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# Neuroimaging Studies of Psychological Interventions for Mood and Anxiety Disorders: Empirical and Methodological Review

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Abstract

This article reviews the methods and results of neuroimaging studies of the effects of structured psychological interventions for mood and anxiety disorders. The results are regarded as consistent with neural models of improved self-regulation. Specific recommendations for future research are outlined, and the clinical and theoretical significance of this research is discussed.

**Keywords:** Neuroimaging, Psychotherapy, Mood Disorder, Anxiety Disorder, Depression.

# Neuroimaging Studies of Psychological Interventions for Mood and Anxiety Disorders: Empirical and Methodological Review

Cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are empirically-supported psychological interventions for mood and anxiety disorders (Butler, Chapman, Forman, & Beck, 2006; Chambless & Ollendick, 2001; DeRubeis & Crits-Christoph, 1998; National Institute for Clinical Excellence, 2004). These treatment approaches are based on sound theoretical and empirically-tractable models of the psychological mechanisms involved in the etiology, maintenance, and amelioration of these disorders. In general, cognitive models posit that schemas or mental networks that represent an individuals' constellation of beliefs and attitudes about themselves, other people in their life, their environment, and their psychological and physiological symptoms moderate their level of vulnerability to cognitive and affective disturbance within the context of stressful life events (Beck & Emery, 1985; Beck, Rush, Shaw, & Emery, 1979; Clark, Beck, & Alford, 1999; Ingram, Miranda, & Segal, 1998; Mathews & MacLeod, 2005). Although a multitude of specific CBT approaches have been developed as interventions for mood and anxiety disorders, most therapies share in common the goals of regulating negative affect and arousal, restructuring negative self-referential cognition, improving problem solving capacity, and increasing positive social-behavioural activity (Dobson & Dozois, 2001). Interpersonal models hypothesize that the way an individual perceives and is perceived by others within social relationships plays an integral role in the degree to which he or she will be vulnerable to experiencing mood and anxiety disorders (Coyne, 1976; Joiner & Coyne, 1999; Hammen, 1991; Segrin, & Dillard, 1992). Accordingly, interpersonal psychotherapy approaches involve a concerted effort to restructure negative interpersonal

relationships and foster positive social interaction as a means of decreasing negative affect and cognition related to mood and anxiety disorders.

Notwithstanding the strong empirical support for the principal tenants of cognitive-behavioral and interpersonal theories and their respective psychotherapeutic orientations toward mood and anxiety disorder treatment, only recently has cognitive-, affective-, and social-psychology research become integrated with the neurobiological study of emotion, depression, and anxiety disorders under the banner of the social-cognitive and affective neurosciences (e.g., Davidson, 2000; Davidson et al., 2002; Lieberman, 2007; Ochsner & Gross, 2005; Murphy, Nimmo-Smith, & Lawrence, 2003). This recent scientific development has begun to traverse historical, disciplinary boundaries between traditional biomedical and psychological approaches to understanding and treating mood and anxiety disorders. Increasingly clinical, cognitive, personality, and social psychologists are teaming with investigators in the clinical neurosciences and biological psychiatry in interdisciplinary investigations of the etiology, maintenance, and effective treatment of mood and anxiety disorders. Some researchers (e.g., Davidson et al., 2002) contend that the synthesis and consilience of psychological with neurobiological approaches to the study of depression and anxiety is of utmost importance to a comprehensive understanding of the etiology and effective treatment of these disorders. Such interdisciplinary endeavors have been facilitated, in part, by the rapid development and research utilization of non-invasive methods for probing the neural processing underlying psychological functioning in humans, including individuals with psychiatric disorders. These approaches include the functional neuroimaging technologies of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

As one such development, the present article reviews the experimental methodology and empirical results of the ten seminal studies that have been published to date that have investigated the effects of participation in structured psychological interventions (CBT and IPT) for mood and anxiety disorders on brain functioning using neuroimaging designs. These studies collectively demonstrate that CBT and IPT effectively alter brain function in individuals with unipolar mood disorders (Brody et al., 2001; Goldapple et al., 2004; Martin et al., 2001), obsessive-compulsive disorder (OCD; Baxter et al., 1992, Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996; Nakatani et al., 2003), panic disorder (Praško et al., 2004), social anxiety disorder (Furmark et al., 2002), and specific (spider) phobia (Paquette et al., 2003; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006) in a manner that is consistent with the decreased psychiatric symptoms that were observed with these treatments. The present article reviews this emerging literature in detail with the following principal aims: 1) To examine the clinical and theoretical significance of the empirical results for the study and treatment of mood and anxiety disorders, and 2) To examine the validity of the research methodologies that have been used in order to make methodological recommendations for future research.

Two previous articles have been published that surveyed the neuroimaging of psychotherapy-outcome literature (Linden, 2006; Roffman et al., 2005). However, neither of these previous reviews involved a detailed methodological evaluation nor was the focus specifically to distill the clinical and theoretical significance of this literature for clinical psychology theory and treatment of the mood and anxiety disorders. In contrast, the present article is motivated by the view that the introductory and formative status of the current literature affords an advantageous opportunity to determine a set of recommendations to guide future research of the outcome of structured psychological interventions for mood and anxiety disorders

on brain functioning. Additionally, this article reviews, in some detail, the brain regions where activations and deactivations were observed in extant pre-post neuroimaging studies of CBT and IPT interventions as a means of ascertaining the extent to which previous findings correspond with emerging findings regarding the neurobiology of affective- and self-regulation (e.g., Ochsner & Gross, 2005).

### *Neuroimaging and Psychotherapy Mechanisms of Change*

Research of the mechanisms of change facilitating positive clinical outcomes in structured psychological interventions for mood and anxiety disorders is still very much in its infancy. It is generally assumed, however, that clinical outcomes can be attributed to both nonspecific factors (e.g., the development of a positive therapeutic alliance), on the one hand, and factors associated with specific interventions, on the other. If some of the specific self-regulatory skills and strategies that are learned in CBT and IPT interventions can be identified a priori, the psychological processes that hypothetically give rise to this learning can be investigated (e.g., DeRubeis et al., 1990; Ingram & Hollon, 1986), as can the neural correlates of these processes.

Generally speaking, CBT and IPT interventions can be considered to involve at least three readily-identifiable if broad-spectrum treatment goals (e.g., Dozois & Dobson, 2001). First, these interventions challenge clients' current ways of coping with stressful life events and problematic interpersonal relationships, and therefore attempt to alter and/or enhance clients' problem-solving capacities. In general, studies of higher-order psychological processes that are involved in problem-solving, executive processing, and working memory suggest important roles for the dorsolateral prefrontal cortex (DLPFC; Cabezza & Nyberg, 2000; Duncan & Owen, 2000), making DLPFC functioning a possible target of CBT and IPT interventions. Second, CBT and IPT interventions are intended to modulate clients' perspectives about themselves and their

relationships, and accordingly may act on clients' sense of self. Neuroimaging studies of the psychological processing that gives rise to self-representation suggest that cortical midline structures, including the ventral anterior cingulate cortex (vACC), dorsal anterior cingulate cortex (dACC), ventral and dorsal subregions of the medial prefrontal cortex (vmPFC, dmPFC), the posterior cingulate cortex, and the precuneus are clearly involved in self-related information processing (see Northoff et al., 2006 for review), making function within these brain areas also potential therapeutic targets of CBT and IPT interventions. Third, CBT and IPT interventions for mood and anxiety disorders attempt to assist individuals in regulating difficult emotional states, and accordingly these interventions may impact brain functions associated with emotional processing, such as within insular cortex, the amygdala, the vACC, and the vmPFC and dmPFC (see reviews by Phan et al., 2002; Murphy et al., 2003).

The brief review above therefore suggests that brain regions of interest for studying the effects of structured psychological interventions for mood and anxiety disorders are readily identifiable based on psychological theory, making investigations of the neural basis of the psychotherapeutic effects of CBT and IPT for mood and anxiety disorders hypothesis-driven rather than purely exploratory. Below the empirical results of neuroimaging studies of CBT and IPT interventions for mood and anxiety disorders are reviewed, and the degree to which the results correspond with a model of these interventions altering affective- and self-regulatory processing is considered.

## *Empirical Review*

### *IPT and CBT for Major Depression*

Brody et al. (2001) and Martin et al. (2001) conducted the first neuroimaging studies of individuals with depression before and after a psychological intervention, both examining the

effects of Interpersonal Psychotherapy (IPT). More recently Goldapple et al. (2004) investigated the neural effects of participation in cognitive therapy (CBT) for depression.

Brody et al. (2001) studied 14 unmedicated middle-aged adults recruited from their institution's surrounding community who received IPT in 12 weekly sessions (following Klerman, Weissman, Rounsaville, & Chevron, 1984). The IPT treated group was compared with a sample of paroxetine-treated depressed individuals ($n$ = 10) and with a non-psychiatric control group ($n$ = 16) of similar gender and age composition. The treatment arms of this study were assigned by participant preference rather than via randomized design, as was the case in Baxter et al. (1992) and Schwartz et al. (1996). PET glucose-metabolic rate was measured for all participants in an awake, restful state at baseline and again 12-weeks subsequently, and regions of interest (ROIs) were defined as the dorsolateral and ventrolateral prefrontal cortex, dorsal and ventral anterior cingulate cortex, and dorsal and ventral caudate nucleus and thalamus. In the IPT group, pre-post decreases were observed in right prefrontal cortex, left anterior cingulate cortex, left insula, and left temporal cortex. Notably, however, differences in metabolism within the insula and temporal areas were not hypothesized a priori as ROIs, at least as explicitly reported in this article. Brody et al. also observed a significant correlation between change in left thalamic metabolism and change in HAM-D scores ($\tau$ = .26). In direct comparisons of the brain-metabolic effects associated with IPT versus PHT mainly commonalities were noted, although with PHT metabolism increased bilaterally in the insula but only within the left-hemisphere with IPT.

Martin et al. (2001) also conducted a study of the brain metabolic effects of IPT for depression as measured by single-photon emission computed tomography (SPECT). Twenty-eight middle-aged adults meeting DSM-IV criteria (American Psychiatric Association, 1994)

criteria for Major Depressive Disorder (MDD) who were referred by their family physicians were studied, 23 of which were randomized either to venlafaxine pharmacotherapy (PHT, n = 11) or IPT (n = 12) (the remaining five elected to participate in one of the two treatment arms by their own preference, four to PHT and one to IPT). Treatment outcome was determined by a single psychiatrist who notably was not blind to treatment arm and in fact was the same psychiatrist who conducted the venlafaxine treatment. In comparison, all IPT sessions were conducted by a single psychiatric nurse, with all patients receiving up to 16 one-hour weekly sessions. Participants were scanned prior to treatment and 6-weeks later, at which point treatment-outcome was also determined. It is therefore particularly noteworthy that the IPT participants in this study were scanned after only their sixth therapy session, consistent with the brain imaging follow-up interval used perhaps being more suitably referred to as a *mid*-treatment as opposed to *post*-treatment outcome. Martin et al. observed an increased blood flow in the right basal ganglia with both PHT and IPT. Additionally, Martin et al. found that in only IPT treated-participants was there also increased right posterior cingulate blood flow post- in comparison with pre-treatment.

Finally, Goldapple et al. (2004) conducted the most recent neuroimaging investigation of pre- vs. post-psychological intervention in depressed individuals published to date. These investigators studied neural responses to cognitive therapy in 14 unmedicated depressed middle-aged outpatients who received CBT (15-20 sessions lasting a mean 26 weeks following Beck, Rush, Shaw, & Emery's [1979] cognitive therapy approach). The results of the CBT group were compared post-hoc with a previously-collected sample of paroxetine-treated (PHT) depressed individuals ($n$ = 13) of similar depression severity at baseline (originally described in Kennedy et al., 2001). PET glucose metabolic rate was measured in the CBT patients within one-week prior

to and after treatment in an awake and restful state, with no explicit instructions given except to avoid "ruminating on any one topic" (Goldapple et al., 2004, p. 35) during the PET fluid uptake phase. A similar scanning procedure was undertaken with the PHT group prior to and following a six-week treatment interval, which is notably a three-to-four fold shorter treatment duration in comparison with the CBT protocol. In the CBT group, Goldapple et al. found pre- vs. post-treatment increases in metabolic activity within the hippocampus/parahippocampal gyrus and dorsal cingulate cortex, and decreases in dorsalateral and ventrolateral prefrontal regions, orbital frontal regions, in the posterior cingulate, in inferior parietal regions, and in inferior temporal regions. Goldapple et al. also found that some of these changes were unique or in a different direction from the regional metabolic changes that were observed with PHT in their previous study (Kennedy et al., 2001). Specifically, increased activation in the dorsal and decreased activation in the ventral subgenual cingulate, as well as decreased activation in the medial and ventrolateral prefrontal and orbital frontal regions were uniquely observed with CBT relative to PHT. Additionally, a converse pattern of activation to that observed with CBT was observed with PHT in the following areas: dorsolateral prefrontal, inferior parietal, and inferior temporal regions (where increases were found with PHT), and hippocampus and parahippocampal regions (where decreases were found with PHT).

As a set of initial findings, the results of these three studies demonstrate that participation in CBT and IPT for depression is associated with changes in brain metabolic activity in depressed individuals. Some consistent findings emerged across the studies despite the differences in the specific psychological interventions (IPT vs. CBT), neuroimaging methods, and follow-up periods utilized, with outcomes in general primarily associated with altered function in prefrontal cortex (including both dorsolateral and ventrolateral, and medial regions)

and in cingulate cortex (including both anterior and posterior regions) during an awake state at rest. These findings are consistent with CBT and IPT altering psychological processing associated with problem-solving capacity, self-perception, and emotion, as hypothesized above. It is widely known that the dorsolateral prefrontal cortex, particularly within the left hemisphere, is a seat for many higher-order cognitive functions such as problem solving and the execution of working memory (Cabezza & Nyberg, 2001; Duncan & Owen, 2000). Altered function within the dorsolateral prefrontal cortex may reflect improved problem-solving, as in effective coping with life stress, or could reflect reductions in negative-affect and associated cognition such as involved in worry and rumination. In contrast, altered activity within ventrolateral prefrontal regions, particularly within the right hemisphere, as well as within anterior and posterior cingulate and medial prefrontal regions may reflect improved mood regulation and self-perception, as these regions are thought to be involved in these psychological functions (Ochsner & Gross, 2005; Northoff et al., 2006).

***CBT for OCD***

Baxter et al. (1992) were the first to conduct a neuroimaging analysis of the effects of a structured psychological intervention on the brain, with their findings subsequently replicated and extended by the same research group (Schwartz et al., 1996). Their inaugural investigations probed the neural effects of CBT for OCD, and more recently a third study of the neural effects of CBT for OCD has been published (Nakatani et al., 2003). Both Baxter et al. and Schwartz et al. investigated glucose metabolism using PET, whereas Nakatani et al. used xenon-enhanced computed tomography (Xe-CT) to study regional cerebral blood flow. Each of these studies investigated neural functioning in awake OCD patients during a restful state (i.e., participants were not involved in a specific psychological task while undergoing brain scanning). The studies

consistently demonstrated altered functioning in the right caudate nucleus (part of the basal ganglia) with CBT, while Baxter et al. and Swartz et al. demonstrated altered functional connectivity of this region pre- versus post-CBT.

In a sample of 18 outpatients with OCD Baxter et al. (1992) predicted and confirmed a decrease in glucose metabolic rate in the right caudate nucleus in response to both pharmacotherapy (PT; $n = 9$ [fluoxetine hydrochloride]) and CBT without medication ($n = 9$). Participants were assessed before and after treatment, approximately 10 weeks later. The neuroimaging analyses were based upon twelve treatment responders (6 out of 9 in each condition). The percentage of change pre- vs. post-treatment in OCD severity (measured by the Yale-Brown Obsessive-Compulsive Scale [Y-BOCS]) was significantly associated with change in the metabolic rate of the right caudate with PT (Kendall's $\tau = .48$). A marginally significant correlation was also observed with CBT ($\tau = .37$). Baxter et al. also reported a differential pattern of correlations among these structures pre- vs. post-treatment that was consistent with alterations in a bilateral caudate nucleus—orbital frontal cortex—thalamic circuit occurring with successful treatment response. Specifically, correlated activity within these regions was significantly positive in treatment responders at baseline ($\tau$'s ranged from .33 to .49) but was not significant at follow-up ($\tau$'s -.21 to .00). Additionally, a positive correlation between left and right caudate glucose metabolic rate was not significant at baseline ($\tau = .28$) but was significant at follow-up ($\tau = .77$), with a similar pattern found for activity between the left caudate and left cingulate gyrus (pre-treatment, $\tau = -.10$, vs. post-treatment, $\tau = +.41$). No other significant differences were found in the direction or magnitude of correlations before versus after treatment. Although the caudate—orbital—thalamic circuit correlations were significantly altered within the full treatment-responsive sample, they were not evaluated separately for each

treatment group, in the control group, or in treatment non-responsive participants due to low sample sizes, consequently limiting inferences about neural functioning related distinctly to CBT for OCD. In this respect it is particularly noteworthy that treatment modality (CBT versus PT) was participant elected rather than randomly assigned in Baxter et al.'s study.

Accordingly a second study was initiated by Schwartz et al. (1996) to replicate and extend these findings with an additional sample of nine unmedicated outpatients with OCD treated with CBT alone, six of whom were considered to be treatment responders and whose PET data were submitted to further analysis. Schwartz et al. replicated the Baxter et al. (1992) finding of a significant decrease in the metabolic rate of the right caudate nucleus with CBT-response and, combining the results from both the Baxter et al. and CBT-treated samples Schwartz et al. demonstrated a significant decrease in the metabolic rate of the left caudate also. No additional baseline vs. follow-up differences in brain glucose-metabolic activity were observed with the Schwartz et al. sample specifically or when the two samples were combined, however. Schwartz et al. also replicated the finding of a marginally significant positive correlation between percentage change pre- vs. post-treatment in the glucose metabolic rate of the right ($\tau = .32$) and left ($\tau = .26$) caudate with percentage change in Y-BOCS scores. A similar pattern of pre- vs. post-differential correlations between structures in the caudate—orbital—thalamic circuit was identified when the Baxter et al. and Schwartz et al. CBT treatment-responding samples were combined (correlations before treatment ranged from .34 to .81, and between -.01 and +.41 after treatment).

A more recent neuroimaging investigation of CBT for OCD was completed by Nakatani et al. (2003), who also studied awake resting-state brain function, this time in 22 Japanese individuals with OCD. Thirty-one individuals with OCD had been initiated into the treatment

trial, although eight were determined to be unimproved and were not scanned by the conclusion of the study (the remaining participant's data was not interpretable due to excessive head movement during scanning). In contrast to the standardized treatment duration implemented in the Baxter et al. (1992) and Schwartz et al. (1996) investigations (approximately 10-weeks), CBT was continued in the Nakatani et al. study until a given participant was considered, by consensus of the clinical and researcher team,to be responsive to treatment. The method used to determine treatment-response was not, however, detailed explicitly in this study. Notably the mean duration between pre- and post-treatment testing in Natakani et al.'s study was 7.55 months, on average more than twice as long as in Baxter et al. and Schwartz et al.; treatment duration was also significantly heterogenous across participants ($SD$ = 4.68). A noteworthy limitation of this study was that all but one of the participants who completed the study had been maintained on Clomipramine throughout the duration of the study, making uncertain the extent to which the brain alterations observed over the course of treatment could be attributed to CBT, PT, or their interaction. Minding these methodological limitations, Nakatani et al. also demonstrated a reduction in blood flow within the right head of the caudate nucleus over the course of the CBT intervention. Furthermore, increases in functional status (Global Assessment of Functioning Scale scores) were significantly correlated with decreases in right caudate metabolism ($r$ = -.46).

As a set of preliminary results, the findings of Baxter et al. (1992), Schwartz et al. (1996), and Nakatani et al. (2003) regarding the neural effects of CBT for OCD are intriguing and consistent with what is currently known about the neurobiology of OCD from resting-state neuroimaging studies (reviewed by Friedlander & Desrocher, 2006). Their studies collectively demonstrate that response to exposure and response-prevention programs, as determined by a

reduction in OCD symptoms, is associated with a significant right-hemisphere or bilateral reduction in the metabolic rate of the caudate, and that the percentage change in the metabolic rate of the caudate correlates with clinical change. Additionally, Baxter and Schwartz and their colleagues have shown that alteration in the metabolic activity of a caudate—orbital—thalamic brain circuit was associated with a positive treatment-response to CBT. It is known that the caudate nuclei, part of the basal ganglia, are involved in the execution of motor-behaviour as partly coordinated by the motor, premotor, and dorsolateral prefrontal cortices, and this system has been implicated in the executive dysfunction and compulsive behaviour accompanying OCD symptomatology (Friedlander & Desrocher, 2006). Therefore these findings may reflect enhanced self-regulatory control in CBT-treated individuals with OCD. Specifically, these findings may signify decreased motor output in the form of reduced compulsive behaviour, or improved inhibition of compulsive behaviour.

***CBT for Panic Disorder***

Praško et al. (2004) are the first and only published investigators to publish on the effects of CBT for panic disorder as assessed by a neuroimaging design. These researchers studied six non-medicated individuals with non-comorbid panic disorder other than agoraphobia before and after a twelve-week group CBT intervention (the proportion of participants who met diagnostic criteria for agoraphobia was not reported). CBT consisted of three 1.5 hour sessions weekly for the first six-weeks, and two-additional booster sessions were conducted during the eighth and twelfth week. The CBT protocol consisted of psychoeducation, cognitive restructuring, instruction in diaphragmatic breathing and relaxation, and interoceptive and in vivo exposure to panic symptom provocation. Participants were randomly assigned to the CBT treatment, with a comparison group of six individuals randomized to receive antidepressant treatment (citalopram

[*n* = 3], sertraline [*n* = 2], or venlafaxine [*n* = 1]). Between group (CBT vs PHT) comparisons were, however, not investigated in this study.

Glucose metabolic rate was examined over 30 minutes in an awake at-rest state (as in the investigations reviewed above) using PET. Praško et al. (2004) observed increased metabolism at post-treatment within an array of brain regions that included the left inferior and right middle frontal cortex, left insula, right precuneus, and right posterior cingulate cortex, as well as left middle and superior temporal cortex and middle and superior parietal cortex. As this is the first, neuroimaging study of a psychological treatment for panic disorder, these findings require replication before their functional significance can be properly elucidated. Indeed the direction of the pre-post differences observed in this study are inconsistent with the majority of other neuroimaging of psychotherapy outcome studies. The findings, however, appear to be consistent with CBT for panic disorder altering problem-solving capacity and emotional processing. For instance, it is possible to speculate that increased metabolism within the left insula would be partly reflective of an increase in parasympathetic (relative to sympathetic) tone (Craig, 2005), indicative of individuals' increased ability to 'feel at ease' within their physical body and surrounding environment as a result of the CBT intervention. Similarly, increased metabolism within medial posterior regions (right precuneus and posterior cingulate) may be implicative of a greater preponderance of 'resting-state' brain activity and reflective function (Gusnard & Raichle, 2001), that is, a more passive or decentered information-processing mode, akin to a brain less actively engaged in or excessively motivated by the need to monitor potentially threatening interoceptive (e.g., heart-rate) and exteroceptive (e.g., escape route) stimuli.

***CBT for Social Anxiety Disorder***

Furmark et al. (2002) conducted the only thus far published neuroimaging investigation of the effects of CBT for social phobia. Eighteen previously untreated middle-aged adults meeting diagnostic criteria for social phobia, without comorbid diagnoses, were studied. Participants were randomized to Cognitive Behavioural Group Therapy (based on Hope & Heimberg, 1993), Citalopram pharmacotherapy (PT), or a waitlist control condition. These groups were matched for the number of individuals who had been diagnosed with generalized (versus non-generalized) social phobia (three per group). Oxygen 15-labeled water PET scans were acquired for all participants pre- and post-treatment (12 weeks later) during an anxiety-provoking public speaking task. Specifically, 20 minutes before scanning, participants were asked to prepare a short speech about a vacation or travel experience and, while being scanned, participants performed this speech in the presence of at least a six-person audience while being recorded by a portable video-camera. State anxiety before and after this task was measured via self-report on a 100-point Subjective Units of Distress Scale as well as with the Spielberger State-Anxiety Inventory. Both treatment groups evidenced significant reductions on psychometric indices of social phobia with treatment as compared with the wait-list control group, who showed no clinically appreciable change on any of the measures. The PHT and CBT groups did not significantly differ on any outcome measure post-treatment. Additionally, both treated groups reported less state anxiety during the speech task post- relative to pre-treatment.

In the CBT group, reduced blood flow was observed bilaterally in the amygdala, hippocampus, periaqueductal gray, and anterior and medial temporal cortex, while increases in blood flow in the right cerebellum and the secondary visual cortex were observed. In contrast, no significant changes in cerebral blood flow were observed in these areas within the wait-list control group. The only significant difference that was observed in a between-group comparison

of changes associated with CBT versus PHT was an increase in blood flow in the right thalamus that was observed with PHT only.

Since these findings are based on only a single study, future replication is necessary before their clinical significance can be elucidated with any measure of certainty. However, that a reduction in activity within the amygdala, hippocampus, and proximal areas within the medial temporal lobe was observed in individuals with social phobia during public speaking post- relative to pre-treatment may be consistent with the diminished fear these individuals experienced in the task by that juncture. In addition, the findings may relate to a perceived lower need to consolidate the subsequent public-speaking experience as a threatening situation to-be-avoided in the future, as these areas have been implicated in fear conditioning and emotional episodic memory (e.g., review by Phelps, 2006).

Strengths of the Furmark et al. (2002) study included the use of a functional task-paradigm with clear relevance to the anxiety disorder under investigation (i.e., public speaking), and the inclusion of a wait-list control group with randomization to treatment, although small sample sizes were employed. Additionally, a strength of this study involved the use of self-report and physiological (heart-rate) monitoring of anxiety during the experimental paradigm as a means of insuring the neural responses studied pre- versus post-treatment were relevant to clinical psychological change. However, associations between these indices and brain responses were not examined directly in an individual differences design.

***CBT for Spider Phobia***

Paquette et al. (2003) and Straube et al. (2006) examined the neural correlates of successful cognitive-behavioural treatment of spider phobia using fMRI at 1.5 Tesla field

strength. In each case, participants viewed images of spiders while blood-oxygenation-level dependent (BOLD) neural responses were recorded before and after CBT.

Paquette et al. (2003) studied twelve medication-free early-adult-aged females with non-comorbid spider phobia before and after a four-session group-CBT program for spider phobia. Prior to being enrolled in the study, potential participants viewed film excerpts of spiders in a simulated MRI environment and were selected for participation if these films evoked in them an experience of intense but tolerable fear, as measured by self-report. Thirteen female non-psychiatric controls were also recruited for comparison purposes at baseline, each of whom were selected based on their absence of fear-responsiveness to the same spider film excerpts. Whereas individuals with spider phobia were assessed both before and after treatment, control participants completed the scanning task on only a single occasion for pre-treatment comparison purposes.

CBT was delivered in the Paquette et al. (2003) study in four three-hour intensive group sessions (6 participants per group) conducted once per week for four consecutive weeks. Treatment followed a graded exposure model. This intervention incorporated homework exercises involving viewing still pictures and films of spiders and, by the final session, as part of the treatment, all participants successfully touched a live tarantula without self-reported fear.

Before and after the above-described CBT exposure regimen, participants in the Paquette et al. (2003) study completed a functional neuroimaging task. In this task, participants viewed ten blocks of 30-second film excerpts which alternated between excerpts depicting living spiders in captivity (the experimental task) and excerpts displaying butterflies occupied in nature (the control or reference task), with order counterbalanced across participants. Immediately after the scanning session, participants rated the degree to which they experienced fear while viewing the spider excerpts on a 9-point scale anchored by an ‘absence of fear’ (rated 0) and ‘fear as intense

as if real spiders were touching a phobic subject's body' (rated 8). Spider phobic participants reported experiencing considerable fear during this spider film-viewing task (M = 6.3, SD = 1.2) whereas the non-psychiatric control group reported limited (if any) experience of fear in response to the same paradigm (M = 0.4, SD = 0.7). It was noteworthy that post-scan debriefing after the pre-treatment scanning session revealed that a large number of the individuals with spider phobia had attempted to control their fear during the task by voluntarily engaging in breath control. Attesting to a successful treatment response, the spider phobia group reported a near total absence of fear post-CBT (M = 0.1, SD = 0.3), with their post-treatment self-report fear ratings now statistically indistinguishable from those of the control participants.

After isolating BOLD responses in the brain uniquely associated with viewing spider film-excerpts from activation also associated with viewing butterfly film-excerpts, individuals with spider phobia displayed significantly greater activation than did controls in the dorsolateral prefrontal cortex and parahippocampul gyrus before treatment. Additionally, within the spider phobia group, significant activations were observed in the right inferior frontal gyrus and the occipital cortex (left inferior-occipital gyrus, left fusiform gyrus, and right middle occipital gyrus). Following CBT, significant reductions in BOLD activity of the dorsolateral prefrontal cortex and parahippocampul gyrus were observed in the spider phobia group, whereas the right inferior frontal gyrus was more significantly active post- in comparison with pre-treatment. This increased activity within the right inferior frontal gyrus was attributed to improved emotion regulation processes within the context of exposure to a previously feared stimulus (Ochsner & Gross, 2005).

The Paquette et al. study demonstrated several methodological strengths, including the use of a neuroimaging paradigm with clear relevance to the psychiatric disorder under

investigation that proved sensitive to treatment effects in terms of self-reported response. However, there were also weaknesses of this study, perhaps most noteworthy of which was that the film excerpts used in the neuroimaging scans were the same as those used in CBT sessions. This fact raises the possibility that the neural changes observed pre- to post-treatment may have been the consequence of repeated testing rather than exposure-therapy per se, which is especially problematic given that control participants' neural responses to the stimuli were examined only at baseline rather than repeatedly and that a spider phobia wait-list control group was not included in the study (Straube et al., 2006).

Straube et al. (2006) remedied some of these methodological problems. These investigators studied 28 women with spider phobia, in comparison with 14 women without psychiatric diagnosis. Twenty-five of the 28 women with spider phobia participated in a second scanning session held two-weeks later, 13 of whom had been randomized to receive CBT for their spider phobia in the interim, and 12 of whom had been randomized to a waitlist control group (the remaining three participants were lost to follow-up due to missed scans [$n = 2$] or an aborted scan due to the occurrence of panic attack [$n = 1$, the latter was a waitlist control participant]). CBT was conducted over two four-to-five hour sessions (following procedures outlined by Öst, 1989, 1996) that were held on two successive days that began the day following pre-treatment scanning. Their treatment involved psychoeducation in addition to an exposure protocol that included training toward holding a living tarantula for approximately 10 minutes, in addition to catching and touching other live spiders without excessive self-reported fear (as measured by a score of less than 50 on a 100-point subjective units of distress scale). All participants were reported by Straube et al. (2006) to have reached these therapy goals.

The task used by Straube et al. (2006) during scanning involved viewing 24s videos depicting either a moving spider (experimental task) or, during separate epochs, a moving black cylinder (control task). None of these images were used as stimuli within the treatment itself. As in Paquette et al. (2003), participants rated, on an interval scale, the extent to which they experienced fear in response to this experimental paradigm As predicted, whereas the spider phobia group as a whole predictably rated the experimental spider videos as more fear-inducing than the non-psychiatric control participants, the CBT-treated spider phobic participants evidenced a reduction in such ratings following the intervention, whereas the wait-list group did not show an appreciable reduction in their fear ratings over the same time interval.

At baseline, spider phobia participants as a group evidenced increased BOLD activation bilaterally in the anterior insular cortex and in anterior cingulate cortex, as well as in left occipital cortex (lingual gyrus) in comparison with non-psychiatric controls. In contrast, increased BOLD activation was observed in the non-psychiatric controls within the left amygdala, bilaterally in the parahippocampus gyrus, and within the pre- and post-central gyri. No significant between-group differences between the CBT and wait-list spider phobia groups were observed at baseline. In contrast, at the follow-up assessment, whereas the CBT group no longer demonstrated a greater response in the insular and anterior cingulate cortex to viewing spiders relative to the cylindrical control object, the waitlist group continued to reveal these effects, and this effect significantly distinguished the groups in a direct between-groups contrast. Additionally, at the second assessment the waitlist group exhibited greater response in the thalamus, left dorsomedial prefrontal cortex, and left precuneus, whereas the CBT group revealed greater response in the right precuneus. Moreover, the post-treatment results did not differ between the CBT and non-psychiatric control groups. In contrast, neural responses to the

spider videos continued to differentiate the waitlist group (second scanning session) from the non-psychiatric controls (baseline scanning). Specifically, the spider phobia group who had not received treatment continued to exhibit significantly greater response within the anterior insula and anterior cingulate cortex. The findings of lowered anterior cingulate and right insular cortex responses to the previously feared spider stimuli in individuals treated with CBT are consistent with lowered negative affective responses, as both structures are strongly implicated in negative emotional responses that generate autonomic nervous system activity (Phan, Wager, Taylor, & Liberzon, 2002; Murphy et al., 2003).

Together the results of Paquette et al. (2003) and Straube et al. (2006) reveal significant differences in brain activation to phobic objects following cognitive-behavioural treatment, which elucidate some of the neural underpinnings of the altered affective experience of these objects as reported by the participants in their studies. Specifically, their findings appear to be consistent with improved affect regulation and coping within the context of exposure to a previously feared stimulus. It is surprising, however, that a limited overlap in the neural regions identified were observed between the two studies given the similar scanning methods. Further studies are therefore necessary to determine which regions most reliably mediate the CBT effects of treatment of spider phobia as well as other specific phobias. The consistently admitted use of controlled breathing by the spider phobia group studied by Paquette et al. during pre-treatment may raise interpretative problems. Specifically, this finding, although presumably clinically reflective of the fear and anxious arousal provoked in response to the phobic stimuli (and perhaps unavoidable as such), is a behaviour that differentiated this groups' responses to the paradigm at baseline from those evoked within the non-psychiatric control group with which they were compared. This fact may therefore account for the differences in brain response

between the groups, specifically, that although both groups of subjects were instructed only to attend toward the films during scanning, the spider phobic individuals additionally attended toward and attempted to regulate their breathing during scanning. This attempted self-regulatory act may therefore partially account for the between-group differences at baseline and the within-group pre-post differences at follow-up. The frequency of occurrence of this behaviour was not noted explicitly in the study by Straube et al. In general, however, the findings are consistent with CBT altering psychological processing associated with emotional processing function.

***Summary***

As a set of introductory findings, the ten studies reviewed above collectively offer preliminary support for the notion that participation in structured psychological interventions for mood and anxiety disorders, such as CBT and IPT, is associated with alterations in neural functioning, specifically changes in brain blood-flow and oxygen/glucose metabolism. More specifically, the empirical results suggest that CBT and IPT interventions impact neural functioning in a manner that is consistent with the amelioration of psychiatric symptoms associated with the mood and anxiety disorders, and they are also consistent with emerging neural models of affective self-regulation (e.g., Davidson, 2000; Lieberman, 2006; Ochsner & Gross, 2005). The cumulative results of these studies that were observed at cortical levels (excluding occipital cortex) are illustrated in Figure 1.

Thus, broadly speaking, the findings are collectively consistent with the notion that CBT and IPT interventions for mood and anxiety disorders alter brain functioning associated with problem capacity, self-related processing, and emotion. For example, both anterior and posterior cortical midline structures that are related to self-referential processing (Northoff et al., 2006) were found to be impacted by CBT and IPT interventions, and altered functioning in sites known

to be involved in the regulation of negative affect such as within the anterior cingulate cortex, medial prefrontal cortex, and right ventrolateral (inferior frontal) cortex (Ochsner & Gross, 2005) were also observed. Studies have also found that activity within the left dorsolateral prefrontal cortex was modulated by psychotherapy for mood and anxiety disorders, which broadly speaking is the brain area most reliably found to be involved in higher cognitive functions such as problem-solving and the execution of working memory (Cabezza & Nyberg, 2000; Duncan & Owen, 2000).

Clearly, however, future research is needed to better elucidate the functional and clinical significance of these findings. In addition, it will likely be sometime before analyses conducted at the neural level will bear significantly on the conduct of psychological interventions, or on clinical psychology theory of psychiatric disorders. Therefore, methodological recommendations are outlined below for use in future neuroimaging studies of the effects of structured psychological interventions, in order to increase the theoretical and clinical merit that might be derived from future studies.

### *Methodological Review*

The studies reviewed above, to a varying degree, exhibit procedural strengths that are pertinent to all forms of treatment outcome research such as the incorporation of formal diagnostic methods, psychometric testing, and behavioural ratings that indicate the degree of symptom severity pre- versus post-treatment. However, additional studies will be required before firm conclusions can be drawn about the potential direct causal links between participation in structured psychotherapeutic interventions such as CBT and IPT and changes in brain function reflective of improved psychological health. Accordingly recommendations for future neuroimaging studies of psychotherapy outcome are offered below with the intention of

maximizing the validity of future study designs and the degree to which future studies will be able to definitively address important questions about the neural effects of CBT, IPT, and other structured psychological interventions for mood and anxiety disorders. These recommendations are described in detail below, and additionally outlined in brief in Table 1 for easy reference. Table 1 also evaluates the extant ten studies already-reviewed above in terms of the degree to which their study designs exhibit the recommended characteristics of a methodologically sound neuroimaging of psychotherapy-outcome study as advocated herein [1].

The first three recommendations listed in Table 1 are relatively straightforward. The first general recommendation is to include non-psychiatric control groups at pre-treatment for baseline comparison purposes. Only half of the studies reviewed above included a non-psychiatric control group for comparison purposes at pre-treatment (Baxter et al., 1992; Brody et al., 2001; Nakatani et al., 2003; Paquette et al., 2003; Straube et al., 2006). These exclusions make interpretation of the findings difficult by prohibiting unambiguous determination of the psychological significance of the distinguishing patterns of brain function demonstrated by clinical participants at baseline. As Thase (2001) astutely noted, if abnormal brain functioning is not confirmed for clinical participants at baseline (i.e., in comparison with non-psychiatric controls), it precludes sensibility to expect participants' possibly already conceivably 'normal' brain function at baseline to 'normalize' further with treatment. Equally important, it is prudent for researchers to assess how representative the neuroimaging profiles of their clinical samples are at baseline in comparison with previous neuroimaging studies of group differences between clinical subjects of similar diagnostic status (i.e., in comparison with non-psychiatric controls). Non-replication of previously published group differences at baseline may be suggestive of the uniqueness of the sample under investigation in a given study, whereas replication would be

more consistent with the ability to generalize the neuroimaging outcomes occurring with psychotherapy in a given study to the population of individuals with the psychiatric disorder under investigation.

Second, it is advisable for studies to include a wait-list control group with the psychiatric disorder under investigation, and that an absence of differences in neuroimaging results between the treated and wait-list groups be established at baseline. Only the Furmark et al. (2002) and Storbeck et al. (2006) studies included wait-list control groups, and only Storbeck et al. explicitly reported whether the treatment and wait-list groups differed with respect to neuroimaging profiles at baseline. The inclusion of wait-list control groups diagnosed with the psychiatric disorder being investigated is essential as a methodological control for brain changes that may occur merely in association with repeated testing and/or over time.

For example, particularly in cases where participants have not been acclimatized to the scanning environment itself prior to baseline testing, subsequent scanning sessions may be perceived as more or less stressful than a previous session(s) as a consequence of experiences taking place during the earlier sessions. Specifically, one concern within the field of neuropsychiatry is that state-functional neural images of contrasts between groups of individuals with psychiatric disorders in comparison with controls may primarily reflect state anxiety-arousal engendered by the scanning procedure itself. It seems advisable that participants' level of fear concerning the scanning procedure itself be measured, and potentially used as a regressor of interest on the brain results obtained. Although fears about the imaging scanner and scanning environment may be germane to the symptoms that are definitive of various specific psychiatric disorders (e.g., fear of being unable to escape from within the bore of an MRI scanner in an individual suffering from agoraphobia), research questions of interest typically do not directly

concern the neural correlates of anxiety reactions associated specifically with brain scanning itself. Thus the question of whether neural differences between groups might be confounded by state anxiety engendered by the scanning procedure bears judicious consideration, perhaps especially within the conduct of resting-state studies where clinical participants with anxiety disorders may find themselves in a decidedly less 'restful' state than control participants during brain scanning. Briefly, a third recommendation, for any study seeking to establish causal significance, is that participants be randomized to the various treatment conditions under study. In less than half of the studies reviewed above were participants randomized to treatment conditions (see Table 1).

A fourth methodological recommendation is that, whenever possible, it is useful for investigators to conduct both resting state and functional neuroimaging analyses at the pre- and post-treatment intervals. Furthermore, it will be important for future studies to examine possible associations between resting state and functional brain responses in individuals with and without the psychiatric disorders under investigation. None of the previously published studies included both resting state and function-experimental neuroimaging conditions.

The inclusion of both resting state and functional response paradigms is important because the two neuroimaging designs are likely to index different neural facets of clinical-psychological presentation. Resting state studies are important to examine as they may be particularly indicative of the tonic clinical presentation of individuals, and they are conceivably less susceptible than are functional paradigms to experimental demand effects (and by nature practice effects). Additionally, there has been increasing interest in the cognitive neuroscience community in understanding the neural processing underlying the resting or 'default-mode' state in humans (e.g., de Luca, Beckmann, de Stefano, Mathews, & Smith, 2006; Fox, Corbetta,

Snyder, Vincent, & Raichle, 2006). Indeed certain investigators envision that this literature may bear significantly on our ultimate understanding of cognition-emotion interactions and of psychiatric symptomatology (e.g., Drevets & Raichle, 1998). It is possible that resting-state findings may be most indicative of a general marker of psychopathological disturbance. For example, by the DSM-IV criteria, a symptom bearing on the diagnosis of many forms of affective illness is that of the individual's perceived difficulty with maintaining his or her concentration and attention, and disturbances in memory also often accompany the diagnosis of mood and anxiety disorders. Differences in resting-state neural function, for example, may be particularly sensitive to these types of general cognitive markers of psychopathology. In studies of this nature, however, it is important that investigators ensure that during the resting-state period psychiatric and non-psychiatric study participants are similarly engaged. For example, psychological processing such as degree of self- versus external-focused attention, frequency of intrusive thought or rumination, and degree of state anxiety or arousal experienced during the resting-state period may differ systematically across individuals with the psychiatric disorder under investigation. Again, in this situation, the experimental conditions may not be parallel in the clinical and control-participants, perhaps then posing interpretative barriers on valid inferences about brain activity in the two groups, particularly when such behaviour is not effectively measured (e.g., by self-report).

Although resting state studies are important to conduct, several theorists have proposed that vulnerability to psychopathology is most appropriately studied when participants' dispositions toward experiencing abnormal psychological states are in a 'primed' or active state (e.g., Ingram et al., 1998). For example, theorists have proposed that vulnerability to depression is conferred primarily when negative self-referential processing is activated during periods of

sad-dysphoric mood; depression-vulnerable individuals may not otherwise appear different from non-psychiatric controls during more euthymic or less affectively-toned states (Ingram et al., 1998). Thus functional paradigms that prime or measure disorder-relevant psychological-neural processing may be more sensitive to group differences between individuals with mood and anxiety disorders in comparison with controls and, accordingly, neuroimaging paradigms that invoke such processing may be more sensitive to group and pre-post treatment differences as well. Additionally, to the degree that functional tasks hold the information processing taking place during scanning constant within (if not between) clinical and control groups, the neural activations that are observed may be more easily interpretable than those obtained from resting-state studies. Specifically, the unconstrained nature of the psychological processing that participants may be involved in during resting-state studies arguably delimits in due measure the number of plausible psychological interpretations about the neural activations that might be speculated about.

At the same time, fashioning an experimental paradigm that comprehensively probes all of the psychological processes clinically relevant to a given psychiatric disorder is probably not possible. In other words, the psychological tasks used in neuroimaging studies are likely to measure only certain facets of a disorder, while being less sensitive to other components of an overall clinical presentation. For example, within the context of the posttraumatic stress disorder (PTSD) literature, a paradigm known as trauma script-driven imagery has been repeatedly used, in which participants are scanned while listening to audio-scripts that recount their traumatic experiences. This paradigm consistently provokes re-experiencing symptoms (e.g., sensory flashbacks, intense emotion, and physiological hyperarousal) and/or depersonalization and derealization in individuals with PTSD, and the neural correlates of these experiences have been

intensively studied (reviewed by Lanius et al., 2005). Whereas this paradigm may effectively index psychological processing that is involved in the re-experiencing and dissociative symptoms of PTSD, it may not be a particularly good indicator of the psychological processing underlying these individuals' emotional numbing symptoms, which nevertheless are arguably just as integral to complex clinical presentations of PTSD (Frewen & Lanius, 2006).

A fifth recommendation listed in Table 1 is that researchers collect self-report, other behavioural, and/or other psychophysiological data during or immediately after the neuroimaging scanning. As examples, such data might represent likert-scale emotion ratings in response to an affect generation paradigm, response times in a vigilance-detection task, or heart-rate or skin-conductance level in response to an arousal manipulation. Not only can such data validate that an expected experimental manipulation took place (i.e., a clinical group responded more strongly to the manipulation than did a control group, or vice versa), but between-participant variability in this data can also be incorporated as regressors of activity in brain ROIs as appropriate to the research questions of interest. The functional neuroimaging studies of psychotherapy outcome conducted to date (Furmark et al., 2002; Paquette et al., 2003; Storbeck et al., 2006) all collected self-report ratings, although none of these studies tested these ratings as predictors of brain activity in their statistical analytic designs (see Table 1). Specifically, collection of this data respects potential individual differences that may emerge not only between clinical and non-clinical groups but also within each group in terms of neuropsychological response to an experimental paradigm. Therefore whereas a clinical group as a whole may show differences from a control group, within the clinical group there may remain a significant level of variability in responsiveness to a particular neuroimaging paradigm. Incorporation of this individual variability in one's modeling of neural responses may account for a greater amount of

variance in the neuroimaging signal measured in comparison with a statistical model that solely attributes variability in neural processing to group-level differences (e.g., see Phan et al., 2003).

A sixth recommendation is that neuroimaging data be correlated with symptom severity, including analysis of both treatment responders and non-responders. Several of the previously conducted studies tested correlations between brain responses and psychometric scores indexing psychiatric symptom severity. However, several studies also excluded treatment non-responders from the outcome analysis. In contrast, where symptom change is measured continuously as opposed to dichotomously, such variation in outcome can be correlated with variation in brain response, an analytic strategy that may more feasibly be inclusive of all pre-treatment participants in the post-treatment analysis, a desirable quality on both methodological as well as statistical grounds.

In addition to symptom-based measures, a final recommendation is that investigators incorporate psychometric measures of change on variables theoretically purported to mediate symptom reduction in a given psychotherapeutic intervention, affording the opportunity to examine neural correlates of change associated with the mediating psychological variable in addition to brain changes signifying symptom remission, which may or may not significantly overlap. In other words, analyses of symptom change alone may result in results that reveal overlapping neural correlates of the effects of psychological and pharmacological interventions, as was found to be the case in several of the studies reviewed in this article (Baxter et al., 1992; Brody et al., 2001; Martin et al., 2001; Furmark et al., 2002). Analyses of psychological change, however, may be more revealing of potential unique neural correlates of structured psychological interventions. For example, within CBT interventions for depression, the intention of clinicians is typically teach participants self-monitoring skills (awareness of negative automatic thoughts)

and skills in cognitive reappraisal, among other things, as a means of regulating their affective states and sense of self. However, whereas at post-treatment a majority of individuals may be determined to be non-depressed by self-report (i.e., survey or clinical interview), participants may nevertheless vary considerably with respect to the degree to which they effectively learned the self-monitoring and cognitive reappraisal skills, as well as the degree to which such learning mediated the depressive symptom reduction they experienced across time. If this variation can be systematically quantified in a manner independent of variation in participants' depressive symptoms, as for example with a validated psychometric scale, interview, or experimental measure of cognitive reappraisal ability, pre-post treatment change of scores on such a measure can be correlated with change in brain responses pre- vs. post-treatment. This analysis would facilitate the identification of brain regions that are directly associated with and perhaps mediate the increased coping and self-regulatory skills learned in CBT, for example, which may indeed not be identical to the neural correlates of symptom remission. In investigations of this nature, future studies may choose to follow the statistical analytic methodology outlined by Baron and Kenny (1986) for testing mediation.

In concluding this section, the studies reviewed above lay the groundwork for additional methodologically rigorous tests of the effects of psychological interventions on brain function to be conducted in the future. As such, the present juncture signifies an opportune time to identify standards for the conduct of these future research investigations of the neural effects of structured psychological interventions for mood and anxiety disorders. Table 1 lists the above provisional recommendations for future studies seeking to test the effects of psychotherapeutic interventions on brain functioning in different psychiatric disorders (see also Beutel et al., 2003,

for a set of general recommendations regarding research collaborations conducted between neuroscientists and psychotherapists).

### *Conclusion*

Although a general movement toward acceptance of the biopsychosocial model of psychiatric disorders largely characterizes the current zeitgeist in mental health research, for some an underlying viewpoint is that each of the three dimensions of the bio-psycho-social model contribute relatively independently to the development of psychiatric disorders. For example, a premorbid neurobiological risk factor (e.g., genetic liability) might be viewed as a predisposing factor for individuals to experience psychiatric problems under specific conditions of elevated psychosocial risk or stress. This kind of an explanation of the biopsychosocial model resounds with an underlying conceptualization of the biological, psychological, and sociological factors contributing relatively independently (either additively or interactively) to the development of the mental and behavioural phenomena that may ultimately signal the diagnosis of a psychiatric disorder.

An alternative viewpoint is that psychosocial mechanisms are *reflected in* neurobiology, just as pathological disturbances in neurobiological systems may express themselves causally in psychosocial behaviour. This point of view examines each of the tri-perspectives of the bio-psycho-social model at different *levels of analysis* rather than as independent contributing factors. This perspective is thus consistent with the idea that psychosocial experiences manifest or express themselves in the brain by altering its structure and function, one general framework that has been put forward for understanding the effects of psychotherapy on the brain (Cozolino, 2002). The view does not, however, posit that neurobiological and psychosocial factors are more or less ‘important’ or that one definitively causes the other. Instead, the model is fully consistent

with a bi-directional influence occurring between brain, behaviour, and environment in the making of psychiatric disorders as in creating psychological experience in general.

Which distinctive perspective of the meaning of the biopsychosocial model one adopts is a decision of considerable consequence in that it may partially determine one's approach to treatment. For example, espousal of the separatist-interactive view would be consistent with the notion that the biological and psychological components of psychiatric disorders require separate treatments, the biological component perhaps treated by pharmacotherapy and the psychological component via a structured psychological intervention like CBT or IPT (e.g., Elkin, Pilkonis, Docherty, & Sotsky, 1988). This dualistic conception therefore would promote the use of combination psychosocial and medical modes to treatment. In contrast, an integrative or 'levels-of-analysis' perspective would posit that psychological interventions also directly impact brain functioning, just as pharmacological interventions impact psychological functioning. In other words, in this view, brain and behaviour are understood to represent distinctive levels upon which one can measure a potentially common treatment effect or phenomenon. This perspective may lead less to combination psychological and pharmacological interventions, or to more optimal use of combination treatments (e.g., a pharmacological agent known to mediate a particular type of learning is used to maximize learning and change associated with a psychological intervention).

The neuroimaging evidence reviewed above that structured psychological interventions such as CBT and IPT alter brain metabolism in neural sites in individuals with mood and anxiety disorders that are consistent with the effects of these therapies is inconsistent with the separatist-interactionist view. Thus older thinking that somatic-medical approaches to psychiatric disorders change 'biology' while psychological approaches may change 'behaviour' but not biology, or

that biomedical approaches change the 'brain' whereas psychological approaches change only the 'mind', may be coming to a pass. Instead, the evidence seems to support the integrative 'levels-of-analysis' view discussed above. Collectively, the evidence reviewed above is consistent with the hypothesis that participation in structured psychological interventions is associated with observable changes in brain functioning over time which, broadly construed, appears to be consistent with improved affective self-regulation in individuals with mood and anxiety disorders. However, as further reviewed, several limitations of this inaugural literature are readily identifiable, and future studies will be required to extend these early investigations, perhaps by incorporating some of the methodological suggestions listed in Table 1.

Given that the theoretical synthesis of psychological with neurobiological perspectives has been regarded by some as the most important endeavor for advancing a unified science and treatment of psychiatric disorders (e.g., Andreasen, 1997, Davidson et al., 2002; Kandel, 1998), it is expected that many more investigations of the effects of psychotherapy on the brain will be conducted in the near future. Hopefully these studies will move us toward a better understanding of the suffering experienced by individuals with mood and anxiety disorders, and how participation in structured psychological interventions helps alleviate this suffering.

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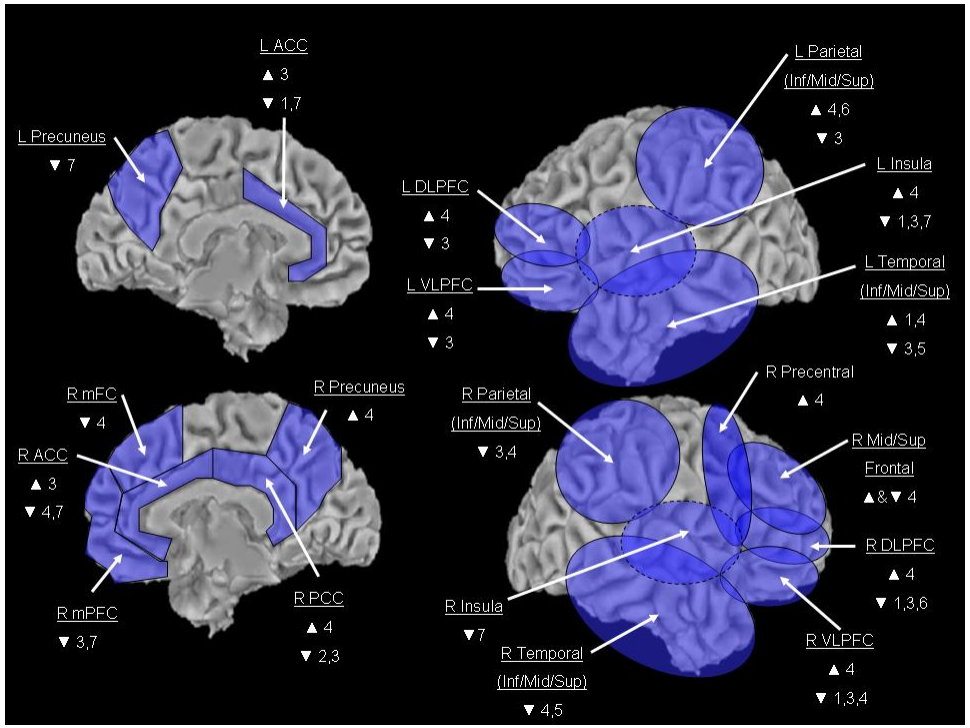
***Figure 1***

***Areas of cortical activation & deactivation in post – pre-treatment neuroimaging studies of the effect of psychological interventions for mood & anxiety disorders on brain functioning***




Note: 1 = Brody et al. (2001), 2 = Martin et al. (2001), 3 = Goldapple et al. (2004), 4 = Praško et al. (2004), 5 = Furmark et al. (2002), 6 = Paquette et al. (2003), 7 = Straube et al. (2006), L = Left, R = Right, ACC = Anterior Cingulate Cortex, DLPFC = Dorsolateral Prefrontal Cortex, VLPFC = Ventrolateral Prefrontal Cortex, Inf/Mid/Sup = Inferior/Middle/Superior, mFC = Medial Frontal Cortex, mPFC = Medial Prefrontal Cortex, PCC = Posterior Cingulate Cortex. The more medial location of the insula is indicated by the hatched lines. Data for occipital cortex and non-cortical regions (e.g., thalamus, basal ganglia) are not illustrated.

***Table 1***

***Recommendations for future neuroimaging research of the effects of psychological interventions on brain functioning***

| | Disorders: | Obsessive Compulsive Disorder | | | Major Depression | | | Panic Disorder | Social Phobia | Spider Phobia | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Studies: | Baxter *et al.* (1992) | Schwartz *et al.* (1996) | Nakatani *et al.* (2003) | Brody *et al.* (2001) | Martin *et al.* (2001) | Goldapple *et al.* (2004) | Praško *et al.* (2004) | Furmark *et al.* (2003) | Paquette *et al.* (2003) | Straube *et al.* (2006) |
| 1 | Inclusion of non-psychiatric control groups at: | | | | | | | | | | |
| | Baseline | ● | ○ | ● | ● | ○ | ○ | ○ | ○ | ● | ● |
| | Follow-up | ● | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 2 | Inclusion of psychiatric wait-list control groups at Baseline & Follow-up | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ● | ○ | ● |
| 3 | Randomization to Treatment Conditions | ○ | n/a | n/a | ○ | ● | ○ | ● | ● | n/a | ● |
| 4a | Inclusion of 'Resting-State' (Non-task) Neuroimaging Condition | ● | ● | ● | ● | ● | ● | ● | ○ | ○ | ○ |
| 4b | Inclusion of Functional (Task) Neuroimaging Condition | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ● | ● | ● |
| 5a | Collect behavioural data during / immediately after scanning, as | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ● | ● | ● |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | appropriate (e.g., Likert-scale ratings, reaction time in functional study) | | | | | | | | | | |
| 5b | Correlate behavioural data with neuroimaging data | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 5c | Collect physiological data during scanning (e.g., cardiac / respiratory rates, skin-conductance) | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ● | ● | ○ |
| 5d | Correlate physiological data with neuroimaging data | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 6a | Collect symptom-change data | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| 6b | Correlate symptom-change data with neuroimaging data | ● | ● | ● | ○ | ○ | ○ | ○ | ● | ○ | ○ |
| 7a | Collect measures of psychological mechanisms of change | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 7b | Correlate psychological mechanisms of change data with neuroimaging data | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

Note: ● = Study met recommended criteria, ○ = Study did not meet recommended criteria.

## Footnotes

[1] It is noteworthy that the majority of these recommendations are equally suitable to clinical neuroimaging trials of pharmacotherapy, although the present focus is directed toward future neuroimaging studies of psychotherapy outcome.