Title

A systematic review and meta-analysis of the neural correlates of psychological therapies in major depression

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Running title: Neural effects of psychotherapy in MDD: systematic review & meta-analysis

Abstract

Longitudinal neuroimaging studies in major depression have revealed cortico-limbic abnormalities which are modulated by treatment. We performed a systematic review and meta-analysis of psychotherapy treatment studies measuring neural function and metabolism using fMRI, PET, SPECT and MRS. Seventeen studies were included in the systematic review, total of 200 major depression participants (mean age 37.6 years), all medication free, and 116 healthy controls (mean age 36.4 years). Neuroimaging assessments were performed prior to initiation of treatment and following course of treatment. Treatment durations were: 16-30 weeks for CBT, 11 weeks for behavioral activation therapy, and up to 15 months for psychodynamic psychotherapy. The meta-analysis consisted of studies in which both groups had same serial scans and comparable tasks; total of 5 studies with visual presentation tasks of emotional stimuli: 55 patients (mean age: 38.7 years) and 55 healthy controls (mean age: 36.3 years). The meta-analysis revealed a significant group by time effect in left rostral anterior cingulate, in which patients showed increased activity following psychotherapy while healthy controls showed a decrease at follow up. Longitudinal treatment effects revealed reduced left precentral cortical activity in major depression. Findings could be indicative of improvements in emotion responsivity that may be achieved following psychotherapy.

Keywords

meta-analysis; neuroimaging; major depressive disorder; cognitive behavioral therapy; psychodynamic; interpersonal, psychotherapy; psychological intervention

1. Introduction

Major depression is the most prevalent of the mental health disorders, affecting an estimated 350 million people globally, and is the leading cause of disability worldwide (Vos et al., 2015). The disorder is associated with a high risk of relapse, which is about 50% following the first depressive episode and increases up to 80% after two episodes (Mueller et al., 1999). Treatments which can reduce the risk of a depressive relapse are essential for supporting recovery and for maintaining interpersonal, social and occupational functioning. While antidepressant medication has demonstrated efficacy in reducing the risk of relapse, a course of treatment with cognitive behavioral therapy is as efficacious in preventing a depressive relapse as ongoing treatment with antidepressant medication (Cuijpers et al., 2014), and psychodynamic psychotherapy is as efficacious as cognitive behavioral therapy for the treatment of major depression (Steinert et al., 2017).

We know that psychological therapies are effective treatments for acute depressive episodes and can aid in preventing a depressive relapse, however the mechanisms of these treatments are not well understood. The different forms of therapy have been founded on distinct principles, which guide the format and procedures in each treatment. Cognitive behavioral therapy considers the interrelationship between the affect, behavior and cognitions which predominates in depression, namely the low mood, social withdrawal and negative thinking style that are characteristic of an acute depressive episode. Cognitive behavioral therapy proposes that addressing the cognitive processes and content that underlie the dysfunctional attitudes and behavior is a key component in alleviating depressive symptoms (Lorenzo-Luaces et al., 2015; Sheppard and Teasdale, 2000). Behavioral activation therapy was developed as a stand-alone component of cognitive behavioral therapy which focuses on engagement and participation in constructive reinforcing activities and reduction of avoidance and withdrawal behaviors (Ekers et al., 2014). Interpersonal therapy is based on the premise that maladaptive communication

processes negatively impact mood and thus attempts to address the interpersonal problems that are common in individuals with depression (Weissman, 2006). Psychodynamic psychotherapy seeks to understand the unconscious processes that impact on interpersonal relationships and day to day functioning in order to help the individual to become aware of these processes and to then be able to modify their responses and behaviors (de Maat et al., 2009).

While different forms of psychological therapies propose distinct formulations, there are also some common factors which contribute to their efficacy in improving depressive symptoms. For example, therapeutic alliance, which is the relationship between the patient and therapist, has been shown to mediate the clinical outcome in psychotherapy (Flückiger et al., 2012; Horvath and Luborsky, 1993; Krupnick et al., 2006; Lorenzo-Luaces et al., 2015), as well as with pharmacological and placebo treatments (Krell et al., 2004; Leuchter et al., 2014). The contribution of common and specific factors to the efficacy of each form of psychotherapy has not been established. If we could identify the components which are most important for their clinical effectiveness, then we may be able to improve clinical outcomes by optimizing these features and we could determine whether there are specific components which are more beneficial for specific features in major depression.

Investigations of mechanisms of psychological therapies in depression though have been largely based on self-report and behavioral measures. Self-report measures are subjective and inherently biased, and behavioral measures may not be able to offer the necessary precision and accuracy. Neuroimaging offers the potential to identify the neural processes that underlie the psychological therapies. Study designs that consist of measures before and following the intervention are able to demonstrate treatment effects when the neural responses that change with the clinical outcome are considered because the effects of treatment would be expected to be most evident in those patients whose depressive symptoms show the greatest improvement.

In order to examine the mechanisms of the treatment, a mediator would need to demonstrate an effect on the clinical outcome, and importantly a change in the mediator would need to precede the change in the dependent variable (Kraemer et al., 2002). Thus, it would be necessary to acquire serial measurements at: baseline prior to the intervention, early in the course of therapy before a change in symptoms occurs, as well as following the course of therapy.

The interplay between the amygdala and prefrontal regions is important for healthy emotional regulation which involves prefrontal modulation of amygdala responses (Costafreda et al., 2008). However, major depression is associated with reduced connectivity between the amygdala and the dorsal anterior cingulate cortex (Costafreda et al., 2013). If there are distinct mechanisms in each of the psychological therapies, it would be expected that there would be distinct neural mediators and correlates. Proposed mechanisms for different forms of psychological therapy have generally been based on data from the early longitudinal neuroimaging studies. Cognitive behavioral therapy is proposed to increase inhibitory cortical control from the prefrontal cortex, in particular the dorsolateral prefrontal cortex (DeRubeis et al., 2008). Behavioral activation is proposed to increase reward based behavior, such as reward anticipation by increased striatum functioning and reward feedback involving dorsolateral prefrontal and orbitofrontal regions (Dichter et al., 2009). Reductions in subgenual anterior cingulate activity following psychodynamic psychotherapy have been proposed to reflect the overcoming of repressed emotions and lessening in unconscious guilt (Abbass et al., 2014)

Longitudinal neuroimaging studies of psychological therapies have most commonly consisted of serial scans prior to and following a course of treatment. Mixed findings have been revealed though, for example amygdala activity at baseline, prior to treatment, has been reported as increased (Buchheim et al., 2012; Fu et al., 2008), decreased (Ritchey et al., 2011), as well as

showing no differences (Yoshimura et al., 2013) in major depression relative to healthy participants. These effects were then followed by reductions in amygdala activity following cognitive behavioral therapy (Fu et al., 2008), behavioral activation therapy (Dichter et al., 2009) as well as to long term psychodynamic psychotherapy (Buchheim et al., 2012). In prefrontal regions, increases (Fu et al., 2008), but also decreases (Buchheim et al., 2012), in anterior cingulate activity have been reported, as well as increases in the medial prefrontal cortex following cognitive behavioral therapy (Ritchey et al., 2011; Yoshimura et al., 2013).

Such variances can be due in part to differences in symptom profiles and concurrent antidepressant medications, experimental paradigms, scanning procedures and treatment durations. An experimental task that involves passive viewing or implicit processing of emotional stimuli is generally associated with greater probability of amygdala activation as compared to active task instructions, tasks needing increased attentional effort or a task that includes a language component (Costafreda et al., 2008), which may then have an impact on any subsequent modulation by therapy. Individual studies tend to generate modest effect sizes due to the relatively small sample sizes (Costafreda, 2012). Meta-analysis of treatment studies can detect consistent findings across studies and may provide more robust conclusions.

We performed a systematic review and meta-analysis of the neural correlates of psychological therapies in major depression. We sought to build on previous systematic reviews, which had not conducted a quantitative analysis (Quidé et al., 2012), or was limited to psychodynamic psychotherapy (Abbass et al., 2014) or to cognitive behavioral therapy (Franklin et al., 2015). Previous meta-analyses had combined depression and anxiety disorders (Messina et al., 2013) or had combined studies using a number of paradigms, as well as including a study in which patients had not responded to a trial of antidepressant medication and were taking them during cognitive behavior therapy (Boccia et al., 2016). We sought to address these confounds of

combining major depression with anxiety disorders, combining the effects of psychological therapy with the effects of pharmacological therapy, and combining cognitive and affective processing tasks.

In the present systematic review and meta-analysis, we examined the neural effects and potential mechanisms of psychological therapies in major depression. We limited the samples to major depression; examined the forms of therapy: cognitive behavioral therapy, behavioral activation therapy, interpersonal therapy and psychodynamic psychotherapy; and included the neuroimaging methods: functional MRI, PET, SPECT and magnetic resonance spectroscopy. A variety of neuroimaging tasks were assessed in the systematic review, but the meta-analysis consisted only of studies in which both the patient and healthy control groups underwent the same serial scans and comparable tasks. The only studies which met these criteria had applied visual affective processing tasks. Furthermore, the meta-analysis directly addressed the potential of a positive reporting bias by including both whole brain and region of interest studies as well as studies which failed to show any baseline group differences.

We examined the following contrasts: (1) to determine the effects of therapy in a group by time interaction analysis in major depression and healthy participants, which accounts for potential confounds of time and repeated scans; (2) to assess the effects of therapy in a pre-treatment (baseline) versus post-treatment contrast in patients with major depression; and (3) to assess the specific neural correlates of therapy in a correlation of the change in neural responses following treatment with the change in depressive symptom severity.

2. Methods

2.1. Systematic review strategy and selection criteria

Studies investigating psychological treatment effects on neural activity were identified through searches of PubMed and Scopus from January 1986 to 1 May 2017 using the search terms: “depression”, "MRI" or “PET” or “SPECT”; and “psychotherapy” or "interpersonal therapy” or “cognitive behavioral therapy” or “psychodynamic”, limited to ‘humans’ and ‘English’ language. References of retrieved papers, reviews (Abbass et al., 2014; Gülfizar, 2012; MacQueen, 2009), systematic reviews (Roffman et al., 2005; Weingarten and Strauman, 2015), and meta-analyses (Boccia et al., 2016; Franklin et al., 2015) were also examined, including Springer Online Archives Collection. Authors were contacted for clarification about their studies, for example if the sample included participants with primary comorbid disorders at the time of recruitment or who were taking concomitant medications. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1) (Liberati et al., 2009).

Inclusion criteria were: 1) adults 18 - 65 years; 2) diagnosis of major depression, ascertained by standard diagnostic criteria (DSM, ICD), that was a first episode or recurrent; 3) participants who were either medication free or drug naïve; 4) treatment with a psychological therapy for a minimum of 6 weeks including: CBT, cognitive analytic therapy, interpersonal therapy, psychodynamic and behavioral activation therapy; 5) sample size of over 5 participants in the treatment group; 6) neuroimaging assessments prior to the initiation of treatment at baseline and following the course of treatment (i.e., psychotherapy for > 6 weeks); and 7) neuroimaging assessment, namely neural activity, connectivity or metabolism (i.e., glucose, serotonin and GABA) using functional MRI (fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT) or magnetic resonance spectroscopy (MRS); 8) English language publications. Exclusion criteria were: 1) comorbid illnesses as primary diagnoses at the time of recruitment; 2) other forms of depression i.e., chronic depression, treatment resistant depression, bipolar depression, old age depression; and 3) concurrent therapy or treatment procedures.

2.2. Data extraction

Demographic characteristics, forms of therapy, neuroimaging tasks and study findings were extracted (Table 1). Quality was evaluated using the criteria of the Quality Assessment Tool for Quantitative Studies (Supplementary Table 1) (QATQS; National Collaborating Centre for Methods and Tools) (Thomas et al., 2004).

From the neuroimaging data, the following data were extracted: sample size, contrasts examined, normalization template (MNI or Talairach), location information (*x, y, z* coordinates of the brain regions), field of view (region of interest (ROI) or whole brain), statistical threshold, threshold type (*p, F, z, t*) and value, filter value (full width at half maximum) (van der Velde et al., 2013).

Depression severity in the included studies was assessed by standardized rating measures (Beck Depression Inventory (BDI), Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HRSD). The change in depressive severity was determined as the difference between post- and pre- treatment depression severity scores. To compare depression severity across studies which used different rating measures, the scores were normalized by dividing the reported score by the maximum possible score on the rating scale.

2.3. Meta-analysis

The meta-analysis consisted of three contrasts: 1) group by time interactions between major depression and healthy participants; 2) pre-treatment (baseline) versus post-treatment responses in patients with major depression; and 3) correlation of the neural changes with change in depressive severity from pre-treatment to post-treatment. Studies which included

healthy participants who had undergone the same scans at the same timepoints were included to account for potential effects of repeated scanning and changes over time.

The meta-analysis was performed using the parametric coordinate-based meta-analysis method (PCM) (Costafreda, 2012), which provides quantitative meta-analytic summaries that address the limitations of methods which tend to treat studies with different statistical thresholds as equivalent. We were able to incorporate both region of interest and whole brain analyses and to integrate regions reported as significant in the original studies as well as sub-threshold non-significant findings to integrate the real but often modest effect sizes into the summary map. This allowed us to generate an unbiased valid pooled effect size summary of studies with varying thresholds while minimizing potential biases towards a positive effect.

Talairach coordinates were converted to the MNI coordinate system by using a non-linear transformation approach (Brett et al., 2001). Differing statistical thresholds were converted into corresponding *Z* scores to achieve a common measure of effect size. Non-significant findings were reported by intervals with the values for the unknown measurements that were less than the reported statistical thresholds (van der Velde et al., 2013).

Effect size summary output maps were produced separately for the three contrasts. The output was obtained after correcting for multiple comparisons, using a statistical threshold of $P < 0.05$ false discovery rate (FDR). Only clusters of voxels which were larger than the chosen extent threshold of 50 mm^3 have been reported.

3. Results

3.1. Characteristics of included studies

The search criteria yielded 99 references in Scopus and 488 references in PubMed databases, and 7 additional manuscripts were identified through reference lists of relevant articles. Following exclusion of duplicate titles, 81 studies were screened.

Seventeen studies met the inclusion and exclusion criteria and were included in the systematic review, consisting of a total of 200 participants with major depression (mean age 37.6 years) and 116 healthy controls (mean age 36.4 years). All studies had used DSM or ICD criteria to diagnose major depression.

Four forms of psychological therapies had been examined in these studies: CBT (*n* = 9 studies, including one internet CBT (iCBT), behavioral activation therapy (BAT) (*n* = 2), interpersonal therapy (IPT) (*n* = 2) and long term psychodynamic therapy (*n* = 4). The duration of treatment ranged from 11-30 weeks for CBT, 11 weeks for BAT, 12-16 weeks for IPT and 4 -12 months for long term psychodynamic therapy.

The neuroimaging assessments were generally performed prior to the initiation of treatment at baseline and following the course of treatment for all studies expect one study which acquired neuroimaging data during treatment at 6 weeks (Martin et al., 2001). Neuroimaging assessments were: task-based functional MRI (*n* = 7) (Buchheim et al., 2012; Dichter et al., 2009; Dichter et al., 2010; Fu et al., 2008; Ritchey et al., 2011; Sankar et al., 2015; Wiswede et al., 2014); resting state functional MRI (*n* = 1) (Shou et al., 2017); FDG-PET to measure resting state regional glucose metabolism (*n* = 3) (Brody et al., 2001; Goldapple et al., 2004; Kennedy et al., 2007); resting state SPECT to measure cerebral blood flow using ^{99m}technetium-labelled hexamethyl propylene amine oxim HMPAO (*n* = 1) (Martin et al., 2001), serotonin transporter (SERT) binding using [^{123} I]-ADAM (*n* = 1) (Amsterdam et al., 2013) and SERT and dopamine transporter (DAT) densities using [^{123}I]nor-β-CIT (*n* = 1) (Lehto et al., 2008); MRS to measure

cortical γ aminobutyric acid (GABA) and glutamate concentrations (n = 1) (Sanacora et al., 2006) and PET imaging to examine striatal and thalamic $D_{2/3}$ receptor binding using [^{11}C]raclopride (n = 1) (Hirvonen et al., 2011), and 5-HT_{1B} receptor binding using [^{11}C]AZ10419369 (n = 1) (Tiger et al., 2014).

Ten studies included a healthy control group who had also undergone the same follow up scans as the patient group: 3 studies were resting state, consisting of FDG-PET (Brody et al., 2001), [^{123} I]-ADAM SPECT (Amsterdam et al., 2013) and resting state functional MRI (Shou et al., 2017); and 7 studies applied a functional task (Buchheim et al., 2012; Dichter et al., 2009; Dichter et al., 2010; Fu et al., 2008; Ritchey et al., 2011; Sankar et al., 2015; Wiswede et al., 2014). The functional task was an affective processing task in 5 studies (Buchheim et al., 2012; Dichter et al., 2009; Dichter et al., 2010; Fu et al., 2008; Ritchey et al., 2011), statements referring to dysfunctional relationship themes in 1 study (Wiswede et al., 2014), and statements assessing dysfunctional attitudes in 1 study (Sankar et al., 2015).

The meta-analysis was conducted on the studies which had comparable tasks: 5 studies which used an affective processing task involving visual presentation of emotional stimuli (Buchheim et al., 2012; Dichter et al., 2009; Dichter et al., 2010; Fu et al., 2008; Ritchey et al., 2011), consisting of 55 participants with major depression (mean age: 38.7 years) and 55 healthy controls (mean age: 36.3 years).

3.2. Systematic review: qualitative analysis

Following treatment with CBT, decreased activity during resting state was observed in the prefrontal cortex, specifically in the ventrolateral prefrontal cortex (VLPFC) (BA11/47) (Goldapple et al., 2004; Kennedy et al., 2007), dorsolateral prefrontal cortex (DLPFC) (BA9/46) (Goldapple et al., 2004) and dorsomedial prefrontal cortex (dmPFC) (Kennedy et al., 2007) in

patients with major depression, while increased activity in the ventromedial prefrontal cortex was found in response to an affective processing task (Ritchey et al., 2011). Following psychodynamic psychotherapy, decreased medial prefrontal cortex (mPFC) activity was also reported (Buchheim et al., 2012; Wiswede et al., 2014) and more generally in the prefrontal cortex following IPT (Brody et al., 2001).

In the cingulate cortex, increased activity was noted following CBT therapy in the dorsal anterior cingulate cortex (ACC) (BA24) in a resting state PET study (Goldapple et al., 2004) and (BA 24, 32) and during an affective processing task (Fu et al., 2008), while activity in the subgenual ACC was found to decrease following CBT as measured during resting state (Kennedy et al., 2007), as well as following psychodynamic psychotherapy (Buchheim et al., 2012). In the poster cingulate, increases following CBT were reported during an affective processing task (BA23, 30, 31) (Fu et al., 2008) and following IPT (Martin et al., 2001), while decreases were also noted following CBT as measured during resting state (BA 31) (Goldapple et al., 2004) and during the DAS task (BA 30) (Sankar et al., 2015).

In the hippocampus, increased arousal related responses were found in an IAPS picture task (Ritchey et al., 2011), as well as increased activity during resting state (Goldapple et al., 2004), and more generally in the medial temporal region (Amsterdam et al., 2013). However, decreased hippocampal activity has also been observed following CBT in response to an affective processing task (Fu et al., 2008) and following psychodynamic psychotherapy in response to emotional stimuli (Buchheim et al., 2012).

In the amygdala, decreased activity was reported following CBT during an affective processing task (Fu et al., 2008), as well as following psychodynamic psychotherapy during a sentence processing task (Wiswede et al., 2014) and in response to emotional stimuli (Buchheim et al.,

2012). At rest, major depression was associated with greater amygdala connectivity with the inferior frontal gyrus following CBT as compared with healthy controls (Shou et al., 2017).

In the striatum, there were no changes in either DAT densities as measured with [^{123}I]nor-β-CIT (Lehto et al., 2008) or in D2/D3 binding potential as measured with [^{11}C]raclopride (Hirvonen et al., 2011) following psychodynamic psychotherapy, nor were there any changes observed in midbrain SERT densities measured using [^{123}I]nor-β-CIT following psychological therapy (Lehto et al., 2008).

3.3. Meta-analysis

3.3.1. Group by time interaction effect, putative effects of psychological therapy

The group by time interaction effect could be investigated from 4 studies (n = 44 major depression, n = 48 healthy participants) as 1 study (Ritchey et al., 2011) did not examine group by time interaction effects. All the studies had applied a whole brain analysis (Buchheim et al., 2012; Dichter et al., 2009; Dichter et al., 2010; Fu et al., 2008).

The meta-analysis revealed a significant group by time interaction effect in the left rostral (pregenual) anterior cingulate, in which there was an increase in activity following psychological therapy in patients with major depression while healthy controls showed a reduction in activity at the follow up scan (MNI coordinates, x = -6, y = 34, z = 4; volume 208 mm^3; Z = -2.76; r = -0.40) (Figure 2).

3.3.2. Main effect in patients with major depression

Four of the 5 studies included in the meta-analysis examined the longitudinal neural changes with treatment in patients (n = 39 major depression) (Dichter et al., 2009; Dichter et al., 2010; Fu et al., 2008; Ritchey et al., 2011). One study applied a ROI analysis (Ritchey et al., 2011), and

3 studies used a whole brain analysis (Dichter et al., 2009; Dichter et al., 2010; Fu et al., 2008), however the pre-treatment versus post-treatment analysis for these studies was only performed with those regions which had a significant group by time interaction, thereby was considered as a ROI analysis.

The meta-analysis found decreased activity in the left precentral gyrus following treatment with CBT (MNI coordinates, x = -34, y = -28, z = 60; volume 616 mm^3; Z = -4.24; r = -0.49) (Figure 3). Clusters in the inferior parietal region, including in the supramarginal gyrus, did not meet the 50 mm^3 extent threshold. No regions showed an increase in response following psychotherapy.

3.3.3. Correlations with improvements in depressive severity

As only one study had examined the association between changes with serial scans and depressive symptoms (Buchheim et al., 2012), this contrast was not examined.

4. Discussion

We sought to delineate the neural effects of psychological therapies in longitudinal prospective treatment studies in major depression. The systematic review consisted of studies which had acquired serial neuroimaging scans prior to and following a course of treatment with a psychological therapy. The meta-analysis was conducted in studies which had a sufficient number of comparable tasks and in which both the patient and healthy control groups had undergone the same set of scans, in order to take into account effects of repeated task presentations and effects of time. The studies included in the meta-analysis had used affective processing tasks with visual presentation of emotional stimuli. The meta-analysis revealed a significant interaction effect of treatment in the rostral anterior cingulate in major depression as compared to healthy participants and a significant main effect of treatment in major depression

in the precentral gyrus. The findings provide some insight into the potential mechanisms and specificity of the treatment effects of psychological therapies.

The group by time interaction analysis revealed a significant effect in the left rostral anterior cingulate gyrus, in which patients with major depression showed increased activity following psychological therapy while healthy controls showed reduced activity at the follow up scan. The ventral-rostral regions in the anterior cingulate have strong connections with core emotion processing regions, in particular the amygdala, and is purported to have a regulatory function on limbic regions (Etkin et al., 2011), as well as in reward processing and decision making (Botvinick, 2007; Bush et al., 2000). Healthy emotion regulation is linked to suppression of amygdala activity through communication with the rostral and dorsal anterior cingulate and dorsolateral prefrontal cortices (Banks et al., 2007; Carballedo et al., 2011; Costafreda et al., 2008). A characteristic feature of depression is the inability to disengage from negative stimuli once they have secured attention (Gotlib and Joormann, 2010), which is evident in the impaired connectivity between the anterior cingulate and amygdala in major depression (Costafreda et al., 2013).

Cognitive control of emotional experience may be attempted using a number of strategies of varying effectiveness: cognitive reappraisal, which involves cognitive re-interpretation of the presented stimuli; suppression, which is an active attempt to inhibit the emotional response; or negative ruminations, which is the process of repetitive passive thinking about the experience of distress (Garnefski and Kraaij, 2006; Nolen-Hoeksema and Davis, 1999). While each process may be used at different times, the predominant use of suppression and negative ruminations has detrimental effects on mood and cognition (Dillon et al., 2007), and healthy emotional regulation includes cognitive reappraisal. Moreover, increased anterior cingulate activity is

predictive of a good clinical response to pharmacological as well as CBT treatments for major depression (Fu et al., 2013).

The increase in rostral anterior cingulate activity following the psychological therapies could reflect improvements in emotion regulation, with the further possibility that a mechanism is improvement in cognitive reappraisal. However, cognitive reappraisal was not an explicit component of the affective processing studies that were included in the present meta-analysis. Furthermore, Rubin-Falcon and colleagues (2018) found that it was reduced activation, including in the subgenual anterior cingulate, which was associated with improved clinical outcome following CBT during an emotion regulation task for negative autobiographical memories.

It is possible that the activity in the rostral anterior cingulate may reflect increased emotional responsivity to the affective processing task, perhaps with an implication of self-referential processing (Nejad et al., 2013). Meta-analyses demonstrate the prognostic significance of increased activity in the rostral anterior cingulate cortex with the likelihood of clinical response (Fu et al., 2013; Pizzagalli, 2011), and psychological therapy, in particular CBT, is associated with a reduced risk of depressive relapse (Cuijpers et al., 2014). Most broadly, the findings suggest that there are cortical top down effects of psychological therapy (Goldapple et al., 2004), although this cannot be empirically demonstrated in the present meta-analysis in the absence of accompanying subcortical modulations.

The specificity of the effects of the different psychological therapies warrants further investigation as the individual studies revealed increased anterior cingulate activity following short term behavioral activation or cognitive behavioral therapy (Dichter et al., 2009; Fu et al., 2008). This finding is also consistent with resting state PET studies, which reported increased

anterior cingulate activity following CBT (Goldapple et al., 2004), though long term psychodynamic psychotherapy was associated with a reduction in anterior cingulate activity (Buchheim et al., 2012).

The meta-analysis also revealed that a longitudinal treatment effect of psychotherapy was reduced activity in the left precentral cortex in major depression. The precentral cortex is primarily associated with motor functions, but it may also be involved in cognitive functioning (Zhang et al., 2012) as it is engaged during negative attributional bias (Blackwood et al., 2000) and working memory load (de Fockert et al., 2001). In major depression, precentral cortical activation has been observed in response to working memory load (Walsh et al., 2007) as well as to negative emotional pictures (Ritchey et al., 2011) and facial processing of sad, angry (Frodl et al., 2009; Fu et al., 2004) and fearful (Arnone et al., 2012) expressions in major depression (meta-analysis: (Zhao et al., 2014). Longitudinal studies have further demonstrated that emotion-regulation dependent reductions in the precentral gyrus after treatment was associated with improved treatment outcome (Rubin-Falcone et al., 2018). A key mechanism in cognitive behavioral therapy is cognitive change, whereby the treatment improves the maladaptive cognitions that are characteristic of major depression (Beck, 1979). A reduction in precentral activation following psychotherapy could be consistent with an improvement in negative cognitive styles with treatment.

While the Boccia et al. (2016) meta-analysis also reported increased activation in prefrontal and cortical regions, the location of the effects differed as they included the left inferior and superior frontal, middle cingulate, middle temporal, and bilateral precentral regions. However, the studies in the meta-analysis (Boccia et al., 2016) had greater heterogeneity in the scanning paradigms, ranging from resting state to task-based studies; in the patient samples, which included recurrent as well as treatment resistant forms of depression (Yoshimura et al., 2013); and in the

medication status of the samples. We were able to delineate an interaction effect in the left rostral anterior cingulate in response to emotion processing tasks, by including only studies with the most comparable scanning paradigms which reduced heterogeneity and increased the power to find a significant effect.

In the present meta-analysis, however, we could not examine correlations between changes in brain activation and treatment response as only one longitudinal study had examined this contrast. One of the most replicated predictors of clinical response is anterior cingulate activity, in which increased baseline anterior cingulate activity is predictive of clinical response (meta-analysis (Fu et al., 2013)). Increases in anterior cingulate activity following psychotherapy has been associated with improvement in rumination (Yoshimura et al., 2013) and treatment response (Goldapple et al., 2004), although improvements in depression severity was also associated with decreases in anterior cingulate following long-term psychodynamic therapy (Buchheim et al., 2012), perhaps indicative of specificity of effects of the different forms of psychological therapies. Longitudinal neuroimaging studies have further revealed reductions in bilateral cerebellum that were correlated with improvement in depression (Rubin-Falcone et al., 2018). Although the cerebellum is usually associated with motor control, language and attention, cerebellar engagement has also been noted during sad mood induction by musical pieces (Mitterschiffthaler et al., 2007).

The systematic review identified that there was attenuated activity in the amygdala following both CBT and psychodynamic psychotherapy which was observed with emotional task-based neuroimaging studies (Buchheim et al., 2012; Fu et al., 2008; Wiswede et al., 2014) rather than resting state studies. While this finding has been noted in meta-analysis of pharmacological treatment studies (Delaveau et al., 2011; Fitzgerald et al., 2008), this was not evident in the present or Boccia et al. (2016) meta-analyses. Whether pharmacological treatments have

greater effects in limbic and subcortical regions (Boccia et al., 2016; Delaveau et al., 2011; Fitzgerald et al., 2008) as compared to psychological treatments is intriguing, but requires further investigation because the number of pharmacological studies to date has been several fold greater than the number of psychological treatment studies.

While all the studies included in the meta-analysis used emotional processing tasks, there was some variability in the valence of the stimuli, in which one study used a reward processing task (Dichter et al., 2009). As well, limited effects were observed from the serotonin and dopamine transporter or dopamine binding studies (Hirvonen et al., 2011; Lehto et al., 2008), although there were only a few studies.

Limitations of the present study include the inability to determine the specificity of the observed treatment effects, despite the observed group by time interaction effects, because none of the studies had a patient group receiving a placebo form of treatment. The inclusion of only published data might have inadvertently introduced a bias, however we were able to incorporate both ROI and whole brain analyses and to account for variations in sample size, statistical thresholds and smoothing kernel, and the PCM method allows integration of sub-threshold non-significant findings (Costafreda, 2012), in contrast to the activation likelihood estimation method, which assumes that a non-significant finding is the same as having an effect size of zero, as applied in Boccia et al. (2016) meta-analysis. Due to the limited number of longitudinal studies meeting eligibility criteria, the analyses were restricted to two contrasts, and pre-post treatment designs could implicate neural changes that are not necessarily related to the treatment mechanism. Study designs that examine changes in neural responses which correlate with changes in clinical symptoms are important to delineate potential mechanisms. Another related, yet important study design that is seldom investigated is group by time interaction effects between responders and non-responders.

Furthermore, the forms of psychotherapy had a range of treatment durations. As a general issue, the length of treatment is based on guidelines for the specific form of psychotherapy, and some are specified in evidence-based guidelines (ex. National Institute for Health and Clinical Excellence (NICE) Guidelines in the United Kingdom), while some durations are governed by individual therapeutic contracts or insurance coverage. The NICE Guidelines for moderate to severe depression, for instance, recommend 3-4 months of treatment with CBT, BAT or IPT, or longer durations (4-6 months) for psychodynamic psychotherapy. In the present meta-analysis, treatment durations using CBT (Sankar et al., 2015, Fu et al., 2008) and BAT (Dichter et al., 2009, 2010) were in line with the recommended guidelines. However, studies have not consisted of serial fMRI scans at regular intervals during their treatment. Hence, it is difficult to ascertain the average length of time in which one can expect to start seeing significant neural changes. We propose that it is possible for some neural changes to be evident early on, before subjective improvements in mood are reported, as observed with treatment with antidepressant medication (Fu et al., 2015).

In summary, treatment with psychological therapy was associated with an increase in rostral anterior cingulate activity during emotion processing tasks in major depression in comparison to healthy participants. The finding is a suggestive demonstration of the effectiveness of psychological therapy in improving emotion responsivity and regulation in major depression. Psychological therapy, in particular CBT, has demonstrated improved rates of depressive relapse that is comparable to maintenance pharmacological treatment. However, whether an improvement in treatment outcome is linked with an increase in anterior cingulate activity following psychotherapy and with improvements in emotion regulation and appraisal would require investigation with specific paradigms that examine these processes in a longitudinal

treatment study. Understanding the mechanisms of treatments on brain activity has the potential for developing diagnostic biomarkers and identifying new targets for beneficial forms of treatment.

Authors and contributors

AM, AS and VL independently performed the literature search. AM, AS and VL independently performed the data extraction for the systematic review, and AS and TA independently performed the neuroimaging data extraction. Any discrepancies were reviewed with CF and SC and resolved by consensus.

AM and AS screened and recorded the titles and abstracts from the databases, assessed individual papers for eligibility and extracted data from relevant studies, which VL and CF verified. AM, AS and VL conducted, discussed and resolved QATQS scoring using an evaluation form and the dictionary designated to score study quality. CF oversaw all aspects of study design, literature search, compilation and discussion of findings, and manuscript preparation.

Declaration of interests

AS, SG and PH report no competing interests. CF has held recent research grants from Eli Lilly and GlaxoSmithKline and has received speaker fees from Roche.

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Figure Legends

Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of search strategy.

Figure 2.

Group by time interaction effects of psychological therapies. There was a significant group by time interaction in the left rostral anterior cingulate cortex, in which participants with major depression showed increased activity following psychological therapy while healthy participants showed a reduction in activity at the follow up scan. Sagittal (*x*), coronal (y), and axial (x) coordinates for each section are presented. Results are $P < 0.05$ FDR corrected.

Figure 3.

Longitudinal changes following psychological therapies. There was a main effect of in the left precentral gyrus, which showed decreased activity following psychological therapy in major depression. The coronal (*y*) coordinate of each section is presented. There were additional regions which did not meet our threshold of 50 mm^3 for significance. Results are $P < 0.05$ FDR corrected.

Figure 1.

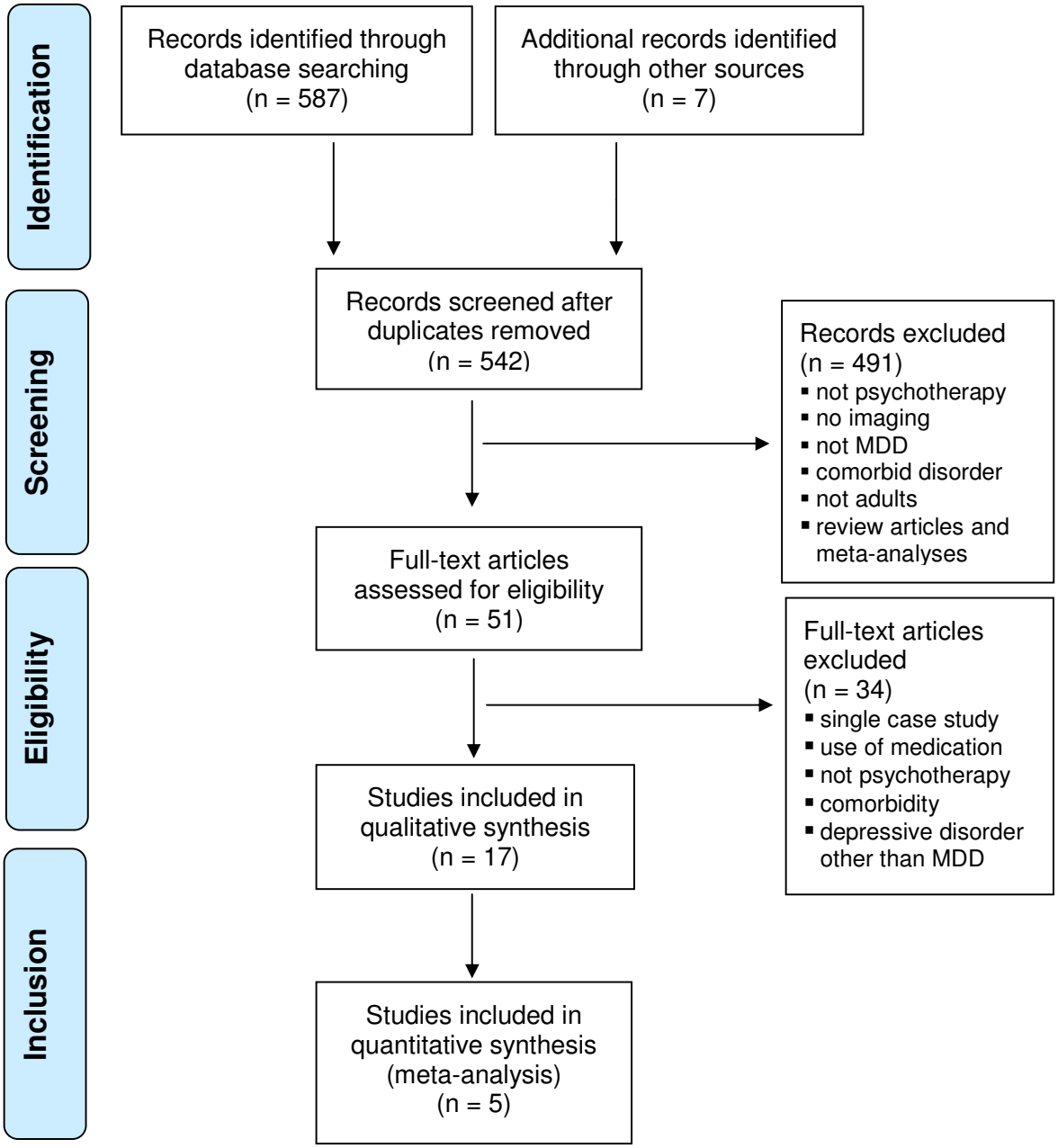
Identification
Screening
Eligibility
Inclusion
Records identified through database searching (n = 587)
Additional records identified through other sources (n = 7)
Records screened after duplicates removed (n = 542)
Records excluded (n = 491)
not psychotherapy
no imaging
not MDD
comorbid disorder
not adults
review articles and meta-analyses
Full-text articles assessed for eligibility (n = 51)
Full-text articles excluded (n = 34)
single case study
use of medication
not psychotherapy
comorbidity
depressive disorder other than MDD
Studies included in qualitative synthesis (n = 17)
Studies included in quantitative synthesis (meta-analysis) (n = 5)

Figure 2.

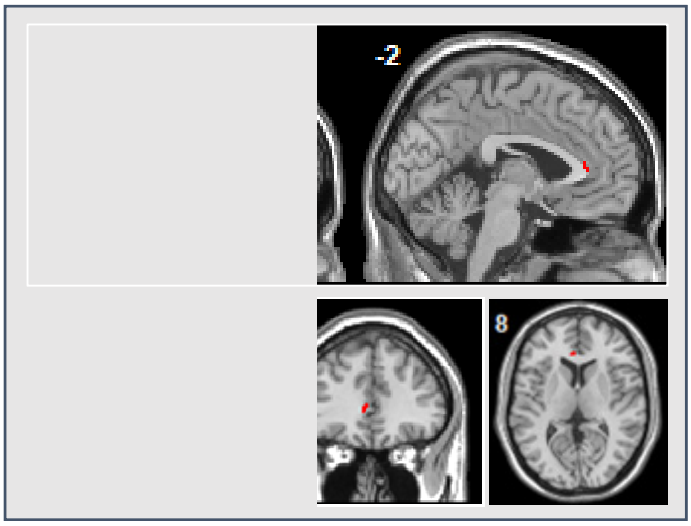

Figure 3.

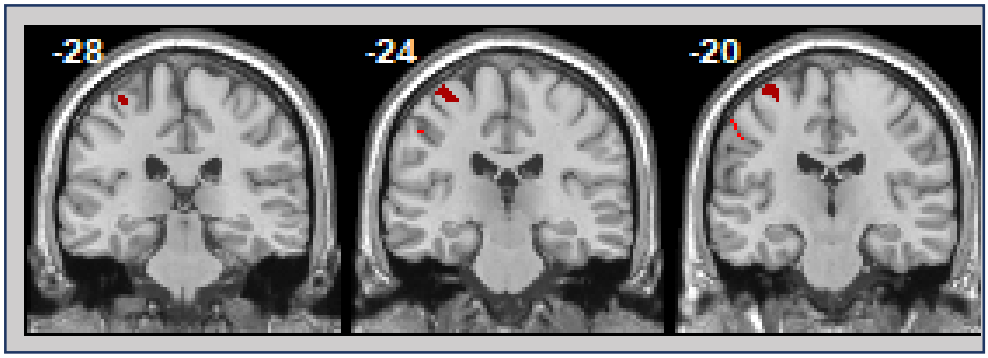

Table 1. Summary of demographic characteristics, psychological therapies and neuroimaging tasks

Study	Year	Number		Age		Diagnosis	Therapy	Sessions	Scan Interval	Imaging	Tasks
		MDD	HC	MDD	HC						
Resting state											
Amsterdam	2013	20 (15)	10 (7)	41±13	45±11	DSM-IV, SCID	CBT	12	12 weeks	[^{123}I]ADAM SPECT	
Brody	2001	14 (6)	16 (8)	41±11	36±18	DSM-IV	IPT	12	12 weeks	FDG-PET	
Goldapple	2004	14 (6)	-	41±9	-	DSM-IV, DSM-III-R, SCID	CBT	15-20	15-20 weeks	FDG-PET	
Kennedy	2007	12 (5)	-	30±10	-	DSM-IV, SCID	CBT	14	14 weeks	FDG-PET	
Martin	2001	13 (4)	-	38±5	-	DSM-IV	IPT	16	6 weeks	Tc-*99m HMPAO* SPECT	
Shou	2017	17	18	32±7	31±10	DSM-IV, SCID	CBT	12	12 weeks	MRI	
Task-based studies											
*Buchheim	2012	16	17	39±12	39±12	DSM-IV, SCID	PDT	-	15 months	fMRI	AAP pictures
*Dichter	2009	12 (6)	15 (6)	39±10	31±10	DSM-IV, SCID	BATD	11	15 weeks	fMRI	wheel of fortune
*Dichter	2010	12 (6)	15 (6)	39±10	31±10	DSM-IV, SCID	BATD	11	15 weeks	fMRI	IAPS
*Fu	2008	16 (3)	16 (3)	40±9	39±9	DSM-IV, SCID	CBT	16	16 weeks	fMRI	emotional faces
*Ritchey	2011	11 (3)	7 (2)	36±10	35±7	DSM-IV, SCID	CBT	21	30 weeks	fMRI	IAPS
Sankar	2015	16 (3)	16 (3)	40±9	40±9	DSM-IV, SCID	CBT	16	16 weeks	fMRI	dysfunctional attitudes
Wiswede	2014	18 (4)	17 (3)	40±13	38±12	DSM-IV, SCID	PDT	-	8 months	fMRI	interpersonal statements
Receptor and MRS studies											
Hirvonen	2011	8 (5)	-	41±10	-	DSM-IV, SCID	PDT	16	16 weeks	[^{11}C]Raclopride PET	
Lehto	2008	11 (0)	-	27±7	-	DSM-IV, SCID	PDT	80	12 months	[^{123}I]nor-β-CIT SPECT	
Sanacora	2006	8	-	-	-	DSM, SCID	CBT	12	12 weeks	MRS	
Tiger	2014	10 (4)	-	48±17	-	M.I.N.I	iCBT	12	14 weeks	[^{11}C]AZ1041936 PET	

The first author and year of study is presented. Number of participants is presented with number of males in parenthesis. Sessions refers to the mean number of therapy sessions which were usually provided weekly, with the exception of Lehto et al. (2008) wherein patients received 2 psychotherapy sessions per week (total = approximately 80 sessions) and Amsterdam et al. (2013) wherein sessions were twice weekly for the first four weeks and weekly thereafter through week 12. Buchheim (2012) reported age (mean, SD) for patients and controls together. Both Buchheim (2012) and Wiswede (2014) refer to the number of months of therapy. For Ritchey and colleagues (2011), mean and standard deviation values are provided for the initial larger sample that included an additional 11 MDD participants and 7 controls, who did not complete treatment

and/or follow up assessment. Five studies had also included a MDD group that received treatment with antidepressant medication: Brody (10 participants (5 males)); Goldapple (13 (13)); Kennedy (12 (4)); Martin (15 (4)); Hirvonen (14 (5)). Mean age is presented in years rounded up to the nearest year $\pm$ standard deviation. '-',not stated/not applicable. Diagnosis refers to the diagnostic criteria used to determine the diagnosis. Studies included in the meta-analysis are denoted by an asterix (*). Abbreviations: MDD: major depressive disorder; HC: healthy controls; AAP: Adult Attachment Projective Picture System; CBT: cognitive behavioural therapy; IPT: interpersonal therapy; PDT: psychodynamic therapy; BATD: Behavioural Activation Therapy for Depression; iCBT: internet cognitive behavioural therapy; SPECT: single photon emission computed tomography; PET-FDG: fluorine-18-fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; IAPS, International Affective Picture System. The radioligands used for the PET and SPECT studies are reported. [^{123}I]-ADAM: measures brain serotonin transporter (SERT) binding; Tc-99m HMPAO: measures cerebral blood flow reflecting brain metabolism; [^{11}C] Raclopride: measures $D_{2/3}$ receptor binding; [^{123}I]nor-β-CIT: measures SERT and dopamine transporter (DAT) densities; [^{11}C]AZ1041936: measures 5-HT_{1B} binding.