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REVIEW ARTICLE

Do psychotherapies produce neurobiological effects?

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Background: An area of recent interest in psychiatric research is the application of neuroimaging techniques to investigate neural events associated with the development and the treatment of symptoms in a number of psychiatric disorders.
Objective: To examine whether psychological therapies modulate brain activity and, if so, to examine whether these changes similar to those found with relevant pharmacotherapy in various mental disorders.
Methods: Relevant data were identified from Pubmed and PsycInfo searches up to July 2005 using combinations of keywords including 'psychological therapy', 'behaviour therapy', 'depression', 'panic disorder', 'phobia', 'obsessive compulsive disorder', 'schizophrenia', 'psychosis', 'brain activity', 'brain metabolism', 'PET', 'SPECT' and 'fMRI'.
Results: There was ample evidence to demonstrate that psychological therapies produce changes at the neural level. The data, for example in depression, panic disorder, phobia and obsessive compulsive disorder (OCD), clearly suggested that a change in patients' symptoms and maladaptive behaviour at the mind level with psychological techniques is accompanied with functional brain changes in relevant brain circuits. In many studies, cognitive therapies and drug therapies achieved therapeutic gains through the same neural pathways although the two forms of treatment may still have different mechanisms of action.
Conclusions: Empirical research indicates a close association between the 'mind' and the 'brain' in showing that changes made at the mind level in a psychotherapeutic context produce changes at the brain level. The investigation of changes in neural activity with psychological therapies is a novel area which is likely to enhance our understanding of the mechanisms for therapeutic changes across a range of disorders.

Keywords: behaviour therapy; brain; functional neuroimaging; neural networks; psychiatric disorders

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Introduction

Recent advances in neuroimaging techniques have helped to enhance the understanding of neural correlates of mental phenomena in psychiatric disorders (1). An area of continuing interest in psychiatric research has been the application of imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (FMRI), to elucidate the brain changes associated with symptoms of the disorder and their treatment with pharmacotherapy (2–5). In several psychiatric disorders, psychological therapies are also known to be effective in reducing symptoms, for example in depression (6,7), phobia (8–10) and panic disorder (11–13). Therefore, a topical question, central to the approach of elucidating the brain basis of mental disorders, is: do psychological therapies have neurobiological effects?

Empirical research has begun to answer this question, with relevant data now emerging from studies in patients with depression, panic disorder, phobia, obsessive compulsive disorder (OCD) and schizophrenia. Brain changes seen with non-pharmacological means in healthy populations, such as increased dopamine tone during

meditation-induced changes of consciousness (14) and increased left-frontal lobe activity, which is generally associated with positive emotions (15,16), during rest as well as emotional challenge in trained meditators relative to (non-trained) controls (17), have also indicated that changes at the mind level are accompanied by changes at the brain level. As pointed out by Baxter et al. (18), this is perhaps not surprising given that even in lower animals such as the sea plug, Aplysia, learning of stimulus-response behaviour, which is germane to many behaviour therapy techniques (19), is mediated by changes at the synaptic level (20,21).

The aims of this article are to describe the known or potential neural effects of psychological therapies in a therapeutic context, to discuss them in terms of possible underlying mechanisms which lead to therapeutic changes, and to compare them with those found to accompany therapeutic changes with relevant pharmacological treatments. To achieve these aims, relevant data were identified from Pubmed and PsycInfo searches up to July 2005 using combinations of keywords including 'psychological therapy', 'cognitive behaviour therapy', 'depression', 'panic disorder', 'phobia', 'obsessive compulsive disorder', 'schizophrenia', 'psychosis', 'brain activity', 'brain metabolism', 'PET', 'SPECT' and 'fMRI'.

Neurobiological effects of psychotherapies

The specific details of all relevant studies are presented in Table I and discussed in the following sections classified by the disorder.

Depression

A well-known neural model of depression implicates limbic-cortical dysregulation (3,22). There is empirical evidence for functional abnormalities of the temporal, limbic, frontal and basal ganglia regions in this disorder (23,24). Increased activity in the ventral structures and decreased activity in the dorsal structures have been particularly associated with a symptomatic depressive state (22,25–27). Neural changes in the prefrontal regions have been most consistently associated with anti-depressant response, although the direction of such changes varies (increases or decreases are seen) across studies and treatments (25,27–29). Hypo-responding of the rostral cingulate has been associated with resistance to pharmacotherapy in depression (30,31).

Randomized clinical trials have shown that patients suffering from both mild and major depression respond equally well to cognitive therapy and antidepressant drug therapy (6,7). The first study (32) to examine the neural effects of a psychological intervention, interpersonal therapy (IPT), reported changes primarily in the frontal and temporal regions with IPT (Table I), which were considered to be associated with clinical improvements. This study also examined the neural effects of paroxetine treatment in a parallel group and reported similar changes as seen in the group treated with IPT. In addition, the paroxetine-treated group showed decreased metabolism in the ventrolateral prefrontal cortex as also reported previously with paroxetine treatment (28). It is difficult to determine from this study whether the effect of paroxetine in the ventrolateral prefrontal cortex was specific to this treatment or was present because of a greater improvement in this group relative to the IPT group (Table I). Another study (33) which examined the neural changes with IPT or venlafaxine hydrochloride reported increased blood flow in the right basal ganglia in both treatment groups but increased limbic blood flow only in the IPT group. However, the symptom reduction was again more prominent in the drug-treated group, and allocation to IPT or drug treatment was based on patient preference as was the case in the first study (32). Although the interpretations of the results of these two studies were complicated by such confounding issues, they opened an important avenue of scientific enquiry in showing the effects of IPT at the brain level in depression

In a more recent study (34) which examined the neural effects of cognitive behaviour therapy (CBT) vs. those of paroxetine, the main neural changes associated with CBT were found to be different to those seen with pharmacotherapy and involved increased activity (post-treatment > pre-treatment) in the cingulate, frontal and hippocampus regions. Interestingly, patients treated with CBT in this study responded as well as those treated with pharmacotherapy, and both groups showed decreased metabolism in the ventrolateral prefrontal cortex, an effect that was previously seen with pharmacotherapy but not with IPT (32). This particular finding strengthens the argument for change in the ventrolateral prefrontal cortex to be associated with an improved clinical state. The neural effects unique to CBT are suggested to reflect a cortical 'top–down' mechanism of action for CBT (35). However, further data would be required to firmly establish this position since this study also allocated patients to CBT based on their preference, and thus the possibility that different pre-treatment

Table 1. Reviewed studies of the effects of psychological therapies on brain activity

Author/s	Disorder	Imaging modality	Subjects and design	Psychotherapy details	Comparison with drug therapy	Experiment	Clinical findings	Neural effects.
Brody *et al.* (32)	Depression	PET	24 patients and 16 healthy controls scanned twice with 12 weeks of interval. All subjects drug-free at the time of initial scan. Between scans, 10 patients (5 M, 5 F) received paroxetine and 14 patients (8 M, 6 F) received IPT. Allocation to treatment type based on patient preference.	Weekly IPT sessions for 12 weeks with a trained therapist. The IPT sessions focused on improvement of patients' social networks and reduction of depressive symptoms. The primary problem foci of therapy were role transition for six patients, interpersonal dispute for three patients, social deficit for one and grief for one patient.	Yes	Resting state	Both treatments produced clinical improvement but this was greater in the drug-treated group.	Decreases in prefrontal cortex and left anterior cingulate and increases in left temporal lobe metabolism in both paroxetine-and IPT-treated patient groups. These changes were not seen in the healthy control group except for an increase in the right inferior temporal metabolism.
Martin *et al.* (33)	Depression	SPECT	28 patients scanned twice (at baseline and then post-treatment). All patients drug-free at the time of initial scan. Between scans, 13 patients (4 M, 9 F) allocated to receive IPT and 15 patients (4 M, 11 F) to receive venlafaxine hydrochloride for 6 weeks 23 patients randomized to receive drug treatment or IPT. Three patients allowed non-randomized venlafaxine and one patient non-randomized IPT who expressed strong preference.	Weekly 1 h IPT sessions with the same therapist for 6 weeks.	Yes	Resting state	Both treatments produced significant clinical improvement with somewhat greater improvement in the drug-treated group.	Both treatments produced increased blood flow in the right basal ganglia. Limbic blood flow increased with IPT only.
Goldapple *et al.* (34)	Depression	PET	14 drug-free patients (initially 17 but 3 did not complete) scanned before and after treatment with CBT. Comparison to an independent group of 13 6-week paroxetine-treatment responders carried out to examine specificity of identified CBT effects.	15–20 individualized session of CBT by a trained therapist according to the treatment manual described by Beck *et al.* (93).	Yes	Resting state	Nine patients met the criteria (at least 50% reduction in depression ratings) for a full response. Remaining five showed no less than 35% reduction in depression ratings. All patients were included in the analysis of treatment effects.	Increased metabolism in the hippocampus and decreased metabolism in the frontal and parietal cortices with CBT. The reverse pattern seen with paroxetine-treatment (i.e. decrease in the hippocampus and increases in the frontal and parietal regions). Additional unique changes seen with each. CBT group: increased metabolism in the anterior cingulate and decreased metabolism in the medial frontal, orbital frontal and posterior cingulate Peroxetine group: Increased metabolism in brain in stem and cerebellum and decreased metabolism ventral subgenual cingulate with paroxetine-treatment. Common to both groups: decreased metabolism in the ventral lateral prefrontal cortex.
Prasko *et al.* (38)	Panic disorder	PET	12 patients scanned twice, before and after CBT. All patients drug-free at the time of initial scan. After the baseline scans, six patients (3 M, 3 F) randomly assigned to receive CBT and six patients (3M, 3F) to receive anti-depressant medication (2 citalopram, 2 sertraline, 2 venlafaxine) for 3 months.	6-week CBT group treatment programme (three group sessions/week) consisting of education and corrective information, cognitive restructuring, training in diaphragmatic breathing and relaxation, introceptive and *in vivo* exposure and problem solving. Two individual booster sessions in the 8th and 12th weeks.	Yes	Resting state	Both groups showed clinical improvement. CBT-treated group appeared to show a more rapid change.	Both treatments increased uptake in the left hemisphere in the prefrontal, temporoparietal and occipital regions and, in the right hemisphere, posterior cingulum and decreased uptake in the in the left hemisphere in the frontal, temporal and parietal regions.

Table 1: (continued)

Author/s	Disorder	Imaging modality	Subjects and design	Psychotherapy details	Comparison with drug therapy	Experiment	Clinical findings	Neural effects.
Paqette *et al.* (43)	Phobia	fMRI	12 drug-free women with spider phobia scanned before and after effective CBT and 13 healthy women scanned once.	Phobic subjects met once a week with their therapists for a 3-h intensive group ($n = 4$/group) session. The therapy consisted of gradual-exposure-based treatment to spiders (9) using guided mastery (94).	No	Activation paradigm. Within a single experiment, subjects were exposed to five 30-s blocks of film excerpts of living spiders in captivity (activation condition), alternating with five 30-s blocks of emotionally neutral film excerpts displaying butterflies in nature (control condition). Activation and control blocks separated by 15-s blank blue screen.	All phobic subjects responded well to CBT. The pre-selected criteria for a response was defined as being able to touch the entire series of pictures showing spiders, the television screen showing the spiders and the real spiders without reporting fear reactions.	Before CBT, fMRI activity in the dorsolateral prefrontal cortex and the para-hippocampal gyrus correlated with transient fear during the viewing of phobogenic the stimuli in phobic subjects. These brain responses were absent in healthy controls and in phobic subjects after they improved clinically with CBT.
Baxter *et al.* (18)	OCD	PET	18 OCD patients scanned twice. All patients drug-free at the time of initial scan. Between the scans, nine patients (3 M, 6 F) received treatment with fluexetine hydrochloride and nine patients (4 M, 5 F) received CBT over 8–12 weeks. Allocation to treatment type based on patient preference. Four healthy controls (2 M, 2 F) scanned twice with 8–12 weeks interval.	Once or twice a week met with their therapist for approximately 1 h for review of assignments for individualized exposure and response prevention exercises which subjects did as homework and self- monitored with graphs/diaries. Many patients also attended CBT group for patients.	Yes	Resting state	Six patients met the pre-established criterion (at least 30% reduction in symptom scores) for a clinical response. Remaining three were poor or non-responders.	Right caudate nucleus metabolism, divided by ipsilateral hemisphere metabolism (Cd/hem) deceased after treatment in both CBT and drug-treated groups. These changes were not detected in the healthy control group at re-scanning.
Schwartz *et al.* (50)	OCD	PET	Nine drug-free patients (2 M, 7 F) scanned twice: before and after 8–12 weeks of CBT. Further, nine drug-free patients from a previous study (18) included in analysis.	Similar procedures as described for Baxter *et al.* (18).	No	Resting state	New sample: six patients met the pre-established criterion for a clinical response. Remaining three were poor or non-responders. Total sample: 12 (out of 18) patients met the criterion for a clinical response.	Bilateral (more robustly on the right side) decreases in caudate nucleus metabolism, divided by ipsilateral hemisphere metabolism (Cd/hem) occurred in treatment responders vs. non-responders.
Lackner *et al.* (80)	IBS	PET	Six medication-free female patients scanned twice (before and after therapy) and five healthy female controls scanned once.	10 weekly sessions conducted in small groups of 3–6 patients. Cognitive interventional protocol involved self-monitoring, cognitive re-appraisal, worry control and problem solving training following a treatment manual developed by Blanchard (95).	No	Rectal balloon distension protocol. Pressure expected but not delivered during the sham condition.	In patients, meaningful changes observed after cognitive therapy on measures of somatic complaints (pain severity, bowel dysfunction, ldefecation, urge) and psychological distress (anxiety, defecation, urge distress, pain unpleasantness, worry, etc.).	Reduced blood flow in the parahippocampal gyrus, amygdala and inferior and posterior anterior cingulate cortex after treatment relative to pre-treatment levels in patients. Controls showed activation in the above regions that were intermediate between pre- post-treatment IBS patients.

CBT, cognitive behaviour therapy; F, female; FMRI, functional magnetic resonance imaging; IBS, irritable bowel syndrome; IPT, interpersonal therapy; M, male; OCD, obsessive compulsive disorder; PET, positron emission tomography; SPECT, single photon emission tomography.

characteristics may be a reason for differential post-treatment effects of CBT and pharmacotherapy cannot be discounted.

A recent meta-analysis (36) has shown that patients who respond well to CBT have different biological deficits to those who respond well to pharmacotherapy. Specifically, limbic–cortical connections have been demonstrated to differentiate responders from non-responders to pharmacotherapy, with additional limbic abnormalities in the non-responder group, while a more limited limbic–cortical connection and additional cortical–cortical connections are found to differentiate responders to CBT from responders to pharmacotherapy. Further studies are required to examine modulation of brain activity with psychological and pharmacological therapies while taking (pre-treatment) patient characteristics, their past treatment history and current preferences into account.

Panic disorder

The neuroanatomical model proposed by Gorman et al. (37) links the clinical phenomena of unexpected panic attacks to discharge of brain stem nuclei, anticipatory anxiety to limbic activation and kindling, and avoidance to medial prefrontal cortical activation. Both pharmacotherapy and CBT are known to ameliorate the symptoms of this disorder (11–13). In the model by Gorman et al. (37), pharmacotherapy is hypothesized to achieve its effect through stabilization of brain stem nuclei and CBT through modification of cognitive processing at the level of the prefrontal cortex and the hippocampus. The predictions relevant to the hypothesized neural effects of CBT seem to have received indirect support from the earlier noted neural effects of CBT in depression.

To date only one study (38) has examined the modulation of neural activity with CBT in panic disorder. This study also examined the neural effects of treatment with an anti-depressant in a parallel-group design and random allocation of patients to receive CBT or anti-depressant treatment. It reported similar neural changes in the frontal and temporal regions (and no change in subcortical regions) and improvements of similar magnitude, with a more rapid decrease in psychopathology with CBT, in both treatment groups. The neural regions affected by both treatments, as suggested themselves by the authors (38), are part of an alarm system that signals danger. Post-treatment neural effects in this study thus seem associated with clinical improvements, regardless of the treatment type. The two forms of treatments may still have different mechanisms of action. This study had only six subjects in each treatment arm and thus may have lacked power to detect additional, perhaps more subtle, neural effects unique to CBT and pharmacotherapy which, if found, may inform about particular mechanisms leading to clinical improvements via CBT or anti-depressant treatment in this disorder.

Phobia

Increased cerebral blood flow in the visual association cortex and decreased blood flow in the hippocampus, posterior cingulate, orbitofrontal, prefrontal and temporal cortices have been reported in association with fear and anxiety generated by phobogenic stimulation (e.g. video of spiders to arachnophobes) in patients with specific phobias (39,40). Of these, increased activity in the visual cortex to phobogenic stimulation has been linked to enhanced visual attention to noted significance (potential threat) of the phobic stimulus and reduced activity in the hippocampus, posterior cingulate, orbitofrontal, prefrontal and temporal cortices to reduced conscious processing of this stimulus and a defence reaction to it (39,40). Hyperactivity in the limbic and paralimbic regions during imagery of the specific phobogenic stimulus has also been seen and interpreted as reflecting autonomic hyperactivity and exaggerated anxiety responses to this stimulus (41). The neural response in the right frontal cortex has been suggested to be directly related to the use of cognitive strategies for coping with the phobogenic stimulus, based on the observations of reduced activation in this region in fearful (but not panic) patients but increased activation in those who showed severe panic (42).

An effective therapeutic approach for reducing the symptoms of specific phobias is CBT consisting of exposure-based treatment to phobogenic stimuli together with education for changing negative cognitive misattributions related to these stimuli (8–10). There is only one published study so far on the neurobiological effects of CBT in this disorder (43). The observations of this study suggest that successful CBT modifies neural activity in the dorsolateral prefrontal cortex (suggested to reflect the use of pro-active meta-cognitive strategies aimed at self-regulation of fear and anxiety) and the para-hippocampal gyrus (suggested to be related to automatic

re-activation of the fear memory) in response to the phobogenic stimulus. These authors (43) posit that their observations lend strong support to the view (44) that 'CBT reduces phobic avoidance by de-conditioning contextual fear learned at the level of hippocampal/parahippocampal region, and by decreasing cognitive misattributions and catastrophic thinking at the level of the prefrontal cortex'.

OCD

Several neuroimaging studies (45–48) indicate that a cortico-striato-thalamic brain circuit is heavily involved in production of OCD symptoms, that is recurrent unwanted thoughts (obsessions) and conscious, ritualized acts (compulsions). There is evidence that both pharmacotherapy using strong selective serotonin reuptake blockers and specific behaviour therapy consisting of exposure and response prevention effectively reduce the symptoms of OCD in most patients (49).

The neural changes associated with behaviour therapy vs. those associated with pharmacotherapy (fluxetine hydrocholoride) in OCD were investigated using PET by Baxter et al. (18) more than a decade ago. These researchers reported similar changes in the right caudate metabolic rate with both forms of treatments. In a later study, the same research group (50) observed changes in caudate function in patients who improved with behaviour therapy but not in those whose symptoms failed to respond to it. These findings have been interpreted as reflecting a normalizing effect of successful treatments on the functions of the caudate nucleus which are implicated in the development of habit patterns and also in determining whether a given stimulus impinges upon the cortico-striato-thalamic circuit involved in OCD and therefore affects the individual's behaviour (18,50).

Schizophrenia

The main candidate brain regions for abnormalities in schizophrenia have been the frontal cortex, temporal cortex, striatum, amygdala, hippocampus and thalamus (51). Typical antipsychotics, which mainly act on the dopamine-D2 receptors, exert their therapeutic effects via their actions in the striatum, though other areas such as the frontal cortex, thalamus and hippocampus are also implicated (2). Newer atypical antipsychotics, which affect dopamine receptors to a lesser extent and, in addition, affect serotonergic, muscarinic, histaminergic and α-1 adrenergic receptors (52), seem to induce more widespread changes in many brain regions, including the frontal cortex, thalamus and basal ganglia regions (4,53,54). In recent years, attention has focused on the benefits of CBT as an adjunct treatment to drug therapy, especially for medication-resistant patients (55–59). CBT addresses positive, behavioural and emotional symptoms while taking into account the stage of the disorder and the person's specific needs and has been shown to reliably diminish positive symptoms of schizophrenia and the related distress (58,60–63). In some studies, CBT has also been shown to have strong effects on negative symptoms and/or depression, with suggestions that they might be secondary to its effects on positive symptoms (64–67). It is further associated with a reduced relapse rate (66,68) and improved social adjustment (69) compared with routine care. The clinical effects of CBT can be medium to large (57,70) and gain may continue over time (57).

One fMRI study (71) has reported increased frontal activity during a working memory task in a group of six schizophrenia patients with severe cognitive difficulties after 12 weeks of cognitive remediation therapy, but there is no published study of the neural correlates of the effects of CBT on symptoms of the illness in schizophrenia. It is plausible that CBT, as in depression (34), also acts via cortical 'top–down' mechanisms in schizophrenia, especially in patients who have not responded well to medication (so far the effects of CBT are most reliably shown in this particular group). On theoretical and empirical grounds, the neural region (within a neural network) likely to be particularly implicated in the effectiveness of CBT in schizophrenia, in terms of its effects on symptoms, depression and subjective mood (65), is the anterior cingulate. It has connections with both cortical and subcortical structures and thus has the capacity to amalgamate emotional and cognitive experiences. The symptoms of thought insertion and alien control in schizophrenia have been attributed to deficits in self-monitoring of thoughts and intentions (72). There is empiric evidence that positive symptoms, such as hallucinations and delusions, reflect impaired awareness of self-generated verbal material and misattribution of speech (73–76). Anterior cingualte has also been implicated in self-monitoring and implementation of selected action in healthy subjects (73,77). Importantly, activation deficit in AC in patients

with schizophrenia, revealed with fMRI, is associated with impaired self-monitoring of performance (78). In an exploratory study (79), cognitive flexibility has emerged as a predictor of responsiveness to CBT; this function may also involve the anterior cingulate given its role in online monitoring, error detection and conflict. On the basis of the evidence in other disorders, the dorsolateral prefrontal cortex and the hippocampus should also be considered of great interest in the investigations of neural mechanisms underlying CBT effects in schizophrenia. It would also be important to establish whether schizophrenia patients who show a meaningful clinical response to CBT have differential brain/cognitive profiles to those who fail to respond or from those who respond well to pharmacotherapy.

Other

Some data very relevant to the aim of this article have very recently emerged from a study of patients with irritable bowel syndrome (IBS) (80). IBS is considered to manifest disturbance in the brain-gut axis (81). IBS patients also show high rates of psychiatric comorbidity (82), temporal patterns of symptoms during sleep-wake cycle (disappearance of symptoms during sleep) (83), and the lack of correspondence between pain intensity and measured gut motility (84). Imaging evidence reveals differences between IBS patients and healthy controls in neural responses to actual or anticipated rectal stimuli (85). Cognitive factors such as the beliefs and thoughts of IBS patients about their symptoms also affect the symptoms of IBS (86,87). Cognitive therapy has been shown to be effective in IBS (88).

A very recent study (80) has shown that cognitive therapy, consisting of self-monitoring, cognitive reappraisal, worry control and problem solving training, reduces limbic activity during rectal balloon distension in patients with IBS. These data suggest that cognitive therapy in IBS produces changes in the network of brain circuits involving limbic regions that are commonly associated with attention to fear-related stimuli and vigilance (89). As noted earlier for OCD, similar neural changes were previously reported by placebo-controlled drug studies of IBS patients (90,91). It is possible that the cognitive therapy and pharmacotherapy of IBS achieved therapeutic gains through a common (presumably symptom related) pathway, though the two forms of treatments may have different mechanisms of action.

Conclusions

The reviewed studies clearly demonstrate that psychological interventions, such as CBT, are able to modify activity in dysfunctional neural circuitries linked to development of various psychopathological conditions. The data available so far, for example in depression, panic disorder, phobia and OCD, clearly suggest that a change in patients' symptoms and maladaptive behaviour at the mind level with psychological techniques could potentially change (normalize) the brain at the functional level in the same way as faulty brain signals resulting from dysfunctional neural circuitries lead to psychopathological behaviour.

Investigation of changes in neural activity with psychological therapies is clearly a novel area in which well-conducted research is likely to have important implications for our understanding of the mechanisms of formation and maintenance of symptoms as well as of therapeutic change. For example, if it is shown that the treatment achieves its effect on a specific symptom by targeting a particular process, it would suggest the involvement of this specific process in maintenance of that symptom (92). The study of changes in brain activity with an effective psychological treatment allows us to establish changes associated with a therapeutic response as it has (if any) minimal side-effects and lacks direct pharmaceutical actions to obscure brain changes directly related to behavioural change, whereas brain changes induced by pharmacological compounds may reflect (i) the therapeutic change, (ii) other side-effects or (iii) merely indicate the primary route of action of the drug irrespective of its therapeutic effects, for example, anti-dopaminergic actions in the case of typical antipsychotics in schizophrenia. Such an approach may also inform about the maintenance of particular symptoms. Although relevant research has begun in some disorders, the mechanism for therapeutic change with drug and/or psychological therapies is yet to be firmly established in most psychiatric conditions. A major limitation has been that not all patients respond to the same kind of therapy, suggesting that variables before the initiation of a particular therapy need to be taken into account. It would be very valuable for future research to investigate predictors of responsiveness to psychological as well as drug therapies in relevant disorders to

devise the most beneficial treatment plan for an individual patient.

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