the pharmacological modification of extinction, with much less work examining this issue in regards to adjuncts that disrupt memory reconsolidation. Perhaps the most widely-studied pharmacological adjunct for enhancing the learning underlying extinction/CBT is D-cycloserine (DCS), a partial NMDA receptor agonist. Following several demonstrations that DCS enhanced the extinction of learned fear in rats (Ledgerwood et al., 2003; Walker et al., 2002), a number of clinical trials reported positive effects of DCS in clinical populations. In the first, acrophobics were given two sessions of Virtual Reality Therapy (VRE; Ressler et al., 2004). Some patients were given a dose of DCS before each of these two sessions (separated by one week) while the others were given a placebo. Only those patients given the DCS exhibited reduced fear (assessed by self-report and SCR) following the two sessions of VRE. The lack of improvement in the placebo-treated participants was not surprising as eight sessions of VRE are usually required to see treatment gains in this setting. In other words, the DCS substantially increased the rate at which treatment gains were observed (also see Chason et al., 2010; Nave, Tolin, & Stevens, 2012). In addition, the treatment gains persisted at a 3-month follow-up, and these participants also reported more instances of self-exposure to heights outside the lab than those given the placebo (i.e., treatment gains generalised outside the Virtual Environment). These positive effects of DCS were replicated in a number of subsequent clinical trials, with other classes of anxiety disorders (for review see Hofmann, Wu, & Boettcher, 2013). However, there are a number of studies that have failed to observe enhanced treatment outcomes following administration of DCS (see Hofmann et al., 2013), with some even reporting a worse outcome in the DCS-treated patients (e.g., Litz et al., 2012).

One possible explanation for these diverse findings is that the populations tested in each study varied on important dimensions or features. A meta-analysis of early DCS studies reported that the improvement in treatment outcome following administration of this adjunct was of a medium effect size (Norberg et al., 2008). It may be the case though that DCS, or any other agent that enhances learning during CBT, will lead to larger treatment gains if greater attention is paid to individual differences (e.g., genetics, past

experiences, etc.). There are many potential candidate individual differences that could influence responsiveness to DCS, or any other agent that enhances learning during CBT (or agents that disrupt memory reconsolidation), and we describe several below for which there is at least some evidence showing that they may affect the effectiveness of the adjunct.

Within-session extinction

Weber, Hart, and Richardson (2007) reported that DCS enhanced extinction retention (i.e., at a test 24 h after extinction training) but only in rats that exhibited significant within-session reductions in fear during extinction training. Those animals that continued to respond fearfully throughout the extinction training session did not benefit from being injected with DCS. This finding has been replicated a number of times. For example, Bouton, Vurbic, and Woods (2008) re-analysed data previously reported as showing no effect of DCS on extinction retention and found the same pattern reported by Weber et al. That is, DCS enhanced extinction retention in those animals that exhibited within-session reductions in fear during the extinction training session but not in those who failed to show such reductions. Using a mouse strain (i.e., the S1 strain) that typically exhibits impaired within-session extinction (i.e., they continue to respond fearfully throughout the extinction training session) Hefner et al. (2008) reported that DCS was ineffective at augmenting extinction retention. In a subsequent study with the same mouse strain, Whittle et al. (2013) employed a "weak" fear conditioning procedure and found that with these training parameters the S1 mice did exhibit within-session extinction (i.e., loss of learned fear across extinction trials). However, these animals exhibited impaired extinction retention, with the extinguished fear returning at test the next day. Administration of DCS in this setting was found to improve extinction retention. In other words, DCS augmented extinction retention in the S1 mouse only when within-session extinction occurred.

Importantly, this pattern has also been reported in clinical settings. That is, in order to detect an improvement in therapeutic outcome following administration of DCS, the patient must exhibit reductions of fear during the session. For example, Smits, Rosenfield, et al., 2013 re-analysed data initially reported as a null effect for DCS and treatment improvements (Tart et al., 2013) and found the same pattern described above. That is, patients given DCS immediately after a therapy session exhibited enhanced treatment gains if, and only if, they exhibited low levels of fear at the end of the session. The patients who still exhibited high levels of fear at the end of the therapy session (i.e., they failed to exhibit evidence of extinction during the session) actually exhibited a worsening of their symptoms if given DCS. These findings dramatically highlight the importance of assessing whether reduction in fear occurs during the session as DCS, or other adjuncts that enhance learning, may actually lead to increased levels of fear/anxiety in those patients that maintain high levels of fear. That is, treatment with DCS, or other adjuncts that enhance the learning that occurs during the session, is likely to enhance whatever occurred during the session; if the session was successful in reducing fear then the adjunct can improve treatment outcome but if the session was not successful at reducing fear then the adjunct may lead to a worse outcome (see Hofmann et al., 2013).

Although not much research has yet been directed at examining whether individual differences alter the effectiveness of agents that disrupt memory reconsolidation, one recent preclinical study in humans has shown that learning (i.e., prediction error) determines whether a well-consolidated memory is destabilised and made susceptible to pharmacological disruption. Specifically, Sevenster, Beckers, and Kindt (2013) employed a differential conditioning procedure where one visual stimulus (the CS+) was paired with electric shock while a second visual stimulus was not (CS-). For some participants, the CS+ was always paired with the shock during training (on day 1) while for others the CS+ was followed by the shock on a partial reinforcement schedule (33% of the time). The next day, the memory of this experience was reactivated by re-presenting the CS+. For some participants, this CS + presentation on Day 2 was followed by shock while for others it was not. In terms of those participants in the continuous reinforcement procedure (i.e., the CS+ was always followed by shock in training), the non-reinforced presentation of the CS + on Day 2 would have led to a prediction error (i.e., what happened was different to what the participant expected; negative prediction error) while the reinforced CS + would not have led to any prediction error (i.e., what happened was what was expected). Because the participants in the partial reinforcement condition had not yet learned to asymptote, the reinforced CS + presentation on Day 2 also led to a prediction error (in this case, a positive prediction error). In both cases where the "reactivation" treatment led to a prediction error, whether negative or positive, ingestion of propranalol caused a disruption in memory reconsolidation (i.e., poor retention performance at test). In other words, memory destabilisation, and therefore increased susceptibility to disruption by propranolol, only occurred when there was an opportunity for the participant to learn something.

Prior drug exposure

Werner-Seidler and Richardson (2007) reported that chronic exposure to either DCS or the antidepressant imipramine (a TCA) reduced the effectiveness of a post-extinction injection of DCS in enhancing the loss of fear in rats. The finding that chronic exposure to DCS reduces its subsequent effectiveness in enhancing extinction retention (at least for a period of time) indicates that care should be taken when multiple doses are administered in a clinical setting. Of greater importance, though, is the finding that chronic exposure to imipramine also reduced the subsequent effectiveness of DCS in enhancing extinction retention. If the results reported by Werner-Seidler and Richardson also occur in clinical settings following chronic exposure to SSRIs, which are a front-line pharmacological adjunct in the treatment of both depression and anxiety disorders, then this individual difference in past drug exposure could markedly affect whether DCS will be effective at enhancing treatment outcomes. However, there are no preclinical studies, to our knowledge, that have examined the effects of chronic exposure to SSRIs on the effectiveness of DCS in enhancing extinction retention. Further, the evidence from clinical trials is not clear at this stage. One clinical study Difede et al. (2014) reported that treatment gains following DCS were larger for participants who were not taking other pharmacological agents, but the sample sizes for the various groups were too small to be meaningfully analysed (i.e., there were only 4 participants who were not taking any other pharmacological agent in the DCS-treated group). Another study, that looked at treatment effects in patients with social anxiety disorder, also found a trend for lessened augmentation by DCS in those who were taking antidepressants, but again the sample sizes were quite small (Rodebaugh, Levinson, & Lenze, 2013). Other studies that have examined this issue in clinical samples have not reported any effect (e.g., De Kleine, Hendriks, Smits, Broekman, & van Minnen, 2014). However, if the preclinical findings are also eventually observed in clinical populations (i.e., once large-scale trials are completed), then one possibility here is that antidepressants impair within-session learning, and thereby reduce the necessary substrate upon which the pharmacological adjunct acts (i.e., new learning). Clearly much more research is needed in this area, both pre-clinically and clinically.

Prior extinction/exposure therapy

There have been many preclinical studies in rodents examining how various pharmacological agents affect extinction, both its learning and its retention (see Myers & Davis, 2007). One feature common to nearly all of these studies has been that the subjects were being extinguished for the first time. The assumption, at least implicitly, of past research in this area was that extinction employed the same neural circuitry, and the same neurotransmitters, whether it was occurring for the first time or the Nth time. However, that is not the case. Some factors (or drugs) that affect extinction the first time do not have any impact on extinction the second time. This is likely to be of particular import in terms of translating findings from the preclinical domain into the clinical setting given that many patients with an anxiety disorder will receive treatment on more than one occasion (e.g., the disorder might relapse years later, necessitating a second bout of therapy). Of relevance to this review are the findings that DCS enhances extinction of learned fear in rats the first time but not the second time. Specifically, if rats are trained to fear a CS (e.g., a noise that has been repeatedly paired with shock), extinction retention is enhanced by administration of DCS either before or following extinction training (for review see Graham et al., 2011). However, if the animal is extinguished drug-free, and then re-conditioned (i.e., given additional pairings of the noise CS and shock), then extinction the second time is not enhanced by DCS (Langton & Richardson, 2008). The transition from NMDAr-dependent extinction to NMDAr-independent re-extinction appears to be both context- (Langton & Richardson, 2009) and time-specific (Langton & Richardson, 2010). Finally, a similar pattern is observed for benzodiazepines. That is, Hart et al. (2009) showed that midazolam impaired extinction the first time but not the second time. This finding was recently extended by Hart, Panayi, Harris, and Westbrook (2014) in an interesting study where a single extinction session was given. If that session was one, long continuous session, then midazolam impaired extinction retention. However, if the extinction session was divided into two distinct sessions (e.g., 5 min of extinction training, a "rest" period in the home cage, and then a second 15 min-long extinction session), then midazolam had no impact on the reductions in fear caused by the second extinction session. There was no benefit of the midazolam treatment in that study, but it clearly did not impair extinction retention. As noted by the authors, even if no enhanced fear reductions occurred following the midazolam, such a treatment might have significant clinical relevance in that patients may be more likely to complete treatment in such a setting. Further, in one other study by the same group, midazolam was actually found to enhance re-extinction (Hart, Harris, & Westbrook, 2010). In this study the second extinction session was either 4-min or 20-min long. In vehicle-treated animals, the longer session caused greater reductions in fear. In contrast, in midazolam-treated animals, both the 4- and the 20- minute extinction training protocols were effective at reducing fear at test. In other words, the midazolam-treated animals needed less extinction training the second time in order to exhibit low levels of fear at test.

Personality factors

In a recent study, De Kleine et al. (2014) examined whether any of a number of various factors affected DCS-augmentation of exposure therapy. Using a sample of PTSD patients, they reported that two personality variables impacted on whether DCS augmentation of therapy occurred or not. Specifically, it was reported that DCS facilitated treatment outcomes in those high in conscientiousness and those low in extraversion (both relative to individuals from the same personality group but given placebo). It should be noted that Smits, Hofmann, et al. (2013) also found an effect of conscientiousness on DCS-augmentation of exposure therapy in individuals with social anxiety disorder. However, the direction of that relationship was different to that reported by de Kleine et al. (i.e., in the Smits et al. study DCS led to better treatment outcomes in those who were low in conscientiousness). Specific personality variables can easily be assessed in pre-clinical human samples, and a number of personality variables (e.g., impulsivity, trait anxiety, etc.) can also be modeled in non-human animals. Examination of whether these personality factors influence the effectiveness of pharmacological adjuncts on the extinction of fear are likely to be useful in determining those factors to next explore in clinical studies.

Conclusions

The gradual increase in cross-communication between the disciplines of Psychiatry and Psychology over the past decade has highlighted a serious problem in our current approach to the treatment of mental illness, which is that combined CBT and pharmacotherapy, often administered blindly, may lead to patients achieving a weaker level of symptom reduction and a shorter period of remission than would be gained with CBT alone. The evidence that we have reviewed strongly suggests that combining traditional anxiolytics (benzodiazepines and propranolol) with CBT leads to worse treatment outcomes than CBT alone, and combined CBT with antidepressants in most cases is no more effective than either treatment alone.

In addition to highlighting this problem, however, the increased cross-communication between Psychiatry and Psychology has meant that research outcomes from one discipline have started to inform the research of the other. The breaking down of the traditional "silo" approach to research has meant that psychological and psychiatric theories on the mechanisms underlying the symptoms of mental illness have started to converge, and as a result, been enriched in recent years. We are currently at the stage where specific cognitive and behavioural characteristics of emotional disorders, studied for years by psychologists, are being mapped onto specific neural and molecular characteristics of emotional disorders, studied for years by psychiatrists. In turn, this has led to comprehensive preclinical models in rodents and humans that may represent the fundamental mechanisms of dysfunction (at the cognitive, behavioural, and neural/molecular levels) common to emotional disorders. We have emphasised the utility of fear conditioning and extinction as procedures that have the potential to model both the underlying deficits in emotional disorders as well as the treatment of these deficits.

One consequence of the merging of psychological and psychiatric theories of mental illness and its treatment has been what we refer to as a "new wave" of thinking about the combined psychological/pharmacological treatments for mental illness. That is, rather than developing drugs that reduce symptom expression, as has been the case with traditional anxiolytics and antidepressants, research has instead turned to the search for drugs that might serve as "cognitive enhancers" of CBT. While this new wave has produced numerous candidate pharmacological adjuncts to CBT, largely through research that has demonstrated the ability of these candidate adjuncts to augment extinction learning, it is disappointing that no single adjunct is now used as part of common practice. This is particularly disappointing in the instance of DCS, whose efficacy as an adjunct to CBT has been demonstrated in multiple controlled clinical trials (see Graham et al., 2011, for review). We suggest that this new wave in research must also focus on understanding individual differences in responses to CBT

adjuncts (see Fig. 2). Such research would mean that health professionals are better placed to identify which treatment (i.e., reconsolidation disruption or exposure) and which adjunct are best matched to the patient on the basis of the presence or absence of individual difference factors that have been demonstrated to be predictive of treatment/adjunct response. We have provided an overview of research that has been conducted in line with this aim. While limited in scope, the existing research does indicate that there are a number of factors that can influence whether adjuncts like DCS or benzodiazepines enhance/impair the extinction of learned fear or not, and whether they enhance treatment gains from CBT or not. There is much more research needed in this area, in order to determine other factors (e.g., genetics) that may or may not affect treatment gains obtained with any particular pharmacological adjunct. There is also a need for this approach in research on agents that disrupt memory reconsolidation. Only by understanding these individual difference factors will we be able to personalise treatments and obtain the most effective outcomes. It is our hope that by taking this approach, and making it easier for health professionals to predict treatment response, the outcomes of this new wave of research will be more amenable to translation from the laboratory into standard clinical practice.

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