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ORIGINAL ARTICLE

Neurobehavioral Therapies in the 21st Century: Summary of an Emerging Field and an Extended Example of Cognitive Control Training for Depression

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Abstract The promise of a new generation of therapies targeted to address neurobiological mechanisms thought to underlie psychological disorders, particularly depression, using cognitive and behavioral techniques is discussed. Relationships between such neurobehaviorally focused therapies and other psychological and rehabilitative interventions are also discussed. Their potential utility as adjuncts to conventional treatment, and the importance of multi-method assessment in their evaluation are emphasized. Finally, initial data from a neurobehavioral ''cognitive control training'' (CCT) adjunctive intervention for severe unipolar depression is presented as an extended example. These data suggest that CCT aids in reducing both physiological mechanisms underlying depression as well as depressive symptomatology.

Key words Depression · Therapy · Neuroscience · fMRI

Introduction

The past century has seen increasing translation of basic cognitive science into interventions for psychological disorders. In the past decade, the cognitive science of clinical disorders has increasingly been informed by results from basic neuroscience. These bridges are just beginning to be translated into the clinic, and their potential has not yet fully been realized (e.g., Tamminga et al., 2002). This article will highlight the promise of such translations, particularly for unipolar depression, and will provide an

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example of initial work in this area being done in our lab. Ideally, this summary will help shape the thinking of investigators hoping to integrate neuroscience into behavioral treatment development research.

What is a neurobehavioral therapy?

We use the term ''neurobehavioral therapy'' to describe interventions that address biological mechanisms believed to underlie psychological disorders, in the same sense that pharmacological and surgical treatments address such mechanisms. Yet, they use behavioral methods to do so.

This concept is not a radical departure from conventional behavioral treatments. The earliest psychological treatments, stemming from Freud, were partly rooted in biological concepts. Early cognitive theorists such as William James also saw links between biological mechanisms and behavioral treatment, which have recently led to speculation regarding biological mechanisms underlying recovery in cognitive and behavioral therapies (e.g., Brewin, 2001; Corrigan, 2004; Tryon, 2005). Most recently, neuroimaging studies of cognitive and behavioral therapies (Brody et al., 1998; Farrow et al., 2005; Goldapple et al., 2004; Paquette et al., 2003; Roffman, Marci, Glick, Dougherty, & Rauch, 2005; Schwartz, 1998; Seminowicz et al., 2004; Siegle, Carter, & Thase, 2006; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006) as well as interpersonal therapy (Martin, Martin, Rai, Richardson, & Royall, 2001) have begun to highlight potential neurobiological mediators of symptom change.

A fundamental difference in the neurobehavioral therapies discussed here is that they are *designed* with specific biological mechanisms in mind. Thus, they often appear different from conventional psychological treatments designed to address observable symptoms or cognitive or behavioral manifestations of underlying mechanisms. Since they target one or a few biological mechanisms at a time, the primary dependent variable in examinations of these studies is not necessarily symptom change. Rather, a more complex strategy for examining efficacy, involving looking for change in both indices of underlying biological mechanisms as well as change in symptoms may be warranted (La Vaque & Hammond, 2002). In addition, few would deny that major psychological disorders such as depression are complex and multifaceted. Because these interventions are focused on one measure at a time, they may best be thought of as adjunctive interventions, and may not be appropriate for all patients. A strong emphasis on pre-treatment assessment of disruptions in one or a few biological mechanisms may be important for recommending neurobehavioral therapies.

Neurobehavioral therapies inherit from multiple lineages. Cognitive and behavioral therapies, which attempt to change specific cognitive and behavioral patterns by targeting mechanisms underlying those patterns represent major influences. ''Neurofeedback'' which uses EEG biofeedback to allow patients to directly modify neural function, is also addressed in the following sections. Finally, cognitive rehabilitation is devoted to remediation of neurological insults through exercises that affect and increase function in either areas that have been damaged, or in surrounding regions that may be useful in compensating for injuries (e.g., Christensen & Uzzell, 2000; Parentâe & Herrmann, 2003; Riddoch & Humphreys, 1994; Sohlberg & Mateer, 2001). Cognitive rehabilitation begins by identifying affected cognitive functions and brain regions through neuropsychological assessment and neuroimaging. Repetitive behavioral exercises are employed to strengthen aspects of cognition thought to be subserved by affected brain regions such as visuospatial processing or memory. Cognitive

rehabilitation has successfully been applied to post-stroke complications, memory disorders, and other brain-injury derived psychological conditions, and addresses many cognitive functions disrupted in psychological disorders such as attention, memory, and cognitive organization. The success of these methods suggests that behavioral exercises may show promise in addressing often similar disruptions of brain function associated with other psychological disorders.

There is also a long history of interventions that purport to treat brain-based aspects of disorder, which have not been subjected to rigorous testing or validation studies. Other apparently efficacious interventions have been suggested to work through specific brain mechanisms but these explanations have not been directly tested or empirically supported. For example, recovery in eye-movement-desensitization reprocessing has been attributed to induction of brain processes that may be useful in reducing the hippocampally mediated associative strength of certain episodic memories (e.g., Stickgold, 2002); while tests of this hypothesis have been proposed, they have not been studied, and other possible mechanisms of action for recovery in this type of intervention have been suggested (e.g., Taylor et al., 2003). For purposes of this review, such interventions will not yet be considered ''neurobehavioral.'' Rather, interventions will be considered neurobehavioral if they were designed with the principals of neuroscience in mind, if strong basic science supports relevant underlying mechanisms, and if there is evidence associating the intervention with change in relevant basic mechanisms as well as change in symptoms.

Why neurobehavioral therapies?

Effective psychological treatments exist for most major mental disorders, either as single interventions or when added to pharmacotherapy. As such, it is important to justify why development of a novel class of behavioral interventions should be considered.

First, current therapies, although empirically validated, are incompletely and often unpredictably effective. Major depression, one of the best-researched and most common psychiatric disorders, is an excellent example. Major depressive disorder affects 7–12% of men and 20% of women across the life-time (Kessler et al., 2003). Antidepressants and modern psychotherapies are effective for only 40–60% of depressed individuals (APA, 2000). In particular, depressive severity is often associated with poorer or more delayed treatment response (Joyce & Paykel, 1989; Thase & Friedman, 1999). Severely depressed individuals are notoriously difficult to treat with either psychotherapy or psychopharmacology (Elkin et al., 1989; Thase & Friedman, 1999; Thase et al., 1997). Although CBT and pharmacotherapy are comparably effective in more severely depressed individuals, mega-analysis suggests that both modes of treatment are associated with relatively high dropout rates (~25%) and incomplete recovery (post-treatment mean Beck Depression Inventory scores >14, Hamilton Rating Scale scores >10) (DeRubeis, Gelfand, Tang, & Simons, 1999). Meta-analyses also suggest that fewer than half of participants achieve remission with either psychotherapy or medication (Casacalenda, Perry, & Looper, 2002) and relapse appears more likely in individuals who do not fully recover during a time-limited course of therapy (Jarrett et al., 2001; Thase et al., 1992). Thus, more intense plans of intervention, such as daily sessions of CBT, have been employed with severely depressed patients (e.g., Thase et al., 1996; Thase, Simons, Cahalane, McGeary, & Harden, 1991). However, obtaining the resources for such a therapist-intensive treatment is impractical in most real-world settings. New interventions that target underlying brain mechanisms could help to treat such severely ill patients.

A second reason for pursuing neurobehavioral therapies is that they are being developed specifically to address underlying mechanisms, which could represent obstacles to recovery in traditional therapies. Targeting these mechanisms early, or in conjunction with traditional therapies, could thus lead to increased recovery in traditional interventions. For example, associations of recovery in CBT and central nervous system dysfunction (Siegle et al., 2006; Thase et al., 1996), could suggest that biological mechanisms represent mediators to recovery. More directly, CBT can be viewed as a method that helps patients exert greater executive control over otherwise automatic emotional reactions. Multiple conditions treated effectively with CBT are characterized by decreased prefrontal function, which has been identified as a primary mechanism underlying executive control (e.g., Koechlin, Ody, & Kouneiher, 2003; Wager, Jonides, & Reading, 2004). Decreased prefrontal control has been observed in unipolar depression (Baxter et al., 1989; Bench, Friston, Brown, Frackowiak, & Dolan, 1993; Mayberg et al., 1999; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002; Siegle, Thase, Steinhauer, Stenger, & Carter, submitted), bipolar disorder (Blumberg et al., 2004; Clark, Iversen, & Goodwin, 2002; Meyer et al., 2004), obsessive compulsive disorder (van den Heuvel et al., 2005), addiction (Fisk, Montgomery, Murphy, & Wareing, 2004; Goldstein et al., 2004; Hester & Garavan, 2004), and schizophrenia (Carter et al., 1998; Leiderman & Strejilevich, 2004; Lewis, Volk, & Hashimoto, 2004; MacDonald & Carter, 2003; Macdonald et al., 2005; Morey et al., 2005). Having adjunctive interventions that target prefrontal control, rather than specific symptoms, could improve the efficacy of conventional therapies for these populations, by allowing patients to overcome specific roadblocks to their success in these therapies.

A third reason for pursuing neurobehavioral therapies is that they may be easier to implement than traditional therapies. Because these techniques often do not explicitly require dealing with aspects of life that are difficult for patients to confront during the therapy (e.g., discussing difficult emotional topics, family circumstances, or finances) many often-noted obstacles to recovery in traditional therapies are not present in some neurobehavioral therapies. Thus neurobehavioral therapies might be most appropriate, particularly as adjunctive treatments, for patients who are not yet ready to talk about their emotions or who have the most difficult time in traditional verbally oriented therapies, e.g., the persistently mentally ill. In fact reports from every investigator we have talked to suggest that patients like and look forward to completing neurobehavioral exercises.

A fourth reason to develop neurobehavioral therapies is that they may not require the same level of training or resources to administer as traditional psychotherapies or medication. Rather, like cognitive rehabilitation, neurobehavioral therapies often consist of exercises that can be automated or administered by a trained technician who is not necessarily a clinically expert therapist. Importantly, we are not suggesting that trained clinicians be removed from treatment. Rather, like other adjunctive treatments such as bibliotherapy, neurobehavioral therapies may represent useful comparatively easy-to-administer components of a complete treatment regimen.

A final reason to explore neurobehavioral therapies is that they stand to integrate many of the benefits of both psychotherapy and psychopharmacology. In particular, they allow for the increased self-efficacy and low side-effect profiles of psychotherapies and the biologically informed mechanistic specificity of pharmacological agents.

Potential insights from the development of non-behavioral neuroscience-based treatments

In contrast to psychotherapy, brain correlates of disorder have long been used to inform advancement and development of other treatments. In neurosurgery, activity in a given region is associated with symptoms, and thus, the offending brain area is removed (e.g., cingulotomy for obsessive-compulsive-disorder). The invasive nature of these procedures and associated side-effects prevent such treatments from common use. That said, newer treatments such as deep brain stimulation (Mayberg et al., 2005), repetitive transcranial magnetic stimulation (rTMS), and vagal nerve stimulation (VNS) all attempt to directly affect relevant aspects of brain function (for a review, see Hirshberg, Chiu, & Frazier, 2005). Understanding how these treatments work, and correlates of manipulation of brain function on behavior will likely be able to inform the development of relevant behavioral means to affect the same conditions.

Pharmacological interventions for these same conditions have long been informed by brain function (e.g., Drevets, 1994; Meyer, 1986). Technology is increasingly becoming available to examine changes in brain function using the same processes examined in drug development, involving identification of putative biological mechanism through basic research, finding agents that target that mechanism, and finally, translation to clinical trials. Other lessons from pharmacological interventions are also useful to consider. For example, trials of drugs that target a single mechanism often suffer from disappointing outcomes because illnesses are multifactorially determined. Thus, characterization of dose-response relationships in large trials, examining the blending of interventions with observed dose–response relationships, and using new agents as adjuncts are often fruitful strategies.

Why now?

The last decade has, for the first time, allowed understanding of brain mechanisms associated with symptoms across multiple psychological disorders, as discussed in reviews of biological contributions to substance abuse (e.g., Nutt, 1999), mood disorders (e.g., Drevets, 2000; Phillips, Drevets, Rauch, & Lane, 2003), anxiety disorders (Bell, Malizia, & Nutt, 1999; Dager, Layton, & Richards, 1996), schizophrenia (e.g., Barr, Bilder, Goldberg, Kaplan, & Mukherjee, 1989; Chaturvedi & Thakur, 2003), and Alzheimer's disease (Felician & Sandson, 1999).

These advances have come largely due to the development of neuroimaging and physiological assessment technologies in the last 10 years. For example, positron emission technology (PET) imaging allows understanding of resting metabolism, neurochemical receptor binding, and functional activity on the time course of tens of minutes throughout the brain. Functional magnetic resonance imaging (fMRI) allows understanding of the time course of brain activity throughout the brain on the time course of seconds. Electroencephalography and peripheral physiological measures allow insights into the time-course of brain function across the scalp, and specific regions that are well-connected to peripheral regions on the time-course of milliseconds. Together we can, for the first time, understand the time course of activity throughout the brain, in real-time in response to both emotional stimuli (e.g., Anderson et al., 2003) and not explicitly emotional cognitive tasks (e.g., MacDonald, Cohen, Stenger, & Carter, 2000). Thus, we can examine (1) what functional brain disruptions are associated with specific

disorders and (2) what changes in brain function are associated with recovery. This information can be used to generate causal models that allow prediction of what structures or systems it would be important to target with behavioral interventions and testing of whether interventions actually target them.

Evaluation of neurobehavioral therapies

As suggested by the previous sections, assessment of the efficacy of neurobehavioral interventions may be somewhat different than assessment of traditional therapies. Of course an ultimate test of an intervention's efficacy may be its effects on symptoms. Yet, the most direct targets of these therapies will be aspects of brain function. Just as behavior therapies directly attempt to change behaviors, and thus behaviors are assessed, we suggest that testing relevant aspects brain function before and after neurobehavioral treatment will be an integral part of establishing whether the treatments are accomplishing what they set out to accomplish. This focus on assessing change in mechanisms is not new to neurobehavioral therapies. The same goal of assessing change in relevant mechanisms using new technologies has, in fact, been levied for cognitive therapy (Kihlstrom & Nasby, 1981), though such testing has often been neglected, potentially because this testing is, in many ways, more difficult for CBT. It is more differentiated, the mandate is broader, and there is a great deal of discretion in how it is administered, even when standardized protocols are used.

In contrast, neurobehavioral therapies are readily evaluated on dimensions other than symptoms. Since the interventions specifically target aspects of brain function, their efficacy is dependent on whether they achieve change in those aspects. Functional neuroimaging allows on-line examination of brain processes. Reduction in abnormalities of brain function associated with the intervention could lead to increased understanding of relationships between cognitive and physiological aspects of disorder and recovery and validate the proposed mechanisms of action in treatment. Moreover, if change in symptoms does not occur as predicted, examining change in brain reactivity is still important. As shown in Table 1, any configuration of change in symptoms, brain activity, or both will provide valuable data for such targeted interventions.

A final consideration regarding evaluation involves the potential for placebo effects. Interventions purporting to ''train your brain'' to act differently could be considered to have extraordinary intuitive appeal. As most patients will not be sophisticated enough to fully evaluate the underlying neuroscience, and may trust that these interventions are from the latest most rigorous scientific developments, they may be especially persuaded that they will be of benefit. Moreover, patients will have regular supportive interactions with technicians who hope they get better (potentially, more regular than in many drug trials). Thus, it may be important to evaluate these interventions vs. similarly structured placebo interventions with similar neuroscientific appeal as that offered for the active intervention.

What's been done so far?

Multiple neurobehavioral therapy trials have been published but have not been collected under the same name. Examples below illustrate their breadth and relative success.

Table 1 Interpretation of relationships between change in symptoms and brain function in neurobehavioral therapies

		Change in Symptoms	
		Observed	Not observed
Change in brain function	Observed	The intervention worked by the predicted mechanism. The intervention may be an important part of recovery from depression	The intervention targeted the proposed mechanism, but change in this mechanism does not translate immediately to symptom change. Changes in brain function may precede symptom change or perhaps, may suggest that change in the mechanism is not, alone, a key to recovery. Recovery in other therapies that similarly change brain function may be moderated by other factors
	Not observed	Increased function in the targeted brain mechanism is not a key part of recovery. Change in this aspect of brain function may not be a key ingredient for other therapies	The intervention did not work, possibly because it did not achieve change in the proposed underlying mechanism. To fully test hypothesis, the intervention must be revised

Neurofeedback

In ''neurofeedback'', electroencephalogram (EEG) biofeedback is used to help participants to monitor and manipulate the activity of relevant aspects of brain function on-line. The general method involves identifying aspects of brain function for which disruptions can be indexed by quantitative EEG, and allowing patients to monitor these markers with the goal of changing them. Basic research on EEG disruptions has led to interventions with demonstrated efficacy for attention deficit hyperactivity disorder (e.g., Butnik, 2005; Cho et al., 2002; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Lubar, Swartwood, Swartwood, & O'Donnell, 1995; Monastra, 2005; Monastra, Monastra, & George, 2002), addiction (Goldberg, Greenwood, & Taintor, 1976; Trudeau, 2005), obsessive compulsive disorder and generalized anxiety disorder as well as depression (for reviews, see Hammond, 2005; Moore, 2000).

For example, prefrontal EEG α-asymmetry is a hallmark of depression associated with poor emotion regulation (Davidson, 1998; Jackson et al., 2003). EEG asymmetry has consistently been associated with disruptions in prefrontal cortex function (e.g., Davidson, 2003). Thus, initial neurofeedback approaches to depression have involved regulation of α-asymmetry (Baehr & Baehr, 1997; Baehr, Rosenfeld, & Baehr, 1997; Rosenfeld, Baehr, Baehr, Gotlib, & Ranganath, 1996). Still, the ability to localize regions of specific disturbance using only EEG is unclear, and thus assessment of whether the implicated structures are addressed by these interventions may best be examined in conjunction with other technologies. Similarly, there is some controversy about the mechanisms of neurofeedback, and whether changes in specific EEG components lead to predicted changes in underlying brain function (Egner, Zech, & Gruzelier, 2004); research relating basic mechanisms to change in neurofeedback is thus ongoing (e.g., Lubar, 1997). Other technologies with better spatial localization ability such as fMRI are

being evaluated as vehicles for neurofeedback (Yoo & Jolesz, 2002). Still, these data suggest that behaviorally induced change in brain function can lead to cognitive change.

Talk therapies informed by principals of brain function

Principals of neuroscience have also been employed in the context of talk therapy. Schwarz and Beyette (1996) have built on a history of neuroimaging data to create a behavioral intervention for obsessive compulsive disorder that targets disruptions in basal ganglia and limbic function. Their basic work involved imaging patients before and after traditional exposure and response prevention treatments for OCD (Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996), observation of brain areas that changed in function with treatment, and finally, reasoning back to how to directly address those functions. The resulting therapy has components that, in many ways, resemble techniques used in other cognitive therapies, e.g., encouraging patients to reattribute obsessive thoughts to a biological cause rather than a personal inadequacy and refocusing attention on topics other than the obsessive thought. Yet, because these principles emerged from underlying imaging data, they have been able to parlay them into predictions regarding recovery.

Along similar lines, Strauman et al. (2006) has focused on the growing literature suggesting that depression is characterized by deficits in brain function associated with behavioral inhibition, activation, and goal pursuit to create a ''Self-System'' therapy, a brief structured intervention intended to improve self-regulation in service of goal attainment. The therapy involves teaching and practicing specific skills e.g., initiation of goal-promotion focused behavior, explicit goal evaluation, and restoring effective self-regulation. Strauman's group is using fMRI to understand whether brain function associated with goal pursuit and self-regulation changes as a result of the new therapy (Strauman, personal communication). Theoretical ways to tune behavioral interventions based on neuroscience perspectives have been advanced for a number of therapies and disorders, particularly dynamic therapies (Beutel, Stern, & Silbersweig, 2003; Cozolino, 2002; De Masi, 2004; Henningsen, 1998; Mancia, 2004; Westen & Gabbard, 2002); cognitive and behavioral perspectives have also been well represented (Brewin, 2001; Tryon, 2005). Potential pitfalls of relying too strongly on neuroscience in guiding therapies dependent on human relationships have also been considered (Fuchs, 2004; Lewis, 1994). To date, though, many of these theoretical perspectives have not yet been formally tested in published trials. Ideally this proliferation of theory will lead to more formal trials of neuroscience-informed psychotherapies in the near future.

Pharmacologically augmented behavioral therapies

Another promising direction involves augmenting behavioral therapies with pharmacological agents that enhance outcomes by affecting biological substrates of therapeutic response. For example, as systematic desensitization involves learning, initial experiments with an agent that, for a short time, increases learning rates (D-Cyclosterine, an NMDA agonist) have been demonstrated to decrease time to effective systematic desensitization for simple phobias (Ressler et al., 2004). Similarly, to the extent that exposure therapies involve re-consolidating emotional memories without fear associations, the use of an agent that, for a short time, decreases physiological mechanisms of anxiety responses in the context of exposure (propranolol)

has been proposed. Initial efficacy of such augmented exposure techniques has been demonstrated in animals (Debiec & Ledoux, 2004; Przybyslawski, Roullet, & Sara, 1999). In each of these interventions, the medications alone would not lead to permanent symptom change—rather knowledge of the neurobiology of disorder leads to the adjunctive use of medications as a catalyst for change.

Cognitive training exercises

Other neurobehavioral treatments are exercise based, following in the model of cognitive-rehabilitation. A history of neuropsychological testing and neuroimaging has identified deficits in prefrontal function in schizophrenia. Cognitive ''remediation'' exercises often oriented towards improving prefrontal executive function, particularly in combination with other more general intervention strategies, have frequently been observed to lead to improvement in aspects of cognitive function in this disorder (for reviews see Bellack, 2004; Krabbendam & Aleman, 2003; Kurtz, 2003; Twamley, Jeste, & Bellack, 2003), though not always above and beyond treatment as usual (e.g., Bark et al., 2003; Lewis, Unkefer, O'Neal, Crith, & Fultz, 2003). Still, while such exercises are often rooted in neuropsychology, the links between the exercises and change in neurobiological parameters are often not tested explicitly. Recently, Penades et al. (2002) found improved performance on tasks known to assess prefrontal function as well as decreased hypofrontality on SPECT scanning following training on tasks that require prefrontal activity in individuals with schizophrenia. Such ''neurocognitive rehabilitation'' exercises have also been proposed and used for treatment of other conditions associated with prefrontal dysfunction such as addiction disorders (Allen, Goldstein, & Seaton, 1997; Cunha & Novaes, 2004). Multiple groups are working on other neurobehavioral therapies and for other disorders, for which forthcoming evidence is compelling and exciting.

An extended example of research embodying these principles: cognitive control training (CCT) for unipolar depression

In the following sections we present our initial data and experiences in developing a neurobehavioral therapy for depression as an example. Steps in gathering the background to justify such an intervention, our implementation, and how we have begun to examine multi-method assessments of its efficacy are described. Severe unipolar depression was chosen because, as previously noted, depressive severity is often associated with poorer or more delayed treatment response in traditional interventions (Joyce & Paykel, 1989; Thase & Friedman, 1999). A largely automated adjunctive intervention that specifically targets underlying brain mechanisms could allow severely depressed individuals to overcome obstacles to change in traditional therapies, such as inability to focus on emotional material without causing intense distress.

Targeted mechanisms

Increased amygdala activity

Unipolar depression is characterized by excessive elaboration and rumination on negative information (e.g., MacLeod & Mathews, 1991; Nolen-Hoeksema, Morrow,

& Fredrickson, 1993). Such information processing disruptions have been implicated in the onset and persistence of depression (e.g., Ingram, 1984; MacLeod & Mathews, 1991; Teasdale, 1988). This elaboration has been explained in terms of increased feedback involving processes responsible for making emotional associations (e.g., Ingram, 1984), leading to observations of sustained physiological reactivity to negative information in depressed individuals (e.g., Siegle, Steinhauer, Carter, Ramel, & Thase, 2003a). In particular, increased and sustained activity in brain regions associated with emotional processing such as the amygdala (a limbic structure shown in Fig. 5) following exposure to emotional stimuli has repeatedly been observed using neuroimaging (Abercrombie et al., 1998; Sheline et al., 2001; Siegle et al., 2006, 2002; Siegle, Thompson, Carter, Steinhauer, & Thase, in press; Surguladze et al., 2005). Such sustained reactivity is associated with self-reported rumination (e.g., Siegle et al., 2003a, 2002).

Decreased prefrontal function

The prefrontal cortex appears to play an important role in emotion regulation, particularly in inhibiting limbic regions such as the amygdala (Davidson, 2000; Drevets & Raichle, 1998; Mayberg et al., 1999; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004). Lack of prefrontal control could thus contribute to the observed increased and sustained emotional reactivity in depression (Davidson, 2000; Siegle & Hasselmo, 2002). Indeed, multiple studies have linked increased and sustained amygdala activity to decreased prefrontal activity (e.g., Drevets & Raichle, 1998; Siegle et al., 2002; Siegle et al., in press). Disrupted prefrontal activity and function has also often been observed in depression (Baxter et al., 1989; Bench et al., 1993; Davidson, 1994; Davidson, Jackson, & Kalin, 2000; Drevets, 1999; Goodwin, 1997; Mayberg et al., 1999; Ottowitz, Dougherty, & Savage, 2002; Siegle et al., 2002; Siegle et al., in press). There is debate about which regions of the prefrontal cortex are most central to emotion regulation. Though the orbitofrontal and cingulate cortices have the most direct anatomical connections to the amygdala (Ghashghaei & Barbas, 2002; Ray & Price, 1993), little data suggests that the these areas serve mood-regulatory functions without ''upstream'' provocation from highly connected regions more directly involved in executive control. The dorsolateral prefrontal cortex (DLPFC; illustrated in Fig. 5), is specifically believed to recruit brain structures used in tasks requiring executive control (Carter et al., 2000) and inhibit others. The DLPFC has thus been implicated in emotion regulation (e.g., Davidson et al., 2000), and activates during tasks requiring conscious emotion regulation (e.g., Ochsner et al., 2004).

Importantly, inhibitory connections from the amygdala back to the prefrontal cortex (Amaral, Price, Pitkanen, & Carmichael, 1992; Perez-Janaray & Vives, 1991) also allow for the possibility that tonic amygdala activity contributes to decreased prefrontal cortex activity (Moore & Grace, 2000), suggesting it may be important to address these mechanisms in parallel.

Translating basic science to intervention

Based on computational simulations of these neuroanatomical systems (Siegle, 1999), we have suggested that increasing prefrontal inhibitory control could be useful in remediating emotional information processing biases, and thus in treating depression. In designing an intervention that increases PFC activity, it is useful to consider its ''usual''

functions, which are decreased in depression, such as working memory and task-related direction of attention (e.g., Ottowitz et al., 2002). Thus, sustained attention and working memory exercises directed at increasing PFC activity may help to interrupt cognitive aspects of depression.

Existing therapies employ techniques that could increase cognitive control. For example, cognitive therapy teaches patients to consider evidence that does not support their automatic thoughts, rather than engage in more automatic ruminative processes. ''Mindfulness based'' therapies directly target attentional allocation (Segal, Teasdale, & Williams, 2001). Indeed, neuroimaging following pharmacological and behavioral interventions has demonstrated associations of increased prefrontal, activity with recovery from depression (Davidson, Irwin, Anderle, & Kalin, 2003; Liotti & Mayberg, 2001; Liotti, Mayberg, McGinnis, Brannan, & Jerabek, 2002). Yet, it is unclear whether recovery or changes in brain function in these interventions is due specifically to increased cognitive control. Moreover, correlates of decreased executive control such as rumination are associated with increased length of depressive episodes (Nolen-Hoeksema, et al., 1993). An adjunctive intervention that specifically targets executive control may thus help to provide necessary substrates for improvement in other psychological interventions.

To more directly target decreased prefrontal function ''Cognitive Control Training'' uses two tasks well explored in the literature. The first is based on Wells' (2000) Attention Control Training intervention, which is designed to improve controlled selective attention in the face of more automatic ruminative cognitions. We believe this task should target prefrontal mechanisms. The second task, an adaptive variant of the Paced Auditory Serial Attention Task (Gronwall, 1977), should activate the prefrontal cortex in the context of a somewhat stressful task associated with emotional reactivity. These tasks, their previous uses, and the rationale for choosing them are described in detail below.

In evaluating this novel neurobehavioral treatment, it is important to show that it is associated with change in both depressive symptomatology and the proposed mechanisms. Towards that end, our initial multi-trait multi-method outcome assessments in a small sample of depressed patients allocated to either treatment as usual, or treatment as usual plus CCT are presented.

These data are preliminary, and the data presented in the following sections are intended to serve primarily as an illustration of the principles described previously. As such, the methods will be more descriptive and less rigorous than in reporting a traditional clinical trial, and results will be used to illustrate relevant points, rather than to present a formal rigorous accounting of the proposed intervention.

Method

Participants

Fifty depressed patients from the Western Psychiatric Institute and Clinic's intensive outpatient day-treatment program (IOP) were screened for this study, of whom 31 passed inclusion and exclusion criteria. Inclusion criteria included having a diagnosis of DSM-IV unipolar depression via structured clinical interview (SCID-I, First, Spitzer, Gibbon, & Williams, 1996) and being 18–55 y/o. Exclusion criteria included bipolar, psychotic, or substance use disorders, or being medicated with tricyclic antidepressants

or Nefazodone. The IOP offered a number of group therapies, typically offered three times each week, and weekly clinical management meetings with an attending psychiatrists. All 31 participants were taking psychotropic medications, primarily including SSRI's (n = 22) but also including mood stabilizers (7), antipsychotics (4), antianxiolytics (9), buproprion HC (7) and stimulants (1), as well as medications for high blood pressure and insomnia, as well as birth control. The duration of medication course varied markedly from a few days to months.

Procedure

The first five consenting and eligible patients were enrolled in the complete intervention protocol, which involved a structured diagnostic interview, pre-testing on cognitive and emotional tasks, treatment as usual in the IOP plus six 35 min intervention visits over 2-weeks using computer-administered versions of the Wells (2000) attention control training and adaptive PASAT tasks, and post-testing using cognitive and emotional tasks. This 2 week experimental intervention was added to the patients' regular IOP treatment program. Subsequently, patients were randomized to either the full protocol or a treatment-as-usual control condition consisting of a diagnostic interview, pre- and post-testing on cognitive and emotional tasks, in addition to the standard care provided by the IOP.

Of the 31 eligible patients, 19 were assigned to CCT and completed at least one assessment. Of these, 15 completed the entire intervention protocol. The other four completed a pre-assessment and 2–6 training sessions. Ten patients were randomized to the treatment-as-usual condition of which eight completed pre- and post-assessments. Two patients did not return after their initial assessment.

Treatment as usual

All participants in both the control and CCT groups received treatment as usual at WPIC's intensive outpatient clinic (IOP), including medication management, supportive group psychotherapy based on the principles of dialectical behavior therapy (Linehan, Heard, & Armstrong, 1993), and milieu therapy. Primary goals include teaching effective strategies for coping with mental health and safety issues. Patients attend the IOP for 3 h, 3 days per week and meet with the program psychiatrist once each week for clinical management. This treatment venue was chosen for a number of reasons for an initial test of CCT, including the presence of a stably maintained severely depressed population and the standardized intensive environment for psychosocial treatment outside CCT. This program minimized the chances that results associated with CCT would stem from group differences in clinical attention.

Components of the intervention

Our proposed intervention has two components, each of which is geared towards activating the prefrontal cortex. The first exercises prefrontal function in the context of likely automatic ruminative cognitions. The second requires prefrontal control and use of working memory in the presence of frustration. The full intervention protocol and computer-based stimuli are available from the authors upon request.

(1) Wells's (2000) Attention Training. Wells (2000) has examined an intervention that requires individuals to learn to direct their attention. Participants are instructed to

focus on one sound at a time occurring in a naturalistic environment; they focus on only that sound, which exercises selective attention processes. Then participants are asked to switch attention between the sounds and count the sounds, all the while, staying focused on the task rather than naturally occurring depressive ruminative thoughts. In this way, the task not only exercises selective attention to specific environmental stimuli, but cognitive control is also needed to stay focused on the task rather than more automatic emotional processes. The protocol, takes approximately 15 min per session. Such an intervention could be useful in helping depressed individuals to regain cortical control of otherwise automatic emotional processes. We suggest that this therapy may be considered one form of neurobehavioral treatment for prefrontal cortex dysfunction.

This protocol has been studied extensively in anxiety disorders; an initial study suggested the intervention was useful in treating four depressed individuals in just a few sessions (Papageorgiou & Wells, 2000). For purposes of standardization, the intervention protocol was automated for this study. The intervention was presented, exactly as described in the protocol, by computer. Bird sounds (from Blinkow, 1999), presented in four-speaker surround sound at randomly occurring intervals, provided the environmental stimuli.

(2) The Adaptive PASAT. Improved mood (i.e., decreased dysphoria) has also been observed following cognitive rehabilitation interventions for other disorders such as Multiple Sclerosis that employ prefrontal-cortex-intensive neuropsychological tasks (Allen, Goldstein, Heyman, & Tiziana, 1998). Thus, we also wanted to include a task known to specifically activate the prefrontal cortex. To increase the functioning of the PFC in the face of amygdala activity, it may be useful to provoke low-level amounts of negative affect (e.g., slight frustration) so that participants can practice using prefrontal executive control even in a slightly emotional situation. Towards this end, we used a variant of the Paced Auditory Serial Addition Task (PASAT, Gronwall, 1977), which involves continuously adding serially presented digits in working memory. Participants are asked to add each new digit to the digit that preceded it (i.e., sum just these digits, and not keep a running sum). Difficulty is manipulated by increasing the speed with which items are presented. Participants are instructed to get as many items right as they can and to resume the task as quickly as possible when they get something wrong. Thus, the task not only taps working memory, but executive control. A recent study in which nine healthy individuals completed the PASAT during assessment with fMRI reported that left middle frontal gyrus activity (including the DLPFC) was increased during the PASAT vs. a control task (Lazeron, Rombouts, de Sonneville, Barkhof, & Scheltens, 2003). Further, depressed individuals have been shown to score lower than controls on the task (Landro, Stiles, & Sletvold, 2001), even when performance on other neuropsychological tasks was controlled for. Similarly, sad mood, in the absence of depression does not affect PASAT scores (Holdwick & Wingenfeld, 1999).

The PASAT is somewhat frustrating (Holdwick & Wingenfeld, 1999). In order to keep the task tolerable by depressed participants (i.e., to control induced frustration on a per-subject basis and likely to engage prefrontal circuitry rather than a ''giving up'' reaction), and to increase the likelihood that the exercise remained useful even after training, a modified version of the task was used that adapted to participants' performance. This version begins at a 3,000 ms inter-stimulus interval (ISI) and speeds up by 100 ms when participants get four consecutive items correct. It slows down by 100 ms when they miss four consecutive items, to keep participants at a constant level of performance. This technique equates the task for difficulty across participants and sessions. Participants completed three 5-min blocks per session. An adaptive variant of

the PASAT has previously been used; the speed of presentation on the task was positively correlated with performance on other tests of executive function (Royan, Tombaugh, Rees, & Francis, 2004).

Measuring outcome via symptom, behavioral, physiological, and neuroimaging measures

There are many ways to assess the outcome of the proposed intervention. Change in depressive symptomatology was the primary outcome measure, and was measured with the Beck Depression Inventory (BDI-II, Beck, Steer, & Brown, 1996). This 21-item self-report questionnaire is frequently used to index depressive severity in clinically depressed individuals. Change in rumination, a specific mechanism of interest, was assessed with Nolen-Hoeksema's Response Style's Questionnaire (Nolen-Hoeksema et al., 1993). This questionnaire is frequently used to index trait rumination associated with depression. It was also useful to have more direct on-line measures of whether the intervention affects the proposed mechanisms. Change in performance on the PASAT task (especially, the time it takes to recover from mistakes) was used as an explicit measure of increased capability for cognitive control. Yet, behavioral assessments alone do not allow direct observation of the time-course of information processing. Rather, assessment of physiological indicators of sustained cognitive and emotional processing allowed examination of whether the proposed mechanisms were actually affected by CCT.

To examine cognitive and emotional processing, tasks that showed clear differences between depressed and healthy individuals in relevant aspects of brain activity as assessed by fMRI (Siegle, Thase et al., submitted) and pupil dilation [a physiological index of cognitive and affective processing (e.g., Beatty, 1982; Steinhauer & Hakerem, 1992) associated with both DLPFC and amygdala activity (Siegle, Steinhauer, Carter, & Thase, submitted)] were employed. fMRI data was collected on a small subset of six individuals before and after the intervention. Pupil dilation was assessed in the remainder of participants. Details of the tasks, their administration, data collection technologies, data preprocessing, and analyses are described in these manuscripts and are available upon request.

Briefly, to examine cognitive processing, particularly involving the DLPFC, it was useful to administer an executive control and working memory task that engages the DLPFC, on which participants had not been trained, before and after the intervention. Towards this end we employed on a digit sorting task, in which participants were required to put 3–5 randomly arranged digits into numerical order in memory. Participants completed 36 trials involving a fixation mask (1s), a set of digits (2s), a mask (5s), and a target (10s). Participants were told that when the digits appeared, they should read them from left to right, put them in numerical order in memory, and remember the middle digit in the sorted list. With four digits, the higher of the middle digits was to be remembered. When the target appeared, they were to push a ''yes'' or ''no'' button indicating whether the target was the middle digit from the previous set, as quickly and accurately as they could. We have consistently observed DLPFC activity and pupil diameter to vary parametrically with difficulty on this task (e.g., Siegle, Steinhauer, Stenger, Konecky, & Carter, 2003b). Depressed individuals display decreased DLPFC activity and pupil dilation on the task (Siegle, Steinhauer et al., submitted; Siegle et al., in press).

To examine sustained emotional processing, we used a task in which participants rated the personal relevance of 60 emotional words (20 positive, 20 negative, 20 neutral;

30 normed, 30 idiosyncratically generated). Trials consisted of a fixation cue (1s), a word (200 ms), and a mask (row of *X*'s; 10.8s). Participants pushed a button for whether the word was relevant, somewhat relevant, or not relevant to them or their lives, as quickly and accurately as they could. This task directs attention towards idiosyncratic emotional aspects of information. Amygdala activity is higher and more sustained in depressed than healthy individuals on this task (Siegle et al., in press). We also administered a similar task in which participants rated the emotional valence of words (positive, negative, or neutral) in alternation with digit sorting (same time-courses, with a 1s screen in between to note the nature of the upcoming trial) during collection of pupil dilation data. Pupil dilation is increased and sustained on emotion tasks alone or in alternation in depressed compared to healthy individuals (Siegle, Granholm, Ingram, & Matt, 2001; Siegle et al., 2003a; Siegle, Steinhauer et al., submitted).

BOLD fMRI data were collected using a reverse-spiral pulse sequence on a GE 3T magnet (TR = 1.5, TE = 5, FOV = 24 cm, flip = 60; 30 axial slices per TR). Images were reconstructed, and aligned over time to correct for small head motions. Linear trends and outliers were removed and images were spatially smoothed and aligned to the same space via a 12-parameter linear transformation. A hand traced amygdala region and Talairach atlas-extracted DLPFC region (defined as areas of the middle frontal gyrus including lateral BA9 and BA46) were employed to extract time-courses for each structure. Pupil dilation data were collected at 60 Hz in a moderately lit room using a table-mounted ISCAN RK726 video-based infra-red pupilometer.

Participants also completed other measures not discussed here. Thus, a combination of behavioral, peripheral physiological, and neuroimaging assessment on cognitive and emotional tasks before and after the intervention was used to understand the intervention's effects.

Results

Evaluation of symptom change

As shown in Fig. 1 depressed participants who received 2 weeks of CCT displayed significantly greater improvements than those in the treatment as usual (TAU) control condition both in terms of depressive symptomatology (BDI-II), $t(20) = 2.81$, $p = .01$, $d = 1.28$, and self-reported rumination (RSQ-rumination scale), $t(20) = 2.75$, $p = .01$, $d = 1.26$. In fact, improvement after 2 weeks of CCT was greater than the average change in BDI scores associated with completion of the 6-week IOP program, based on historical data regarding all IOP completers in 2002 (ΔBDI = –7.7, $n = 117$). Figure 2 shows the trajectory of change in these variables for all 19 participants who began the intervention, including the five non-completers. This figure shows that symptom severity decreased continuously throughout the intervention, $F(7,77.6) = 8.4$, $p < .0005$, as did rumination, $F(7,47.2) = 6.06$, $p < .0005$; relevant statistics and estimates were computed using a mixed effects analysis in which subject was the random factor and day was a repeated measure, using an AR1 covariance structure.

Evaluation of tolerability

Client satisfaction with the intervention has been uniformly positive. On the Client Satisfaction Questionnaire (Larsen, Attkisson, Hargreaves, & Nguyen, 1979) patients reported high levels of satisfaction with their treatment (CSQ8 $M(SD) = 29.0(2.1)$ out

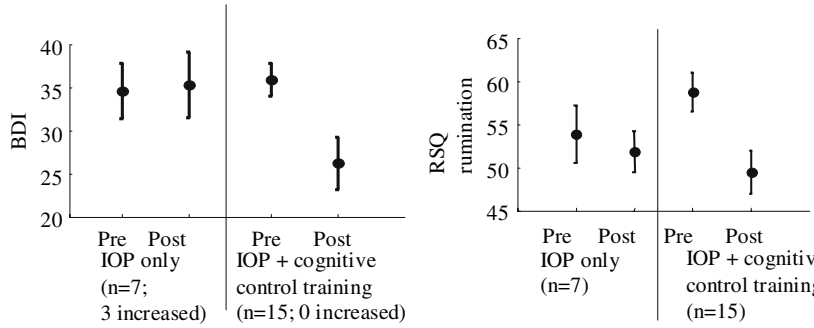

Fig. 1 Greater change in severity (BDI) and rumination (RSQ) during the first weeks of treatment in the treatment as usual (Intensive outpatient program; IOP) combined with CCT (CCT + IOP), compared to treatment as usual alone (IOP only)

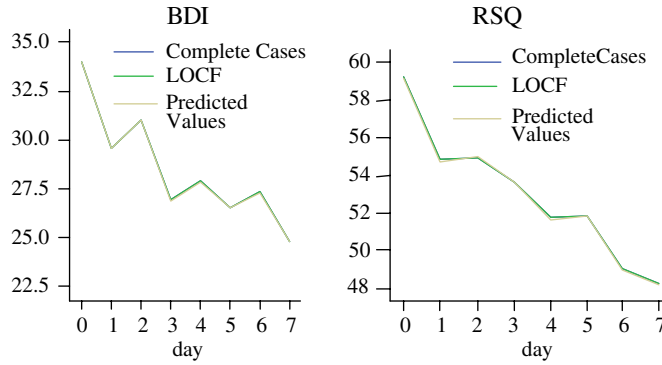

Fig. 2 Trajectories of recovery in severity (BDI) and rumination (RSQ) with three methods for handling missing values including the use of only completers (n = 15), an intent to treat (LOCF) formulation (n = 19), or mixed model estimation for missing values (n = 19). The lines overlap almost entirely

of a possible 32, n = 15). These data reflect higher mean levels of satisfaction than in other published studies of therapeutic interventions with the CSQ (Attkisson & Greenfield, 1999). Moreover, on every item on this questionnaire as well as the expanded 18 item version, the mean was >3 of a possible 4 points. Possibly more telling than quantitative outcomes were subjects' reports of their experiences with the intervention. For example, one subject stated, "I felt that the intervention's tasks helped me to be able to concentrate on a task that at first was overwhelming and frustrating. I learned that through forcing my brain to do the math task I was able to see that I can and will get frustrated but that I can recover and still do the math... The "birds" intervention... helps me to focus on just the sounds and not what thoughts keep recurring like traffic I was in to get to my appointment, etc. Overall, the IOP and this study I think helped my progress immensely." Other subjects' stories echoed this one. For example, one subject stated "I haven't had the extreme thoughts as much lately... When I'm doing the puzzle I can think about nothing but the puzzle. I wasn't able to do this as much before. There was a constant barrage of thoughts that would interrupt what I was doing." Clinicians from the IOP have also repeatedly stated that the patients who

had concurrently participated in the adjunctive intervention were responding better than they had previously at the day program.

Evaluation of change in behavioral indices of executive function

Figure 3 shows that each day participants did the adaptive PASAT, their performance increased (i.e., median ISI decreased), until they were 18% (500 ms) faster than their starting speed, suggesting they improved on that task; mixed effects $F(5,31.9) = 6.0$, $p < .0005$. Figure 4 shows that on the non-adaptive PASAT task, which participants did not practice, patients performed more poorly than a group of healthy controls before the intervention. Following the intervention only patients who received CCT performed better than controls, group × day interaction, $p = .003$. Figure 4b shows that before the intervention, depressed individuals tended to make consecutive mistakes following an error, potentially suggesting that errors were accompanied by frustration, which impaired performance. Following CCT, patients recovered more quickly yielding decreased error rates following an initial error.

On the digit-sorting task, our other measure of executive function, performance was at ceiling (>95% correct for nearly all participants at both pre- and post-testing sessions). Future tests should therefore include other behavioral measure of executive function.

Evaluation of change in DLPFC, amygdala, and gross physiological reactivity

Six depressed participants completed fMRI assessment before and after CCT. Mixed effects analyses were employed on regions of predefined interest, in which subjects were random factors, and scan within trials, condition (emotional valence or (of digits), and day were fixed repeated measures. These data suggested that as expected, depressed participants displayed decreased disruptions in amygdala activity on an emotion task (personal relevance rating) and DLPFC activity on a cognitive task (digit sorting), on which they were not trained, following the intervention.

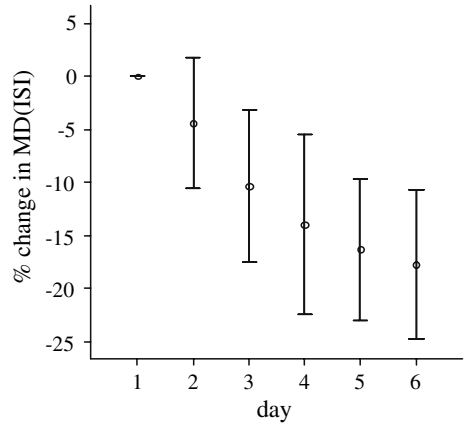

Fig. 3 Mean Change in behavioral performance (Median Inter-stimulus Interval (ISI)) on the adaptive Paced Auditory Serial Attention Task (PASAT) over six sessions ($n = 13$)

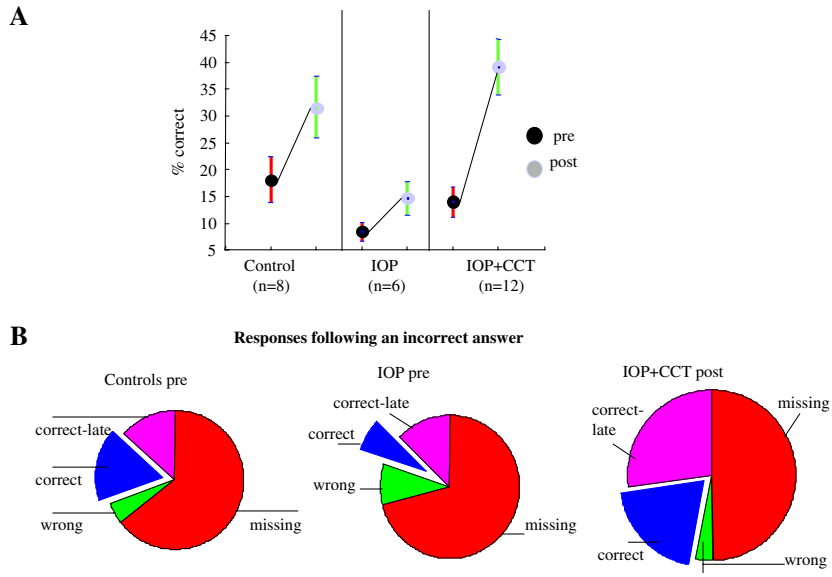

Fig. 4 (**a**) Improvement in percent correct on the non-adaptive PASAT in healthy controls, Treatment as usual (IOP only), and CCT (CCT + IOP) groups. (**b**) Increased correct responses following errors on the non-adaptive PASAT in following treatment

On the personal-relevance rating task, right amygdala activity varied reliably within trials, scan main effect $F(7,155.1) = 1.9$, $p = .08$, $\eta^2 = .07$. As shown in Fig. 5a, from pre- to post-intervention, amygdala responses increased in response to positive words, but decreased to negative and neutral words, day × valence $F(2,227.3) = 5.6$, $p = .004$, $\eta^2 = .05$. To illustrate, Fig. 5b shows that the time-course of amygdala activity in response to negative words appears more sustained before than after the intervention. A day × valence interaction was also present in the left amygdala, $F(2,238.0) = 6.7$, $p = .001$, $\eta^2 = .05$; responses to positive words again increased, and neutral words decreased, but differences in responses to negative words were negligible.

On the digit sorting task, left DLPFC activity varied reliably within trials, scan main effect $F(11,193.0) = 3.7$, $p < .0005$, $\eta^2 = .17$. As shown in Fig. 5c, from pre- to post-intervention, left DLPFC responses decreased in response to the easiest condition, but increased in response to the hardest, day × condition $F(2,359.6) = 3.7$, $p < .03$, $\eta^2 = .10$. To illustrate, Fig. 5d shows that the time course of left DLPFC activity in response to the 5-digit condition appears higher after than before the intervention. The same general pattern was present on the right, day × condition $F(2, 294.6) = 7.02$, $p = .001$, $\eta^2 = .05$.

We examined change in sustained pupil dilation to emotional tasks in the rest of the sample, including the control group. Figure 6 a, b shows that on both the personal relevance rating (SRET) and an alternating emotion identification/digit sorting task, sustained pupil dilation in the 10–20 s following the stimulus decreased. On the SRET, participants responded by pressing a button for whether the word applied to them not at all, somewhat, or a lot. On the alternating task participants indicated whether the word was positive, negative, or neutral, followed by a trial in which they put 5 digits in numerical order (18 s). On the SRET, participants had a mean of $M(SD) = .12(.07)$ mm

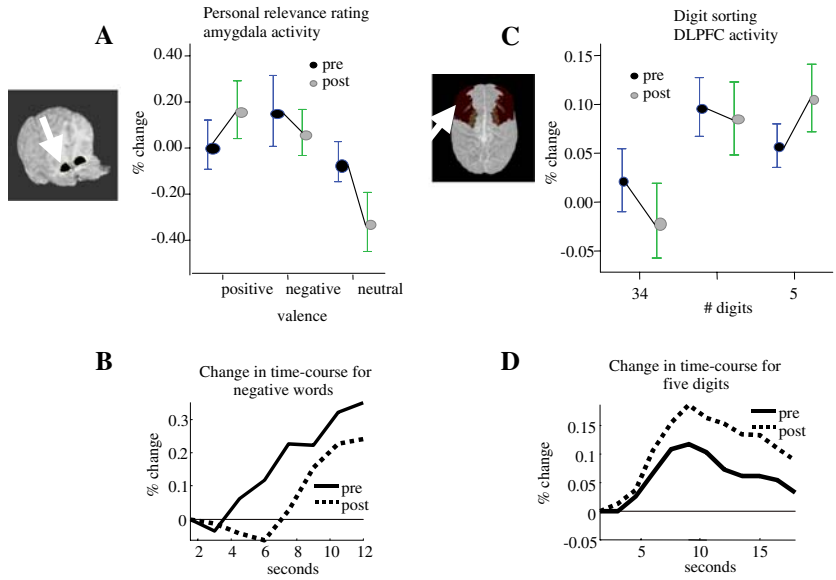

Fig. 5 Decreased disruption in amygdala and DLPFC function post, compared to pre-CCT. (**a**) Increased amygdala activity on the personal relevance rating task for positive words and decreased amygdala activity for negative words. (**b**) Illustration of time-course of activity for negative words. (**c**) Decreased prefrontal activity for the easiest stimuli (3-digits) and increased prefrontal activity for the hardest stimuli (5-digits) on the digit sorting task. (**d**) Illustration of the time-course of activity for the 5-digit condition

dilation 5–8 s after the word at their initial assessment, compared to .02 (.14) mm at their final assessment, d = .92. Similarly on an alternating task, participants initially displayed .17 mm dilation relative to their baseline 5–8 s after the word, compared to .1 mm at their final assessment, d = .56. Yet, as shown in Fig. 6c, d, similar reductions in sustained pupil dilation were noted in the treatment as usual group.

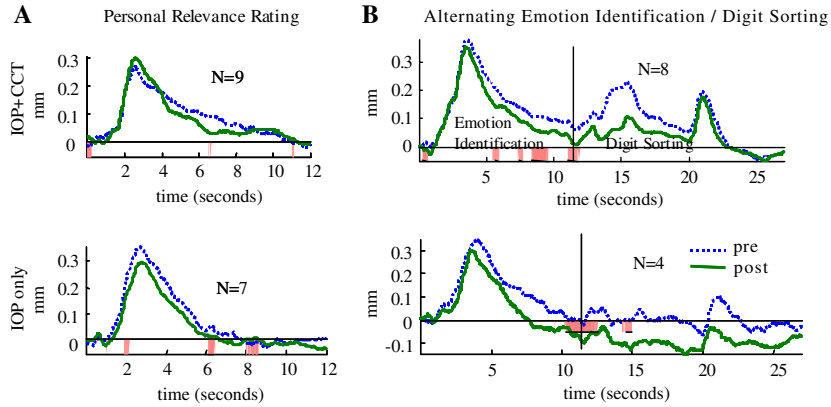

Fig. 6 Decreased sustained pupil dilation during emotional information processing tasks following two weeks of treatment in either CCT + IOP or the IOP only

Discussion of initial CCT data

Taken together, these preliminary data suggest that in 2 weeks, an adjunctive intervention directed at brain correlates of depression is associated with decreased depressive severity and is well tolerated by a hard-to-treat population. Participants who received the adjunctive intervention for two weeks had greater decreases in depressive symptomatology and rumination than participants who had only treatment as usual in a well-validated treatment regime for the same period. Moreover, participants who received the adjunctive intervention displayed normalization of disruptions in the brain mechanisms targeted by the intervention. Thus, initial data on the intervention tasks is promising. This approach to designing an intervention based on data from neuroscience yielded a treatment that does not look like conventional psychotherapy but follows many of its principals. Detailed pre- and post-assessment helped to validate the mechanisms of change. Whether change in relevant underlying mechanisms is unique to the adjunctive intervention is unclear given the similar changes in an external physiological measure (pupil dilation) in both groups in response to emotional information. Admittedly, the examined sample is small and the obtained data are preliminary. Moreover, there is still a strong potential for observed changes in the intervention to be a placebo effect. Still, they suggest that a larger, adequately powered trial may yield additional valuable data.

Towards future investigations of neurobehavioral treatments

There are a number of steps left for neurobehavioral therapies yet to take. In particular, there is a strong need for excellent active-placebo designs that control for the powerful nonspecific factors that could accompany such a novel and intuitively appealing type of intervention. If neurobehavioral interventions proposed as adjunctive treatments, it is unclear what therapies they would best be adjunctive for. For example, in the current trial, many participants stated that the tasks helped them to ''practice'' the staying-present-centered skills they had been exposed to from dialectical behavior therapy—whether this intervention would work similarly as an adjunct to cognitive behavioral or interpersonal therapies is unclear.

More basic science is necessary to understand specific brain mechanisms underlying psychological disorders. Full integration of assessment of relevant mechanisms with trials of novel therapies is still largely a future goal. We believe that increasing specificity of mechanism will lead to increased automation and exercise-like regimens for targeting specific aspects of brain function. This is not to suggest that neurobehavioral therapies should be considered reductionistic or straightforward. Rather, their goals are limited, and in conjunction with an appreciation for the complexity and multifaceted nature of psychological disorder, may provide important pieces to a difficult puzzle.

Similarly, the goal of neurobehavioral treatments is generally to address specific symptoms or symptom clusters. Thus they may be most appropriate for a subset of people with a specific disorder. This goal is different from that of many conventional therapies, which treat a broad range of symptoms and may be more generally applicable. Similarly, the overlap, in practice, of what goes on in neurobehavioral, vs. conventional therapies could profitably be explored. For example, in the current trial, subject reports sound much like that from existing therapies (focus on the present

moment, ability to disengage from emotional content, etc.). Future research is necessary to understand the optimal use of these interventions, alone, or in conjunction with existing validated treatments, potentially via head-to-head or treatment-augmentation designs with conventional treatments such as cognitive behavior therapy.

That said, the neurobehavioral treatments discussed in this article stand on rigorous science and follow in the footsteps of disciplines that have produced effective treatments by appealing to brain function. Ideally future basic science will allow understanding of neural mechanisms which are general to features of multiple disorders, and thus may be appropriate for intervention with generally applicable neurobehavioral techniques and also what neural factors and hence intervention requirements are more specific to specific symptoms. In addition, understanding of common substrates of pharmacological and behavioral interventions increase, the field is poised to better integrate these types of intervention. Initial data from neurobehavioral treatments around the country and in our own lab are promising. Thus, neurobehavioral treatments appear to represent a promising direction for future treatment research. Ideally they could become the ultimate ground for integrating cognitive, behavioral, neurobehavioral, and clinical research in psychological disorders.

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