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The Modification of Attentional Bias to Emotional Information: A Review of the
Techniques, Mechanisms and Relevance to Emotional Disorders

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Abstract

A negative bias in the deployment of attention to emotional stimuli is commonly found in both anxiety and depression. Recent work has highlighted that such biases are causally related to emotional vulnerability suggesting that interventions which ameliorate them may be therapeutic. Here, we review the evidence that attentional bias can be modified using both pharmacological and psychological interventions. We highlight the behavioral and neuroimaging studies which suggest that these interventions impact upon attention via alteration of distinct neural mechanisms. Specifically, pharmacological interventions appear to influence the initial deployment of attention via an effect on the amygdala based stimulus appraisal system whereas psychological interventions influence attention at later time points and may alter activity in the lateral prefrontal cortex. Finally, we suggest a conceptual framework which embraces both pharmacological and psychological approaches and consider the possible implications of this work for future research and treatment development.

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A wealth of data from behavioral, neuroimaging, pharmacological and genetic studies has served to highlight the centrality of attentional processes in our understanding of anxiety and depression. Aberrant deployment of attention, particularly in relation to emotional information, occupies a pivotal position in many of the contemporary models of these disorders in which it is considered a causally relevant, proximal illness process. This view suggests that interventions which modify the habitual deployment of attention to emotional information should impact upon illness expression. In the current paper, we will review the evidence that emotional attention may be modified in both experimental and clinical settings. In doing so we will highlight the data which demonstrate that this modification may be achieved by targeting at least two distinct control mechanisms. Finally we will consider the implications of this work, particularly with regard to future research and treatment development.

What Evidence Links Abnormalities of Emotional Attention and the Emotional Disorders?

Both depression and anxiety have been associated with biases in the processing of emotional information; patients with these disorders habitually interpret, attend to and/or remember information in a more negative manner than non-clinical control participants (Mathews & MacLeod, 2005). Cognitive theorists suggest that these habits of thought are causal factors in the etiology and maintenance of the disorders (Beck, 1976; Mathews & Mackintosh, 1998; Mathews & MacLeod, 2005; Mogg & Bradley, 1998; Williams, Watts, MacLeod, & Mathews, 1997).

Anxiety has particularly been associated with a tendency to attend to threatening information; a phenomenon which has been termed “negative attentional bias” (see Figure 1 for a summary of the common tasks used to assess attentional bias) (Fox, Russo, & Georgiou, 2005; MacLeod, Campbell, Rutherford, & Wilson, 2004; Mathews & MacLeod, 1985; Williams, Mathews, & MacLeod, 1996). Recent work, much of it discussed in the body of this paper, has employed simple computer based tasks in order to induce attentional biases in non-clinical populations (see MacLeod, Koster, & Fox, 2009; Mathews & MacLeod, 2002 for review). Critically for psychopathology, these studies provide direct support for a causal role of attention in anxiety by demonstrating that inducing a negative attentional bias can lead to symptoms of anxiety in non-clinical participants.

Figure one about here

In depression the most consistent cognitive abnormalities were initially described in measures of memory (Gilboa-Schechtman, Erhard-Weiss, & Jeczemien, 2002; Mathews & MacLeod, 2005; Ridout, Astell, Reid, Glen, & O’Carroll, 2003; Williams et al., 1997), however there has been increasing interest in the possibility that attentional biases may exist in this disorder as well. Specifically depression has been shown to be associated with a tendency to attend to the spatial location of negative words (Bradley, Mogg, & Lee, 1997; Donaldson, Lam, & Mathews, 2007; Mogg, Bradley, & Williams, 1995) and faces (Gotlib, Kasch et al., 2004; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2007; Leyman, De Raedt, Schacht, & Koster, 2007). Negative attentional biases are also demonstrable in previously depressed, currently euthymic patients (Joormann & Gotlib, 2007) lending

support to the proposal that they are involved in the vulnerability to depression rather than solely reflecting a state marker or symptom of the illness.

Although depression and anxiety have both been associated with attentional bias towards negative stimuli there are differences in how this bias manifests between the disorders. Most obviously there appears to be a variation in how long a stimulus must be presented before the bias becomes evident; whereas anxiety is associated with an attentional bias occurring from 10 to 500ms after stimulus presentation, in depression the bias seems to occur between 500 and 1000ms (Gotlib, Kasch et al., 2004). These timing effects are consistent with dual process accounts of brain organization which describe the existence of two distinct information processing streams; an automatic stream which processes information in a rapid but inflexible manner and a strategic stream which provides slower, more flexible processing (see Carver, Johnson, & Joormann, 2008 for a recent review of dual process models relevant to the emotional disorders). It has been suggested (Mathews & MacLeod, 2005) that anxiety is associated with abnormalities in the early, automatic processing of information and depression with abnormalities in later processing stages. In terms of attentional function this may be reflected by abnormalities of the initial engagement of attention in anxiety with difficulties in disengaging attention being characteristic of depression (Leyman, De Raedt et al., 2007; see also De Raedt & Koster, this issue). Despite the differences seen in experimental paradigms, it is notable that individuals very often experience both anxious and depressive symptoms concurrently (Maser & Cloninger, 1990; Mineka, Watson, & Clark, 1998) and that there is a large overlap in the evidence based treatments for these disorders (NICE, 2004, 2007). Thus while there are some differences in the expression of attentional biases in anxiety and depression

there remains a strong possibility that these disorders share at least some pathological processes.

In summary, there is evidence that a tendency to preferentially attend to negative information is a feature of both anxiety and depression. Differences in the timing of the attentional biases found in depression and anxiety can be accounted for by dual process models which postulate the existence of temporally separable attention control processes.

What Processes Control Emotional Attention?

The control of attention to emotional information is often conceptualized within a biased competition framework (Bishop, 2007; Desimone & Duncan, 1995; Mathews & Mackintosh, 1998; Vuilleumier, 2005). Broadly this suggests that the deployment of attention is influenced by biasing signals which act to encourage the focus of attention towards or away from particular stimuli. Two neural systems have been implicated in generating signals of particular relevance to emotional stimuli. A bottom-up, amygdala based system generates a signal which reflects the perceived salience of stimuli (Adolphs, Tranel, Damasio, & Damasio, 1995; Davis & Whalen, 2001) and is thought to cause attention to be directed towards those stimuli. The anterior cingulate cortex (ACC), and lateral pre-frontal cortex (IPFC) are considered to be part of a top-down control system which is involved in detecting and resolving processing conflict with the result that attention may be maintained on relevant stimuli, even in the presence of distraction (Bishop, Duncan, Brett, & Lawrence, 2004a; MacDonald, Cohen, Stenger, & Carter, 2000). These neuroanatomical models predict that the negative attentional biases characteristic of emotional disorder may arise from perturbation of either of these systems. Supporting this contention,

experimental studies report increased amygdala activity to negative stimuli in both depression (Fales et al., 2008; Fu et al., 2004; Sheline et al., 2001; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002) and anxiety (Bishop, Duncan, & Lawrence, 2004b; Schneider et al., 1999; Shin, Rauch, & Pitman, 2006; Straube, Mentzel, & Miltner, 2006; Tillfors, Furmark, Marteinsdottir, & Fredrikson, 2002) whereas frontal activation to the same stimuli has been found to be decreased in both disorders (Bishop et al., 2004a; Fales et al., 2008; Mayberg et al., 1999; Shin et al., 2001; although see also Straube et al., 2006; Tillfors et al., 2002). A notable discrepancy arises when comparing this data to the behavioral literature; whereas differences in the temporal characteristics of the biases associated with anxiety and depression are evident when assessed behaviorally (see above), neuroimaging studies do not seem to reliably differentiate the disorders. This may be due to constraints on the temporal resolution of functional imaging techniques or the fact that neuroimaging studies have tended to simply present emotional stimuli without manipulating participants' attention (see Bishop et al., 2004a for an example of a study in which attention is manipulated). Such manipulations allow the effects of attention to be isolated from those due simply to the emotional properties of a stimulus. Nevertheless, the temporal specificity of the attentional effect demonstrated in the behavioral studies of anxiety versus depression remains unexplained by current neuroimaging data.

A further consideration when interpreting the neuroimaging data is that the biasing signals which influence attention seem to have "direction" as well as "magnitude". For example, whereas depressed patients show decreased activity in the anterior cingulate cortex during anticipation of loss, they show *increased* activation during anticipation of gain (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008). Similarly, amygdala activity is increased in response to positive stimuli in extroverted

participants as well as to negative stimuli in anxious individuals (Canli, Sivers, Whitfield, Gotlib, & Gabrieli, 2002). These findings suggest that, rather than solely arising from an absolute alteration of function (e.g. decreased attentional control), emotional disorders may also reflect alterations in the valence of information to which the systems preferentially react (e.g. decreased attentional control for negative information and increased control for positive). Accordingly, the interventions reviewed in this paper which alter attention to emotional information, may be understood as altering this preference rather than fundamentally changing the efficacy of the system.

Generally however, the neuroimaging data compliment the behavioral findings in that the most commonly reported neuroimaging abnormalities in the emotional disorders would be expected to lead to negative attentional biases. These abnormalities, increased amygdala and decreased frontal activation in response to attended negative stimuli, are evident in both depression and anxiety and lead to the prediction that interventions which alter the function of either one or both of these systems will influence emotional attention and in turn current anxious and depressive symptomatology.

Can the Effects of Treatment on Cognition be Disentangled from the Effects of Mood?

The interpretation of studies which investigate the effects of treatments on cognition can, paradoxically, be hampered when the treatment is effective. The problem is particularly acute in studies of clinical populations in which treatments are expected to improve clinical state. These studies inevitably compare groups which differ on two accounts; exposure to treatment (e.g. administration of antidepressant vs. placebo) and current levels of psychopathology (e.g. mood). While such studies

are essential to examine the effects of a treatment on the relevant population, it is difficult to be certain whether any differences observed in behavior or neural activity reflect the direct action of the intervention or are general effects of clinical status. The influence of this confounding factor can be reduced by studying non-clinical populations who generally do not experience profound changes of mood and who can thus provide important complimentary data to the clinical studies. As the critical issue in the current paper concerns the mechanisms by which treatments may work we will consider both studies of clinical populations and those solely involving non-clinical participants.

Pharmacological Methods of Modulating Attention to Emotional Information

Neurochemical probes have been used to examine how neurotransmitter function may modulate attentional bias both in healthy volunteers and patients. One key strategy has been to see whether biases apparent in depression and anxiety can be mimicked by depletion of the neurochemicals known to be involved in these disorders.

Tryptophan Depletion

The synthesis of serotonin in the brain is dependent on the availability of its precursor amino acid, tryptophan, from plasma. Acute administration of an amino acid mixture that selectively lacks tryptophan is effective in decreasing availability of tryptophan to the brain through processes of increased protein synthesis (lowering plasma tryptophan levels) and increased competition for transport across the blood-brain barrier (Reilly, McTavish, & Young, 1997). Tryptophan depletion (TD) transiently lowers mood in recovered depressed patients, although there is no

consistent effect on mood in healthy volunteers (Ruhe, Mason, & Schene, 2007). Recently, however, TD has been used as an experimental tool to examine the role of serotonin in the processing of emotional information in healthy volunteers (Booij, Van der Does, & Riedel, 2003). That TD is seen to effect cognition in non-clinical participants without altering mood suggests that cognitive measures, such as the attentional tasks examined in this paper, provide a more proximal or, at least, more sensitive marker of the effects of this intervention than mood measures. A number of studies (see Table one) have suggested that reduction of serotonergic function using TD increases the interference associated with negative words in emotional Stroop tasks, both in never (Evers, van derVeen, Jolles, Deutz, & Schmitt, 2006) and previously depressed populations (Hayward, Goodwin, Cowen, & Harmer, 2005; Munafò, Hayward, & Harmer, 2006). Interestingly, a study in which participants took tryptophan supplementation, an intervention predicted to increase serotonergic function, suggested that attention towards negative words was decreased in females (Murphy, Longhitano, Ayres, Cowen, & Harmer, 2006). However, other studies have produced inconsistent results. First, in previously depressed participants TD was found to slow responses in the emotional Stroop task to positive words suggesting increased attentional interference from these positive cues (Booij et al., 2005). A further study found no effect of TD on a visual-probe task involving threat related words (Merens, Booij, Haffmans, & Van der Does, 2008). Thus, while TD demonstrably influences the processing of emotional information, there is a degree of inconsistency to this effect.

Two neuroimaging studies have investigated the effects of TD on tasks in which emotional valence was manipulated, although neither explicitly manipulated attention. Both reported increased amygdala activation in response to negative stimuli

following TD, although this effect was qualified by participant characteristics, which may explain some of the variance in the behavioral data. Thus in a non-clinical sample TD increased amygdala activity to fearful vs. happy faces but only in those with high scores on the behavioral inhibition subscale of the BIS/BAS measure (Carver & White, 1994; Cools et al., 2005). Similarly, a second study reported increased amygdala activation following TD in a group of healthy women, but only those with a family history of depression (van der Veen, Evers, Deutz, & Schmitt, 2007).

Taken as a whole, these findings suggest that TD increases attention to negative emotional information and that its effect is associated with alteration of amygdala function; however, as has been noted using non-attentional measures of cognition (Robinson, Cools, Crockett, & Sahakian, 2009), this effect is qualified by individual differences in the participants.

Table one about here

Antidepressant Administration

An alternative strategy in the investigation of the effects of neurotransmitter function on attentional bias is to characterize the effects of the pharmacological treatments of the emotional disorders. Serotonergic function can be potentiated using antidepressant medications which specifically block the reuptake of serotonin from the synapse, a strategy recommended in the treatment of both depression and anxiety (NICE, 2004, 2007; Nutt, 2002). A number of experimental studies have assessed the influence of these serotonergic antidepressants on emotional attention in non-clinical groups (see Table one). A single dose of the antidepressant citalopram was associated

with an increased bias towards positive words in a visual-probe task (Browning, Reid, Cowen, Goodwin, & Harmer, 2007), whereas seven days of citalopram decreased attention to briefly presented fearful faces, an effect not seen with the norepinephric antidepressant reboxetine (Murphy, Yiend, Lester, Cowen, & Harmer, 2009). As predicted and contrary to the effects of TD, serotonergic antidepressants decrease amygdala activation to negative stimuli in both clinical (Fu et al., 2004; Sheline et al., 2001) and non-clinical populations (Arce, Simmons, Lovero, Stein, & Paulus, 2008; Del-Ben et al., 2005; Harmer, Mackay, Reid, Cowen, & Goodwin, 2006; Murphy, Norbury, O'Sullivan, Cowen, & Harmer, 2009). There is less evidence that antidepressants alter activity in frontal control regions, two studies report such an effect (Fales et al., 2009; Kennedy et al., 2001) although both of these involve clinical populations indicating that the findings may be secondary to improved clinical status rather than treatment effect. An event related potential (ERP) study has examined the effects of citalopram and reboxetine on the processing of emotional information in healthy volunteers (Kerestes et al., 2009). The high temporal acuity of ERP allowed the authors to demonstrate that both antidepressants influenced processing relatively shortly after stimulus presentation (250ms) with the effect being found in a component of the ERP known to be sensitive to spatial attention (Eimer, Holmes, & McGlone, 2003). The neuroimaging findings are thus consistent with an initial effect of antidepressants on the amygdala, with alteration of frontal control regions occurring later on in treatment and potentially reflecting improvement in clinical status. Interestingly, a single study has demonstrated that reboxetine also reduces amygdala activity to negative stimuli (Norbury, Mackay, Cowen, Goodwin, & Harmer, 2007) despite apparently having no effect on spatial attention to threat (Murphy, Yiend et al., 2009). A possible explanation of this discrepancy is provided

by recent models of norepinephric function which suggest that it acts specifically as a temporal filter in the control of attention (Aston-Jones & Cohen, 2005). Thus the behavioral effects of norepinephric manipulation may best be assessed using measures of the deployment of attention in time rather than space. De Martino and colleagues (De Martino, Strange, & Dolan, 2008) report a series of three studies which examine the influence of the beta-blocker propranolol and reboxetine on an emotional version of the attentional blink task, which specifically assesses the deployment of attention in time. The authors report a generally deleterious effect of propranolol on attentional function in that it caused poorer task performance regardless of stimuli salience. Reboxetine was found to improve task performance, although only in trials involving negative emotional stimuli. No positive stimuli were used in the study limiting conclusions as to the specificity of reboxetine's effect although they would be in keeping with its effect on attention being primarily evident in the temporal domain.

Together these studies indicate that serotonergic antidepressants alter attention to emotional information by encouraging a relatively more positive bias. Again these effects are associated with an effect of the medication on amygdala function.

Alternative Pharmacological Strategies

Based on clinical findings suggesting that acute administration of glucocorticoids reduce the symptoms of Post Traumatic Stress Disorder (PTSD) (Schelling, Roozendaal, & De Quervain, 2004), Putman and colleagues (Putman, Hermans, Koppeschaar, van Schijndel, & van Honk, 2007) used an emotional Stroop task to demonstrate that a single dose of the glucocorticoid cortisol reduced interference from masked negative stimuli (fearful faces) in healthy men. The same group had previously reported a similar effect when a single dose of testosterone,

which has antidepressant activity (Pope, Cohane, Kanayama, Siegel, & Hudson, 2003), was administered to females (van Honk, Peper, & Schutter, 2005). Lastly a single dose of the benzodiazepine diazepam, which has acute anxiolytic effects, has been found to increase attentional bias towards masked happy faces in a non-clinical population (Murphy, Downham, Cowen, & Harmer, 2008) with a complementary effect of reduced amygdala activation to emotional stimuli being reported for another benzodiazepine, lorazepam (Paulus, Feinstein, Castillo, Simmons, & Stein, 2005). Thus a diverse range of medications, all of which have antidepressant or anxiolytic activity, have been found to reduce negative or increase positive attentional bias.

Summary

A number of pharmacological interventions have been shown to alter attention to emotional stimuli. Taken as a whole the behavioral data suggest that interventions which improve anxiety or depression (tryptophan supplementation, antidepressant medication, steroids, benzodiazepines) tend to result in attention being directed away from negative and towards positive stimuli. Tryptophan depletion, which leads to a worsening of symptoms in vulnerable individuals, tends to have the opposite effect on attention. As can be seen from table one, the majority of these effects are seen early on in the deployment of attention, with a number of studies demonstrating an effect with masked stimuli. The timing of the attentional effects suggests that these interventions are altering the function of the bottom-up, stimulus appraisal system; a conclusion supported by the neuroimaging studies in which altered amygdala activity in response to negative stimuli is the most common finding.

Cognitive Behavioral Therapy (CBT) is a complex psychological intervention which has been developed specifically to change the patterns of thinking and behavior which impact on how an individual interacts with the environment and their resulting emotional state (Hollon, Stewart, & Strunk, 2006). CBT is recommended as a first line treatment for both depression and anxiety (NICE, 2004, 2007). A single study examining the effect of CBT on attentional function in anxiety disorder suggests that it reduces the negative attentional bias found pre-treatment (Mathews, Mogg, Kentish, & Eysenck, 1995). However, as discussed above, such a finding may be attributed to non-specific effects of clinical status rather than as necessarily a direct effect of treatment. Unfortunately, the complexity and variability of CBT can limit the extent to which it may be applied in controlled experimental trials. Perhaps because CBT is difficult to administer in experimental studies, there has been an increasing interest in developing simpler cognitive tasks which target the key hypothesized emotional processes and which lend themselves to controlled experimentation. While many of these tasks involve the explicit and effortful control of emotion (McRae et al., 2009; Ochsner & Gross, 2005; Phan et al., 2005), a number of techniques have been developed recently to specifically alter the habitual deployment of attention to emotional information (Dandeneau, Baldwin, Baccus, Sakellaropoulo, & Pruessner, 2007; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). The most commonly used technique (e.g. MacLeod et al., 2002) employs a variant of the visual probe task (see Figure one) in which the location of the probe is constrained such that it always replaces the neutral (for “avoid-threat” training) or negative (for “attend-threat” training) word. The task involves many experimental trials over the course of which participants learn to direct attention towards the type of stimuli which predict the probe location; e.g. if the probe always replaces negative stimuli participants

develop the habit of attending to negative stimuli generally, a negative attentional bias. Importantly there is increasing evidence that using such tasks to encourage a positive attentional bias (“avoid-threat” training) in clinical populations results in improvement in symptoms (Amir, Beard, Burns, & Bomyea, 2009; Dandeneau et al., 2007; Eldara, Ricona, & Bar-Haim, 2008; Hazen, Vasey, & Schmidt, 2008; Schmidt, Richey, Buckner, & Timpano, 2009). Concerns about the generalizability and duration of these training effects have to some extent been countered by preliminary evidence that the beneficial effects on anxiety symptoms persist for at least four months after training (Schmidt et al., 2009). A number of studies have assessed the effects of these so called “attentional training / attentional bias modification” tasks on measures of emotional attention (see Table 2) in both clinical and non-clinical populations. Generally the tasks are seen to influence attention in the manner expected although, as can be seen from Table 2, they have only ever been shown to influence attention to unmasked stimuli presented for 500ms or longer. A caveat to this observation is that the training tasks themselves generally involve a version of the visual probe task in which stimuli are presented for 500ms, raising the possibility that earlier effects on attention may be observed if the training task was altered to present stimuli for a shorter time. However, the published data to date differ from those involving pharmacological manipulations in which effects are reported during earlier stages of information processing. If this behavioral observation is valid it would suggest that cognitive training tasks and pharmacological interventions may alter distinct mechanisms of attentional control, a hypothesis that has previously been raised by a number of authors (DeRubeis, Siegle, & Hollon, 2008; Harmer, 2008). We have recently completed a neuroimaging study which tests this view; the effect of attentional training in healthy volunteers was assessed (Browning et al. unpublished

data) using an fMRI paradigm that varied both emotion and attention (Pessoa, Padmala, & Morland, 2005). The study indicated a significant effect of the training on activity in the IPFC and rostral ACC with no effects demonstrable in the amygdala. In keeping with their role in mediating attentional control, activity in the IPFC and ACC was increased specifically when participants' attention was directed in the opposite direction to that encouraged by the training task, that is when the need for control was high. Interestingly, a number of studies have suggested that the explicit reappraisal of emotion is mediated by changes in similar areas (McRae et al., 2009; Ochsner & Gross, 2005; Phan et al., 2005). When considered together with the neuroimaging studies reviewed above in which pharmacological manipulation was seen to alter amygdala activity, these results support the conclusion that cognitive and pharmacological interventions could target distinct processes in the control of emotional attention.

Summary

Cognitive training tasks (also known as cognitive bias modification tasks) have been shown to alter both attention to emotional information and clinical status in a predictable manner, though further studies deploying the experimental tasks in clinical populations are needed. The extant results suggest that this effect occurs later in the deployment of attention than that found with pharmacological manipulations raising the possibility that different attentional control mechanisms are targeted.

Synthesis

A variety of techniques have been shown to alter emotional attention in clinical and non-clinical populations. Across all of these methodologies, interventions

which improve anxiety and depression also cause attention to be preferentially deployed away from negative and towards positive information. The greatest amount of data is available for the pharmacological manipulation of the serotonergic system and for the use of cognitive attention training tasks. Characterization of the attentional effects of these interventions using both behavioral and neuroimaging outcomes suggests that they target different components of the attentional control system. Specifically pharmacological modifications appear to alter the initial deployment of attention, via an effect on the amygdala based appraisal system whereas cognitive training interventions may influence attention some time later, possibly via an effect on frontal control regions.

Implications for Treatment

Current evidence supports the efficacy of serotonergic antidepressants in the treatment of both anxiety and depression. Attentional training interventions have initial evidence suggesting efficacy in anxiety (MacLeod et al., 2009) but have yet to be applied to depressed groups (although a single positive study has been reported in a non-clinical dysphoric group; Wells & Beevers, 2009). However, in real world situations, the ability of either pharmacological or cognitive treatments to induce remission is at best moderate (for example DeRubeis et al., 2005 report remission rates of 40-50%). A number of studies have examined the combination of psychotherapy and antidepressant medication with mixed results (Foa, Franklin, & Moser, 2002; Furukawa, Watanabe, & Churchill, 2007; Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004), however all of these studies have used complex psychotherapeutic interventions rather than procedures designed to target specific cognitive systems, such as attentional training. An intriguing possibility raised by the

observation that antidepressant medication and cognitive training influence distinct information processing stages is that, if combined, their effects on attention may be additive. If true, this would predict that concurrent administration of both interventions in a clinical setting would improve efficacy over either on its own. However, this prediction rests on the untested assumption that the two interventions combine additively. As an alternative, it is conceivable that the learning which underlies the cognitive training task depends on an intact emotional signal provided by the amygdala; that is, in order to train attention to emotional stimuli the participant must be able to detect the emotional content of the stimulus, if detecting this signal depends on amygdala function then antidepressant treatment, which can interfere with this function, may block the effects of training. A study in which the effects of the combination of these interventions on attentional function were gauged would be relatively simple to design allowing the competing hypotheses to be tested. Lastly, it is worth noting that a number of alternative augmentation strategies exist which may bolster the effects of attentional training. In particular, D-Cycloserine, a partial NMDA agonist, has been shown to facilitate learning with early studies suggesting that it may be therapeutically useful when combined with psychotherapy (Norberg, Krystal, & Tolin, 2008; Wilhelm et al., 2008). It has yet to be demonstrated that this agent can augment the acquisition of attentional habits, but were this to be the case then it seems reasonable to hypothesize that it would increase the efficacy of training.

Are These Results Relevant to Depression?

A quick appraisal of the studies summarized in tables one and two demonstrates that both pharmacological and psychological manipulations of attention have been assessed using relatively brief stimulus presentations, with all but one of

the studies presenting stimuli for 700ms or less. Consequently it may be easier to argue that these findings are relevant to anxiety, which is associated with perturbations of early attentional deployment, than to depression, which is associated with later effects (Mathews & MacLeod, 2005). Indeed, the single study which employed longer presentation times (Wells & Beevers, 2009) presented stimuli for a much longer duration than that reported in the depression studies. It is not necessarily the case that there are no effects at the latencies typically reported for depression but rather that the studies which would assess these effects have yet to be performed or published. If the modification of attention is indeed relevant to the treatment of depression then it would be expected that both pharmacological and cognitive interventions would alter attention when measured at 1000ms. In addition, as suggested by the anxiety literature, reduction of the negative attentional bias measured at 1000ms using a training paradigm would be predicted to improve the symptoms of depression.

Future Directions

Although we have focused on using measures of emotional attention to dissect the effects of clinical and experimental interventions, the same measures may also be sensitive to individual differences in genetic risk. For example, the long allele of the promoter region of the serotonin transporter gene (5-HTTLPR), which may confer resistance to emotional disorders (Munafò et al., 2009), has recently been found to be associated with a positive attentional bias (Fox, Ridgewell, & Ashwin, 2009). Alterations in measures of attentional bias may thus provide a proxy marker by which both risk factors and treatment can be compared, within sub-groups of patients and ultimately within a single individual. The identification of intermediate processes,

such as attentional bias, which are believed to play a key role in the transition of risk to illness and treatment to response, is an essential first step in tailoring treatments to individual patients. An interesting initial approach to this issue would be to assess the interaction between genotype and attentional modification; specifically, do particular genotypes increase or decrease the effects of antidepressants and cognitive training on attention?

Conclusion

In the current review we have argued that the alteration of attentional bias (assessed using both behavioral and neuroimaging outcomes) is a sensitive, proximal measure of treatment effect for the emotional disorders. We have demonstrated that both pharmacological and cognitive interventions are able to alter attentional biases and that they seem to do so via distinct mechanisms. Future work needs to compare these manipulations directly using similar outcome measures to understand to what extent they have similar and distinct actions. By unifying our understanding of evidence-based pharmacological and psychological treatments of emotional disorders, recent advances in cognitive-emotional science provide a guiding framework by which such treatments can be rationally combined and developed. This exciting approach offers a theoretically based, clinically informed opportunity to improve treatment efficacy.

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Table 1: Studies Which Have Reported the Effects of Pharmacological Manipulations on Measures of Attention to Emotional Information.

Paper	Intervention	Population Studied ^a	Attentional Task	Type and Duration of Stimulus	Duration of Stimulus ^b	Result	Notes
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(Evers et al., 2006)	Tryptophan depletion	Non-clinical females (n=19 using a within subject design)	Emotional Stroop	Positive, negative and neutral words	200ms	Increased interference of negative words after TD	Result derived from error rate. No effect for reaction time
(Booij et al., 2005)	Tryptophan depletion	Patients in complete or partial remission from depression who were still taking SSRI medication (n=20 using a within subject design)	Emotional Stroop	Positive, negative and neutral words	Up to 1500mms	Increased interference from positive words	Complex experimental design with participants completing cognitive tests on four separate occasions
(Hayward	Tryptophan	Patients (n=24)	Emotional	Negative and	400ms	Increased	Effect seen in both

<p>et al., 2005)</p>	<p>depletion</p>	<p>with a history of depression who no longer met diagnostic criteria and healthy controls (n=24)</p>	<p>Stroop</p>	<p>neutral words</p>		<p>interference from negative words</p>	<p>clinical and control group. Counting version of the emotional Stroop task used.</p>
<p>(Munafò et al., 2006)</p>	<p>Tryptophan depletion</p>	<p>antidepressant medication (n=24), no medication (n=24) and non-clinical controls</p>	<p>Emotional Stroop</p>	<p>Negative and neutral words</p>	<p>Unmasked (until response) or masked (14ms) conditions</p>	<p>Increased interference from negative words in both masked and unmasked conditions</p>	<p>Effect only seen in previously depressed group who were still taking medication</p>

		(n=24)					
		Patients (n=16		Neutral vs.			
		using a within		threat words			
		subject design) in		and			
(Merens et	Tryptophan	complete or partial	Visual	depression	500ms	No significant	
al., 2008)	depletion	remission from	probe	relevant vs.		effects.	
		depression who		positive			
		were still taking		words.			
		antidepressant					
		medication					
					Unmasked	Decreased	
(Murphy et	Tryptophan	Non-clinical	Visual	Positive,	(500ms) and	attention to	Result derived from
al., 2006)	Supplementation	females (n=19 per	probe	negative and	masked	negative words	error rate. No effect
		group)		neutral words	(14ms)	in unmasked	for males.

					conditions	condition	
					Unmasked	Increased	
(Browning et al., 2007)	Single dose of citalopram or placebo	Non-clinical group (n= 15 per group)	Visual probe	Positive, negative and neutral words.	(500ms) and masked (14ms) conditions	attention to positive words in both masked and unmasked conditions	
					Unmasked	Citalopram reduced	
(Murphy, Yiend et al., 2009)	Seven days of citalopram, reboxetine or placebo	Non-clinical group (n=14 per group)	Visual probe	Happy, fearful or neutral facial expressions	(100ms) and masked (16ms) conditions	attention to fearful face in unmasked condition	Effect seen only for citalopram, no effect of reboxetine
(Putman et	Cortisol or	Non-clinical males	Emotional	Fearful or	Masked	Decreased	

al., 2007)	placebo	(n=20 using within subject design)	Stroop	neutral facial expressions	(14ms) presentation	interference from fearful faces	
(van Honk et al., 2005)	Testosterone or placebo	Non-clinical females (n=16 using a within subject design)	Emotional Stroop	Fearful, happy or neutral facial expression	Masked (14ms) presentation	Decreased interference from fearful faces	No effect on happy faces. No mention of the effect of trial order in relevant analysis
(Murphy et al., 2008)	Diazepam or placebo	Non-clinical volunteers (n=12 per group)	Visual Probe	Fearful, happy or neutral facial expressions	Unmasked (100ms) or masked (14ms) presentation	Increased attention towards happy in masked condition	Authors argue that increased attention towards happy is similar to decreased negative bias as in the relevant trials happy

and neutral stimuli
are presented together
and the neutral
stimuli is relatively
more threatening.

^a Unless otherwise stated studies used a between subjects design.

^b Certain task designs (see figure one) allow inference as to the timing of the temporal effects of an intervention on attention. In studies which employ such a design and report significant findings the relevant duration is presented in bold.

Table 2

Studies Which Have Reported the Effects of Psychological Manipulations on Measures of Attention to Emotional Information.

Paper	Intervention	Population studied ^a	Attentional task	Type of stimulus	Duration of stimulus ^b	Result	Notes
(Mathews et al., 1995)	Seven session group CBT for anxiety management	Patients with GAD (n=24) were compared to non-clinical controls (n=23) both before and after treatment	Emotional Stroop and visual search	Negative and neutral words	Until response	Borderline significant reduction of negative attentional bias in the anxious group using emotional Stroop (p=0.06) and visual search (p=0.07)	Emotional Stroop task used cards rather than computer to present stimuli.

	Single session				Unmasked	Training	
(MacLeod et al., 2002)	of attend- threat or avoid-threat training.	Non-clinical (n=32 per group)	Visual probe	Negative and neutral words	(500ms) and masked (20ms)	influenced attention in unmasked condition	Two studies performed, both demonstrating similar effect.
		Non-clinical (n=12 per group) sample					
(Hazen et al., 2008)	Five sessions of avoid-threat or sham attentional training	with high score on worry scale (includes participants who would meet	Visual Probe	Negative and neutral words	500ms	Avoid-threat training reduced attention to negative words	

		diagnostic criteria for GAD)					
(Eldara et al., 2008)	Single session of attend- threat or avoid-threat attentional training.	Non-clinical (n=13 per group) children aged 7-12	Visual probe	Angry and neutral faces	700ms	Attend-threat training influenced attention	This effect was only significant for the faces used in training itself— no generalization to novel faces.
(Wadlinger & Isaacowitz, 2008)	Single session of attend- positive or avoid-positive training	Non-clinical volunteers (approx n=22 per group)	Eye tracking	Positive and neutral words	8000ms	Positive training caused decreased fixation on negative areas of images	Attentional training was visual probe type

<p>(Li, Tan, Quan & Liu, 2008)</p>	<p>7 sessions of daily avoid-threat/attend-happy or sham training</p>	<p>Non-clinical volunteers with high score on a social anxiety scale (n=12 per group)</p>	<p>Visual probe</p>	<p>Threatening and happy faces</p>	<p>500ms</p>	<p>Active training caused significant decrease in negative bias</p>	<p>Significant differences in measures of anxiety between groups at end of training may confound interpretation of attentional effects. The negative pictures were selected as being “threatening” rather than displaying a specific emotion. As the threatening pictures were paired with positive pictures these results could also be interpreted</p>
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							as showing an increase in positive attentional bias.
(See, Macleod, & Bridle, 2009)	14 sessions of daily avoid-threat or sham training	Non-clinical volunteers (approx n=19 per group)	Visual probe	Negative and neutral words	500ms	Avoid-threat training caused significant decrease in negative bias	Significant differences in trait and state anxiety between groups at end of training may confound interpretation of attentional effects
(Amir et al., 2009)	8 sessions of avoid-threat or sham training over 4 weeks	Patients with GAD (approx n=14 per group)	Visual probe	Negative and neutral words	500ms	Avoid-threat training caused significant decrease in negative bias	Significant differences in trait and state anxiety between groups at end of training may confound interpretation of attentional effects

<p>(Wells, & Beevers, 2009)</p>	<p>4 sessions of avoid-threat or sham training over 2 weeks</p>	<p>Non-clinical volunteers with BDI > 8 (n=17 per group)</p>	<p>Visual probe</p>	<p>Negative and neutral faces and pictures</p>	<p>Faces were presented for 3000ms, pictures for 4500ms</p>	<p>Avoid-threat training caused significant decrease in negative bias</p>	<p>Significant differences in depressive symptomatology between groups at end of training may confound interpretation of attentional effects. The stimuli were presented for an unusually long time.</p>
<p>(Dandeneau et al., 2007)</p>	<p>Single session of positive visual search or control</p>	<p>Non-clinical group (n=76/147 per study in two</p>	<p>Emotional Stroop (study 2a) and visual</p>	<p>Negative, positive and neutral words (Stroop task).</p>	<p>1200ms for Stroop task. During visual probe</p>	<p>Positive training caused decreased interference from negative words</p>	<p>A significant effect of training was only found in those with low self-esteem. The influence of</p>

training studies). For probe Happy, angry, task stimuli and increased self esteem was assessed analysis the (study 2b) neutral faces presented for interference from by splitting groups using groups were (visual probe **500ms** positive words a median split in study further task) during the Stroop one and by adding self divided into task. Positive esteem as a regressor in high and low training reduced study 2. A variety of self-esteem statistical techniques (see note) were used to analyze behavioral responses in the separate studies. Stimuli were presented for 3400ms during the visual search training.

(Dandeneau Single session Non-clinical Emotional Negative, 1200ms Trend level results

& Baldwin, 2004) of positive visual search or control training group (n=49 in total). For analysis the groups were further divided into high and low self-esteem by a median split Stroop positive and neutral words suggest training decreased interference from negative words

BDI = Beck Depression Inventory, CBT = Cognitive Behavioral Therapy, GAD = Generalized Anxiety Disorder

^a Unless otherwise stated studies used a between subjects design.

^b Certain task designs (see figure one) allow inference as to the timing of the temporal effects of an intervention on attention. In studies which employ such a design and report significant findings the relevant duration is presented in bold.

Legends for Figures

Figure 1

Behavioral methods of assessing emotional attention. Example trials from the two most common behavioral paradigms used to assess attentional function; the emotional Stroop (A) and visual probe (B) tasks. Behavioral tasks such as these are often the preferred method of assessing cognition as they do not rely on the self-report of internal states which is notoriously unreliable (Nisbett & Wilson, 1977).

During standard emotional Stroop tasks (A) participants are required to ignore the emotional content of a word stimulus while reporting its font color, the rationale being that the emotional aspect of the stimulus interferes with the required behavior and therefore slows response times. The demonstration of a specific slowing of response times to emotional stimuli is argued to demonstrate that more processing resources (i.e. attention) have been captured by the stimuli (Williams et al., 1996) although this interpretation has been disputed (Algom, Chajut, & Lev, 2004; Larsen, Mercer, & Balota, 2006). Emotional Stroop tasks are insensitive to the timing of attentional effects, instead they provide a general indication that task interference has occurred at some point. The one exception to this is when masked stimuli are presented; in this case the relevant stimulus is briefly presented and followed by a non-emotional mask which prevents explicit identification of the stimulus. In such cases it seems reasonable to assume that early stimulus appraisal processes lead to the task interference.

Controversy in the interpretation of Stroop data has led to the increased popularity of visual probe tasks (B). Based on paradigms developed by Posner and colleagues (Posner & Petersen, 1990) these have been argued to provide a purer estimate of

spatial attention. The most common variety of this task involves the brief presentation of emotional and neutral stimuli followed by a probe, to which the participant must respond, in the location of one of the stimuli (MacLeod, Mathews, & Tata, 1986). It is assumed that reaction time is improved if attention is focused at the location in which the probe appears, that is if the stimulus previously found at that location had drawn attention. An estimate of attentional bias for emotional stimuli is calculated by comparing reaction times when the probe is found in the location of emotional stimuli compared to when it is found elsewhere. An advantage of visual probe tasks is that they provide information on the temporal characteristics of attention, specifically they have been described as providing an estimate of attentional deployment at the time the probe is presented (Cooper & Langton, 2006).

Figure 1

