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Review Article

Cognitive behavioural therapy for depression: systematic review of imaging studies

Franklin G, Carson AJ, Welch KA. Cognitive behavioural therapy for depression: systematic review of imaging studies.

Objective: Although cognitive behavioural therapy (CBT) has been shown to be an effective treatment for depression, the biological mechanisms underpinning it are less clear. This review examines if it is associated with changes identifiable with current brain imaging technologies.
Methods: To better understand the mechanisms by which CBT exerts its effects, we undertook a systematic review of studies examining brain imaging changes associated with CBT treatment of depression.
Results: Ten studies were identified, five applying functional magnetic resonance imaging, three positron emission tomography, one single photon emission computer tomography, and one magnetic resonance spectroscopy. No studies used structural MRI. Eight studies included a comparator group; in only one of these studies was there randomised allocation to another treatment. CBT-associated changes were most commonly observed in the anterior cingulate cortex (ACC), posterior cingulate, ventromedial prefrontal cortex/orbitofrontal cortex (VMPFC/OFC) and amygdala/hippocampus.
Discussion: The evidence, such as it is, suggests resting state activity in the dorsal ACC is decreased by CBT. It has previously been suggested that treatment with CBT may result in increased efficiency of a putative 'dorsal cognitive circuit', important in cognitive control and effortful regulation of emotion. It is speculated this results in an increased capacity for 'top-down' emotion regulation, which is employed when skills taught in CBT are engaged. Though changes in activity of the dorsal ACC could be seen as in-keeping with this model, the data are currently insufficient to make definitive statements about how CBT exerts its effects. Data do support the contention that CBT is associated with biological brain changes detectable with current imaging technologies.

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Summations

- Ten studies have examined the effects of CBT using brain imaging. They consistently demonstrate that it is associated with measurable changes in brain function.
- Changes in anterior cingulate cortex activity following CBT are most consistently reported. Given the role of this region in regulating cognitive control it is a predictable target for CBT effects.
- Though the model has appeal, the imaging data available to date do not fully support the proposal that CBT works by increasing an individual's capacity for 'top-down' emotion regulation.

Considerations

- To date only a relatively small number of studies have examined the effects of CBT with brain imaging, and study heterogeneity hampers comparison of findings across studies.
- Ethical considerations prevent comparison of CBT-associated brain changes to those occurring in an untreated depressed group.
- The current study cannot disentangle effects specific to CBT to those consequent simply to being in a therapeutic relationship.

Introduction

Over the last few decades our understanding of psychiatric illness has been transformed by elucidation of its associated biological abnormalities. Depression, for example, is associated with particular allelic variants, demonstrable endocrine abnormalities and replicated structural and functional brain changes (1). Further, the mechanism of antidepressant action has been examined with both structural and functional imaging (2).

This 'biological' understanding of depression must however acknowledge the efficacy of psychological treatments, and raises the question of whether these treatment effects are also biologically identifiable. Of psychological treatments, cognitive behavioural therapy (CBT) has arguably the strongest evidence base. It was developed by Beck in the 1960s, building on his cognitive model of depression which proposed that the individual has a profoundly negative view of oneself, the world and the future, with biased information acquisition and processing crucial to depression onset and maintenance (3). These biases are demonstrable experimentally, and functional neuroimaging can associate them with changes in brain function. It has been shown, for example, that the depressed show amygdala hyperactivity when processing emotionally negative information (4), this excessive activity persisting after the aversive stimulus is removed (5). This explains why depressed individuals are more likely to attend to negative stimuli (6), and experience a stronger and longer lasting neural response. In another example, activity in the right ventrolateral prefrontal cortex (VLPFC), right dorsolateral pre-frontal cortex (DLPFC) and right superior parietal cortex is decreased compared with healthy controls when shifting attention from negative stimuli (7,8). This may reflect dysfunction of these regions, potentially underpinning the reduced ability to shift attention from stimuli associated with negative affect (9).

Related to the above is a body of evidence emphasising the centrality of 'cognitive control' in brain function. This refers to those executive processes that allow information processing and behaviour to vary adaptively from moment to moment depending on current goals, rather than remaining rigid and inflexible. In a highly influential synthesis of these and other data related to prefrontal cortex (PFC) function, Miller and Cohen proposed that the PFC represents and maintains context for responding or goals, which in turn biases processing in posterior and premotor areas in order to support task appropriate responding (10). The depression-associated cognitive biases outlined above can easily be conceptualised to reflect changes in these processes, their reduced efficiency also potentially underpinning the deficits in attention, concentration and executive function reproducibly reported in depression (11). Consequently, if CBT does operate through normalising deranged cognitive control processes, one may expect imaging studies to identify effects in the PFC and related subcortical circuits important in executive function.

Though psychological treatment effects may be assumed too subtle to detect with structural imaging, existing evidence suggests this is not so. CBT for chronic fatigue syndrome has been shown to increase DLPFC volume for example (12), and skill acquisition in the healthy can be associated with both grey and white matter changes (13–15). It is in this context that we undertook a systematic review of imaging studies examining the effects on the brain of CBT for depression. Though previous reviews have examined functional brain changes associated with psychological treatment, they have tended to pool findings for different psychotherapies and/or psychiatric conditions (14–16).

Aims of the study

We sought to systematically review all studies which utilised functional or structural imaging to examine changes in brain function or structure associated with treatment of depression using CBT. Given what is known about brain structural and functional changes in depression, we expected treatment with CBT to be associated with changes in frontal and subcortical regions important for cognitive control, and the limbic system.

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Methods

The systematic review was conducted according to PRISMA guidance (16). The databases EMBASE (from 1980), PsycINFO (from 1980) and MEDLINE (from 1980) were searched for papers published up to November 2014 using the following criteria: (imaging OR magnetic resonance imaging (MRI) OR functional magnetic resonance imaging (fMRI) OR nuclear magnetic resonance imaging OR positron emission tomography (PET) OR single photon emission computer tomography (SPECT) OR spectroscopy OR diffusion tensor imaging OR diffusion weighted imaging AND cognitive behavioural therapy (CBT) AND depression) (limit to human). This was supplemented by examining citations of identified studies. Hits from the three search portals were collected in Endnote.

Ideally a study aiming to identify brain changes specific to CBT would randomise a cohort of depressed people to no treatment (control group), a non-CBT talking therapy (active control group) and CBT. The active control group would balance for therapeutic benefit resulting from a sympathetic relationship, enabling the specific effects of CBT (distinct from the non-specific therapeutic relationship effects) to be distinguished. This is important, as the non-specific benefits of being 'in therapy' contribute much efficacy of all psychological treatments (17). Studies of complex treatments with active controls are difficult to conduct however, and rarely undertaken. We therefore considered any study examining CBT effects by comparing brain structural or functional measures before and after treatment in a depressed cohort. As any changes observed could occur spontaneously, ideally changes in CBT-treated patients would be compared with untreated depressed patients. Given the ethics of depriving unwell people of treatment however, we imagined the comparator group would generally be antidepressant-treated patients. This obviously may obscure some effects, as both treatments could bring about similar changes.

Studies were also included if the comparator group were healthy receiving no intervention. These studies, unable to control for spontaneous recovery effects, could conversely overestimate CBT effects. Studies including non-responders to treatment in analyses were included, while acknowledging this may reduce sensitivity to identification of CBT effects bringing about remission. If separate analyses included and excluded non-responders, both will be discussed. Given the increased risk of confounding in non-randomised studies, greater weight must be given to those with randomised design. Comparison of imaging data across studies can be hampered by inconsistent labelling of brain regions. The use of the Brodmann area system can facilitate comparison, and for this reason when Brodmann areas were not given they were determined using Talairach Demon (if necessary after converting coordinates from MNI to Talairach space using MNI2Tal) (18,19). This can facilitate, if feasible, meta-analytic synthesis of findings.

Results

Our search strategy, after omission of duplicates, yielded 199 papers. On review of abstracts 143 were clearly not relevant to this study, the remaining 56 being obtained in full text form. Of these nine met inclusion criteria (outlined in Table 1). Common reasons for exclusion included not focussing on a depressed group and lack of longitudinal data. One additional eligible paper was identified in the process of peer review.

The 10 included studies are summarised in Table 2. Eight had a comparator group; in five healthy controls, in the others antidepressant treated depressed patients. Randomisation to treatment was only potentially possible in the latter, and only Kennedy *et al.* did actually randomise treatment allocation (20). The other two studies comparing changes to antidepressant-treated patients used comparison data from an earlier study (21,22). Treatment was generally at least 12 sessions of individually delivered CBT, though one study used group treatment (23), and one internet-based treatment (24). The reported efficacy of CBT in reviewed studies was generally comparable to existing efficacy data (25). Studies generally defined response as a >50% reduction on a depression rating scale; this was achieved in more than half of patients in all studies reporting it. Seven studies analysed all CBT-treated depressed patients with a second scan together. Others analysed treatment responders and non-responders separately (20,26,27).

Table 1. Inclusion/exclusion criteria

Subjects meet DSM IV or ICD-10 diagnostic criteria for unipolar depression (Major Depression) and/or met cut-off for diagnosis of depression in recognized depression rating scale
Treatment and (if relevant) control groups both contain at least five patients
The therapy given is CBT rather than another psychological therapy (e.g. Cognitive Analytic Therapy, Interpersonal Therapy, Mentalisation, etc.)
CBT must be given for a minimum of 12 weeks in majority of patients
There must be imaging at baseline and after treatment, changes over time being ascertained and/or compared in treatment and control groups
Articles included must be written in English and peer reviewed

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Table 2. Summary of study findings

Study	No. depressed and treated with CBT/ comparator (M : F) age (SD)	Characteristics of comparator group and allocation	Def. of dep.	Medication status	Treatment given	Criteria for inclusion in analysis	Imaging modality	Measure assessed	CBT vs. comparator differences at study entry	Significant changes following CBT treatment	Changes compared to comparator group
Goldapple et al. (21)	17 (6 : 11)/13 (13 : 0) Cases aged: 41 (9)	Treatment with paroxetine. Non-randomised *post-hoc* allocation	Met DSM IV criteria MDE (uni-polar)	No antidepressant t/m in last month	15–20 sessions of outpatient CBT. 14 completed t/m, 9 ≥ 50% reduction in HDRS	All who complete t/m included in analysis	PET, resting state fluorine-18 labelled deoxyglucose	Regional cerebral glucose metabolism. Whole brain analysis as well as reduced threshold analyses targeting ventral cingulate, dorsal ACC, DLPFC, hippocampus, posterior cingulate	No significant differences	Decreased metabolic activity in DLPFC (BA9/46), VLPFC (BA11/47), superior and inferior medial frontal regions (BA9,10,11), posterior cingulate (BA31), inferior parietal (BA40) and inferior temporal cortex (BA20). Increased metabolic activity in hippocampus and dorsal midcingulate (BA24b/c)	Inverse effects seen with paroxetine treatment in DLPFC (BA9), inferior parietal cortex (BA40) and hippocampus effects in dorsal midcingulate (BA24), VMPFC (BA10/11) and posterior cingulate (BA31) unique to CBT. Decreased metabolism in ventral PFC (BA47) seen with both treatments
Yoshimura et al.*(23)	23 (16 : 7)/15 (8 : 7) Ages: 37.3 (7.2)/ 36.7 (8.2)	HC Not random allocation	Met DSM-IV criteria MDD (uni-polar) not responded to 8 weeks of antidepressant treatment	All maintain on antidepressant t/m, unchanged during course of study	12 small group sessions of outpatient CBT. BDI reduced from 21.4 to 13.1 in treatment group	All returns included in analysis	fMRI while judging whether positive or negative words described them (self-reference condition), or another (other reference condition)	Brain activity while judging whether emotional trait words applied to them or another. Whole brain analysis	HC increased activation in left ventral ACC (BA32), superior temporal cortex (BA39) and MPFC (BA8) in the self/positive condition. Patients increased activation in ventral ACC and MPFC in the self/ negative condition	Activation in ventral ACC (BA32), superior temporal cortex (BA39) and MPFC (BA8) increased for self/positive condition and decreased for self/ negative condition. Improvements in depressive symptoms negatively correlated with ventral ACC activity during self-referential processing of negative stimuli	Following CBT activation in the MPFC (BA8) and vACC (BA32) was increased for positive stimuli and decreased for negative stimuli in patients relative to controls

Table 2. *(Continued)*

Study	No. depressed and treated with CBT/ comparator (M : F) age (SD)	Characteristics of comparator group and allocation	Def. of dep.	Medication status	Treatment given	Criteria for inclusion in analysis	Imaging modality	Measure assessed	CBT vs. comparator differences at study entry	Significant changes following CBT treatment	Changes compared to comparator group
Fu et al. (28)	16 (3 : 13)/16 (3 : 13) Ages: 40 (9.4)/ 39.2 (9.3)	HC with HRSD <8	Met DSM-IV criteria MDD (uni-polar). Score >17 on HRSD	No psychotropic medication for >4 weeks (8 weeks for fluoxetine) Medication free through study	16 sessions individual CBT. HRSD decreased from 20.9 to 6.4. 9 met criteria for full remission	All returning patients included in analysis	fMRI during task. Subjects indicated gender of faces representing three intensities of sadness (low, medium and high)	Brain activity during implicit processing of sad facial expressions of varying intensity. Whole brain analysis and ROI analysis focused on amygdala	Patients showed elevated mean right amygdala activity and reduced activity in AC, extending to superior frontal gyrus, posterior cingulate gyrus, inferior parietal cortex, and precuneus	Decreased right AHC activity during task. Increase ACC activity (BA24,32) extending to superior frontal gyrus (BA8), posterior cingulate (BA31), inferior parietal cortex (BA40), and precuneus (BA7). Decreased activity in fusiform and lingual gyri (BA19), left lateral temporal (BA21, 22, 37) and inferior parietal (BA40) cortices, PCC (BA23, 30, 31), precuneus (BA7), and cerebellum	No differences between groups in AHC after treatment, though amygdala activity was increased in controls at study entry. Though activity lower in ACC in depressed group at study entry, it was greater in this region in CBT treated depressed group vs. controls after treatment
Kennedy et al. (20)	Total randomised: 17/14 Received treatment: 14/13 Follow-up achieved: 12/12 Responders: 7/9 Age 20–50	T/m with Venlafaxine randomised allocation	Meet DSMIV criteria MDD. Score >19 on HAM-D	Free of antidepressant medicines for 2 weeks (or 4 weeks for fluoxetine).	7–16 sessions of individual CBT. All responders received 12 or more sessions. 7 of 12 in whom follow up achieved were 'responders', defined as >50% reduction in HAM-D	All returning patients included in analysis. Treatment responders and non-responders analysed separately	PET, resting state fluorine-18 labeled deoxyglucose	Regional cerebral glucose metabolism in resting awake state while told to avoid rumination. Whole brain analysis as well as reduced threshold targeting OFC, DLPFC, anterior and posterior cingulate cortices, thalamus, striatum, and amygdala	Reported no significant differences	Decreased glucose metabolism bilaterally in the OFC (BA11,47) and left DMPFC (BA8), increased metabolism in the right inferior occipital cortex in responders to either modality. In CBT responders metabolism decreased in thalamus and increased in anterior subgenual cingulate/ ventromedial frontal cortex (BA32) and right occipital-temporal cortex (BA19)	Posterior cingulate (BA29) metabolism increased in venlafaxine responders but decreased in CBT responders. Converse seen in left inferior temporal cortex (BA20,21). Metabolism decreased in thalamus and increased in anterior subgenual cingulate/ ventromedial frontal cortex (BA32) and right occipital-temporal cortex (BA19) only in CBT responders

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Table 2. *(Continued)*

Study	No. depressed and treated with CBT/ comparator (M : F) age (SD)	Characteristics of comparator group and allocation	Def. of dep.	Medication status	Treatment given	Criteria for inclusion in analysis	Imaging modality	Measure assessed	CBT vs. comparator differences at study entry	Significant changes following CBT treatment	Changes compared to comparator group
Ritchey et al.*(29)	22 (9 : 13) depressed recruited, 15 returned for second scan, of whom 11 had useable data (3 : 8) Longitudinal changes not compared to HC (due to scanner change), but baseline scans compared to 14 HCs. Ages: 36.1 (10.1)/ 34.6 (6.9)	No longitudinal comparator (baseline scans compared to HC)	Met DSM-IV criteria for current MDD, at least moderate severity Score >16 on BDI.	Free of antidepressant medicines (including herbal remedies) at least 2 months	10–35 sessions of individual CBT. 12 of 15 with second scan had clinically sig. improvement (BDI scores change by at least 8 points and score <=14)	All returning patients included in analysis.	fMRI during task. Subjects made emotional evaluation while exposed to pos., neg., and neutral pictures. Instructed to experience any feelings or thoughts the pictures might elicit, and then rate their pleasantness.	fMRI during exposure to pictures compared to fixation cross. Regions which were focus of analysis for CBT-associated changes chosen on the basis of pre-treatment difference between cases and non-depressed comparators. Various comparisons made: all exposures vs. fixation cross; positive and negative valence vs. neutral; and negative vs. positive valence	All exposures collapsed vs. fixation cross: Decreased activity in VMPFC (BA11) and regions of parietal and visual cortex in depressed. Positive and negative valence combined vs. neutral: Reduced difference in activity in depressed in amygdala, right caudate, and bilateral hippocampus. Negative vs. positive valence contrast: greater activity to positive than negative stimuli in control vs. patients in various regions. Greater activity to negative than positive stimuli in patients vs. controls in right insula, right DLPFC, and cluster spanning ATL/VLPFC (BA38, 47)	All exposures vs. fixation cross: Increased activity in VMPFC (BA11) Positive and negative valence combined vs. neutral: Greater increase in brain activity post-treatment in right amygdala, right caudate, and left hippocampus Negative vs. positive valence contrast: Reversal of baseline effects in the ATL (BA38); i.e. enhanced response to positive vs. negative stimuli	N/A

Table 2. *(Continued)*

Study	No. depressed and treated with CBT/ comparator (M : F) age (SD)	Characteristics of comparator group and allocation	Def. of dep.	Medication status	Treatment given	Criteria for inclusion in analysis	Imaging modality	Measure assessed	CBT vs. comparator differences at study entry	Significant changes following CBT treatment	Changes compared to comparator group
Siegle et al. (26)	49 (9 : 40)/35 (12 : 23) Ages: 19–55/21–54	HC	Met DSM IV criteria for MDD	Free of antidepressant medicines for at least 2 weeks (6 weeks fluoxetine)	At least seven sessions of individual CBT (majority 16–20 sessions)	All returning after at least seven sessions of CBT. Remitters (50% reduction in BDI or HDRS) and non-remitters analysed separately	fMRI while rating if positive, negative, or neutral words were personally relevant	fMRI while rating words. Whole brain analysis as well as ROI analysis focused on subgenal ACC (BA 25), amygdala, DLPFC and VMPFC (BA24)	Not focus of study	No clear evidence that SGACC activity reduction with treatment, though high post-treatment activity (non-significant) more common in non-remitters. Participants with lowest pre-treatment sustained SGACC reactivity in response to negative words displayed most improvement after CBT. Impact of CBT on brain activity in other brain regions not examined.	Not focus of study. Main focus was if pre-treatment measures could predict response to CBT
Sancora et al. (22)	15 recruited, 8 completed study. 19 antidepressant or ECT treated comparitors	Treatment with ECT (8) or paroxetine (11). Non-randomised allocation, comparator groups being from earlier studies	Meet DSM-IV criteria for MDD and score >20 on HDRS-25	Free of psychotropic medicines for at least 3 weeks	12 sessions of individual CBT. Mean HDRS score decreased from 28.1 to 12.3	All returning patients who completed t/m with CBT	Proton MRS was employed to measure GABA concentration	Occipital cortex GABA concentration during resting state	Not discussed	No significant change in cortical GABA concentrations after treatment with CBT despite significant decrease in HDRS-25 rating	Significant increase in cortical GABA concentration seen with both SSRI and ECT treatment. Post-CBT GABA concentration correlated with change in HDRS scores from pre- to post-treatment

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Study	No. depressed and treated with CBT/ comparator (M : F) age (SD)	Characteristics of comparator group and allocation	Def. of dep.	Medication status	Treatment given	Criteria for inclusion in analysis	Imaging modality	Measure assessed	CBT vs. comparator differences at study entry	Significant changes following CBT treatment	Changes compared to comparator group
Amsterdam et al. (27)	20 (15 : 5)/10 (7 : 3) Age: 41.0 (12.8)/ 44.8 (10.93)	HC	DSM-IV criteria for MDD and score >16 on HAM-D	Drug free >12 months	16 sessions individual CBT. Two had partial course, as did two controls. Mean HAM-D score decreased from 20.3 to 11.6. Ten 'responders', (50% reduction in HAM-D)	All enrolled included in analysis, but divided into respon-ders and non-responders for some analyses	[123I]-ADAM to examine brain SERT binding standardized uptake ratio (SUR).	Change over time in SERT binding before and after CBT. Measured as SUR. ROI focusing on the basal ganglia, midbrain, and MTL regions	Depressed had significantly lower SUR values for the midbrain ($p < .005$), right MTL ($p < .0005$), left MTL ($p < .004$), right basal ganglia ($p < .03$), and left basal ganglia ($p = .016$)	No direct comparison of pre-treatment and post-treatment SPECT scans	Comparing all CBT group to controls, increase in mean SUR values for the midbrain ($p = .011$), right MTL ($p = .008$), and left MTL ($p = .0001$) Increase over time in mean SUR values for treatment responders (vs. HC) for the right MTL ($p = .029$) and left MTL ($p = .012$)
Sankar et al. (30)	16 (3 : 13)/ 16 (3 : 13) Age: 40.0 (9.3)/ 39.9 (9.5)	HC	DSM-IV criteria for MDD and score >17 on HAM-D	Free of psychotropic medicines for at least 4 weeks at (8 weeks for fluoxetine)	16 sessions of individual CBT. Mean HAM-D score decreased from 20.9 to 6.3. 13 'responders' defined as 50% reduction in HAM-D	All enrolled included in analysis	fMRI while rating agreement to various DAS statements	fMRI while rating agreement to statements; analyses examined were regular attributions relative to control DAS statements, and extreme attributions relative to control DAS statements	During extreme attributions patients had increased activation in left hippocampal region ($p < 0.005$), left inferior parietal lobe (BA40, $p < 0.005$) and left precuneus (BA7, $p < 0.005$); and decreased in left cerebellum $p < 0.005$	Decreased activation in right posterior cingulate gyrus (BA30, $p < 0.01$) for extreme attributions. Positive relationship between changes in HAM-D score and overall activity in the left precentral gyrus (BA 6, $p < 0.005$) for extreme attributions	Both depressed patients and healthy controls showed decrease in activation in the left parahippocampal gyrus (BA37) for extreme attributions to DAS statements at the follow-up scans, but to a lesser extent in patients ($p < 0.05$)
Tiger et al. (24)	10 (4 : 6)	No comparator	Moderate MDD. MADRS score 20–35	No psycho-pharmacological treatment for at least one month	10 modules of internet-based cognitive behavioural therapy	All enrolled included in analysis	PET with 5-HT1B receptor selective radioligand [11C] AZ10419369	Change over time in 5HT1B receptor binding before and after CBT in various ROIs		[11C]AZ10419369 binding potential reduced in the dorsal brain stem ($p < 0.001$), suggesting a decrease of available 5-HT1B receptors in this region	

ACC, anterior cingulate; ATL, anterior temporal lobe; CBT, cognitive behavioural therapy; DAS, modified Dysfunctional Attitudes Scale 48; DLPFC, dorsolateral PFC; ECT, electro-convulsive therapy; fMRI, functional magnetic resonance imaging; HAM-D, 17-item Hamilton Depression Rating Scale; HC, healthy control; HDRS-25, modified 25-item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, Major depressive disorder; MDE, major depressive episode; MRS, magnetic resonance spectroscopy; MTL, medial temporal lobe; PET, positron emission tomography; [123I]-ADAM, 123I-labelled ((2-((dimethylamino)methyl) phenyl)thio)-5-iodophenylamine; ROI, region of interest; SERT, serotonin transporter; SGACC, subgenual ACC; SSRI, selective serotonin re-uptake inhibitor; VLPFC, ventrolateral PFC; VMPFC, ventromedial PFC; VPFC, ventral PFC.

*BA not given, BA identified via Talairach Demon (if necessary after converting given coordinates from MNI to Talairach using MNI2Tal).

No identified studies examined CBT effects with structural MRI. Five applied fMRI, two PET with fluorine-18 labelled deoxyglucose, one PET with a 5HT1A receptor ligand, one SPECT with a serotonin transporter ligand, and one magnetic resonance spectroscopy (MRS). The PET studies measuring deoxyglucose levels examined the brain in the resting sate, whereas the fMRI studies all examined brain activity during processing of emotionally laden words or images. Many studies undertook whole brain analyses supplemented with targeted analyses focussing on specific regions, generally determined *a priori*. These regions were most commonly the amgygdala, hippocampus, cingulate and regions of the frontal cortex.

The study with arguably the highest quality design, having an antidepressant comparator group and randomly allocating patients to treatment, was Kennedy *et al.*'s PET study (20). Twelve of 17 patients randomised to CBT completed treatment (15 having 12 sessions or more), seven fulfilling criteria for treatment response. By contrast, 12 of the 14 patients randomised to Venlafaxine were followed up, nine responding to treatment. Changes unique to CBT were decreased resting-state metabolism in the thalamus and posterior cingulate and increased metabolism in the left inferior temporal cortex, subgenual cingulate/ventromedial prefrontal cortex (VMPFC, BA32) and right occipital-temporal cortex (BA19). As not seen in antidepressant responders, it seems reasonable to assume that these changes are associated with CBT treatment rather than treatment response *per se*. Of course, changes seen with both CBT and antidepressant treatment could still theoretically be attributable to CBT, they would just represent common effects. Common effects were decreased metabolism bilaterally in the orbitofrontal cortex (OFC, BA11, 47) and in the left dorsomedial prefrontal cortex (DMPFC, BA8), and increased metabolism in the right inferior occipital cortex.

The study most directly comparable to Kennedy *et al.* is the PET resting state study of Goldapple *et al.*, undertaken by the same group (21). They compared brain metabolism before and after treatment with 15–20 sessions of CBT, with *post hoc* comparison to paroxetine treatment. This study also reported decreased metabolism in various frontal regions with CBT. In common with Kennedy *et al.*, decreased metabolism in the OFC/VLPFC (BA11, 47) was seen in both treatment groups. They also reported that reduced metabolism in the posterior cingulate was unique to CBT treatment. Unlike Kennedy *et al.* however they did not report CBT-associated increased subgenual ACC/VMPFC (BA32) activity or thalamic effects. Whereas Kennedy *et al.* reported increased metabolism in the (left) inferior temporal cortex (BA 20), Goldapple *et al.* reported CBT-associated decreased metabolism in this region. Goldapple *et al.* also reported CBT-associated increased metabolism in the hippocampus, which was reduced with paroxetine.

The four fMRI studies used different emotion-processing tasks, hampering comparison between them. Fu *et al.* utilised a task seeking to engage implicit processing of sad facial expressions (28). They reported CBT treatment was associated with a significant decrease in right amygdala–hippocampal complex (AHC) activity during task. Conversely within task activity was increased following CBT treatment in regions including the ACC (BA24, BA32) and extending to the superior frontal gyrus (BA8), posterior cingulate (BA31), inferior parietal cortex (BA40), and precuneus (BA7). Though baseline right AHC activity was elevated in depressed compared to controls, treatment-associated change resulted in no significant difference between case and control within-task AHC activity at follow-up. The increase in ACC and posterior cingulate within-task activity following CBT treatment meant patient activity in these regions actually exceeded controls at the second scan.

The other three fMRI studies used explicit emotion processing tasks. Yoshimura *et al.* examined brain activity during processing of positive and negative emotional trait words (23). This was compared before and after treatment with 12 sessions of group CBT. Both change over time and comparison to controls at each time point was examined. Following treatment activation in the left ventral ACC (BA32), superior temporal cortex (BA39) and medial prefrontal cortex (MPFC, BA8) was increased when depressed patients considered if positive words described them, but decreased considering negative words.

In the uncontrolled study of Ritchey *et al.*, participants were shown pictures designed to evoke positive, negative or neutral emotions and instructed to experience feelings or thoughts evoked and rate picture pleasantness (29). They undertook various contrasts and reported increased VMPFC activity post-CBT (BA11, so synonymous in this study with the OFC), when comparing all picture exposures vs. baseline activity (fixation cross). In the combined arousal contrast, they reported a larger difference in the positive and negative valence exposures versus neutral contrast post-treatment in the right amygdala, right caudate, and left hippocampus; that is a correction of the reduced increase in activity in this contrast in depressed (compared with controls) before CBT. The increased activity in the anterior temporal lobe to negative versus positive stimuli seen at baseline was reversed after treatment. After treatment activity in this region was (similarly to controls) greater on exposure to positive than negative stimuli.

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Siegle *et al.* compared brain activity in 49 depressed patients and 35 healthy controls while they rated if positive, negative, or neutral words were personally relevant (26). The depressed group were scanned before and after at least seven sessions of individual CBT. The primary focus of this study was to examine if pre-treatment measures could predict response to CBT, but the impact of treatment on subgenual ACC (BA25) activity on exposure to negative words was specifically examined. Though they state there is no clear evidence CBT reduces this, they report that high post-treatment activity was more common in non-remitters and that three of five remitters with high pre-treatment subgenual ACC activity had decreased activity post-treatment.

The most recent study, by Sankar *et al.*, compared brain activity of 16 depressed patients endorsing extreme responses to dysfunctional attitudes before and after 16 sessions of CBT to 16 healthy controls (30). Within the patient group task-related activation in right posterior cingulate gyrus (BA 37) decreased following CBT ($p < 0.01$). Activation in the left parahippocampal gyrus (BA 37) also decreased, but this reduction was less than that observed in the control group.

Amsterdam *et al.* used [123I]-ADAM single photon emission computed tomography (SPECT) to compare serotonin transporter (SERT) binding in 20 depressed patients before and after CBT to that in 10 untreated healthy controls (27). Depressed subjects demonstrated low pretreatment mean SERT standardised uptake ratios, speculated to reflect low brain serotonin levels, which significantly increased over time in the midbrain ($p = 0.011$), right medial temporal lobe ($p = 0.008$), and left medial temporal lobe ($p = 0.000$) regions. Tiger *et al.* demonstrated reduced binding potential of a 5-HT1B receptor selective radioligand in the dorsal brain stem after treatment with internet-based CBT (24). Sanacora *et al.* undertook the only study examining the effects of CBT using MRS (22). They examined resting state occipital cortex gamma-aminobutyric acid (GABA) concentrations before and after 12 sessions of CBT. Changes in the eight patients completing treatment were compared to those in two previous studies examining the effects of selective serotonin re-uptake inhibitors (SSRIs) and electroconvulsive therapy (ECT). There was a significant decrease in HDRS scores in the CBT treated patients, but whereas an increase in occipital GABA concentrations was observed in the earlier two studies this was not seen with CBT. While the authors acknowledge that small sample size means the study is underpowered to definitively state that GABA content is unchanged after CBT, they suggest CBT may have different effects on GABA content than SSRIs or ECT.

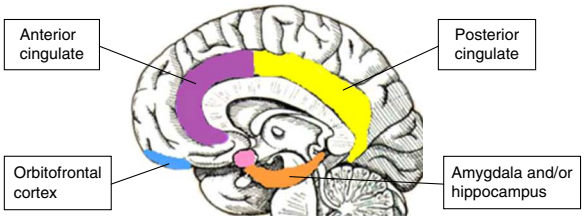

Fig. 1. Regions most commonly identified as exhibiting change in activity following treatment of depression with cognitive behavioural therapy.

Discussion

Overall, changes in ACC activity following CBT are most consistently reported. This region is often defined as BA 32 (dorsal anterior cingulate), but also includes BA24 (ventral ACC) and BA33 (pregenual area). In one of the highest quality studies, that of Kennedy *et al.*, decreased resting state activity in BA32 after CBT was reported (20). The other PET resting state study reported that activity in adjoining cingulate regions in BA24 were increased after CBT, though they describe this region as more dorsal midcingulate than ACC proper (21). Yoshimura *et al.* reported that following CBT activity in the ACC (BA32) was decreased when considering if negative words described them (but increased on considering positive words) (23), and Fu *et al.* that it was increased (in a region encompassing BA24 and BA32) during implicit processing of negative facial expressions (28). Siegle *et al.*'s 2012 study focused on the adjoining subgenal ACC (BA25) (26). Though they acknowledge no clear evidence that subgenual ACC activity reduces with treatment during processing of negative words, high post-treatment activity was more common in non-remitters. Kennedy *et al.* and Goldapple *et al.* compared CBT-associated changes to those seen with antidepressants; in both studies ACC changes were unique to CBT (20,21).

After the ACC, the regions most commonly reported to exhibit change in activity following CBT were the OFC/VLPFC (BA11, 47), posterior cingulate (BA 30, 31), and amygdala and/or hippocampus. This is summarised in Fig. 1 Kennedy *et al.* and Goldapple *et al.* both reported decreased resting state metabolism in BA11/47 (20,21), also seen after antidepressant treatment. Ritchey *et al.* however reported a greater increase in activity in this region during the task of rating picture pleasantness versus baseline state following CBT treatment (29); this is not necessarily incompatible with the resting state findings, and could potentially be explained by reduced baseline activity in the region. Four studies also reported changes in posterior cingulate (BA31) activity following CBT. The two resting state studies both reported it reduced

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(and this was unique to CBT), though Kennedy *et al.* localised the activity change to BA29 (20,21). Fu *et al.* reported decreased activity after CBT in BA23, BA30 and BA31 (all include the posterior cingulate) during implicit processing of sad facial expressions (28). Sankar *et al.* reported decreased activation in right posterior cingulate gyrus (BA30) during extreme attributions from the DAS (30). Changes in amygdala or hippocampal activity following CBT were seen in three studies (21,28,29). Activity in the hippocampus was increased in Goldapple *et al.*'s resting state study, decreased in the amygdala (extending to hippocampus) during implicit processing of sad facial expression in Fu *et al.*'s fMRI study, and increased in the right amygdala and left hippocampus (in the combined contrast of positive and negative valence pictures vs. neutral) in Ritchey *et al.*'s study (21,28,29). Though specifically examined, Kennedy *et al.* and Sankar *et al.* did not report any change in amygdala activity following CBT (20,30).

Two fMRI studies reported post-CBT increases in superior frontal gyrus/DMPFC (BA8) activity when processing emotional stimuli, though Yoshimura *et al.* found it increased on judging whether positive emotional trait words applied to them and Fu *et al.* increased on processing sad facial expressions (23,28). Activity in this region was decreased in Kennedy *et al.*'s (20) resting state study (23,28). Kennedy *et al.* and Goldapple *et al.* reported changes in opposite directions in the inferior temporal cortex (BA20) (20), while Yoshimura *et al.*, Fu *et al.* and Ritchey *et al.* reported changes in other temporal cortex regions (23,28,29).

Limitations and themes arising

The limitations of this review arise predominantly from the relatively small numbers of studies identified as eligible for inclusion and the striking heterogeneity of these studies, a fact which precluded any meaningful meta-analytic synthesis of findings. Studies differ in sample characteristics (e.g. proportion experiencing first depressive episode vs. recurrent illness), amount of therapy, regions chosen for reduced threshold analyses, scanner resolution and nature/existence of comparator group. Possibly even more fundamental differences are neuroimaging technique employed, and whether resting state or task-dependent brain activity is examined. Considering imaging technique, PET with fluorine-18 labelled deoxyglucose measures glucose metabolism whereas fMRI measures deoxyhaemoglobin concentration. Given that these are different physiological parameters, and the modalities differ in temporal (PET acquires a single scan over 60–90s, fMRI over 1–2s), and spatial (2 mm with fMRI, but generally less with PET) resolution (31), one would expect findings from the two modalities could differ considerably. Whether resting state or task-related activity is examined (and in the latter the nature of the task used), could also lead to apparently divergent findings. Expanding on the latter point, it has been established that individuals with major depression show amygdala hyperactivity when processing emotionally negative information (see Introduction). If CBT addresses this information processing bias, then post-CBT amygdala activity may be expected to be decreased on exposure to sad faces, but unchanged (or even increased) with happy faces. Other stimuli characteristics, for example whether pictorial or linguistic, could also influence brain region activated and/or magnitude of associated brain activity. It is particularly striking that no studies used structural imaging approaches. Given that CBT-associated structural brain changes have been identified in treatment of other conditions, this is a clear gap in the research data.

Given the level of study heterogeneity, the degree of consistency in brain regions identified as exhibiting activity change following CBT is notable. First, ACC activity does seem decreased following CBT, both in the resting state and when processing negative words. It seems however increased when processing positive words and (possibly more unexpectedly) negative facial expressions. Posterior cingulate activity was reduced in both resting state studies, as well as when processing sad facial expressions and endorsing extreme responses to dysfunctional attitudes. Resting state activity in OFC/VLPFC also seems decreased following CBT, though the task-associated increase in activity observed rating picture pleasantness may be greater following CBT. There seem different CBT-associated changes in the amygdala and hippocampus. Though activity in the former may be decreased following CBT (both resting state and when processing sad facial expressions), resting state hippocampal activity is reported increased. The attenuation of left parahippocampal activity observed on follow-up scanning of healthy controls endorsing extreme dysfunctional attitudes is reduced in depressed patients treated with CBT.

What do these findings tell us about the impact of CBT on brain function?

The regions exhibiting activity changes following CBT are all parts of the limbic system and functionally related neocortical structures. This is unsurprising given the centrality of these regions to emotional experience and memory, abnormalities of

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which underpin depression. The cingulate, regions of frontal cortex, and the amygdala/hippocampus are crucial parts of a fronto-limbic network central to these functions, and numerous studies have identified functional (and some structural) abnormalities of these regions in depressed people (32).

In studies including a healthy control group there is a tendency for CBT-associated changes to 'normalise' brain function, that is for functional imaging findings to be more like those in healthy individuals. This is reported in both resting state PET (23) and task-dependent fMRI (28) studies. Intriguingly however, some studies examining how antidepressants work suggested this is not actually as simple as 'normalising' the depressed brain, with compensatory changes also important (1). In short, rather than restoring brain function to that seen in controls, treatment brings about changes in brain function which compensate for the abnormalities giving rise to depression. In-keeping with this, the rapid (and potentially transient) effects of ECT (33) argue against it working through (presumably protracted) processes of neurogenesis and receptor synthesis. In studies explicitly comparing the effects of CBT and pharmacotherapy, though some common effects are seen (such as decreased ventral prefrontal cortex metabolism), other changes are frankly divergent. Opposite effects with each treatment are reported in the DLPFC and inferior parietal cortex by Goldapple *et al.* (21), and posterior cingulate and left inferior temporal cortex by Kennedy *et al.* (20). It is thus conceivable that the relative degree to which each modality brings about remission through 'normalisation' of brain functional abnormalities versus 'compensatory' processes differs.

So what is CBT actually doing?

Previous writers have incorporated imaging findings into a parsimonious account of how CBT and pharmacotherapy work, and how their effects differ (33). As discussed above, functional imaging studies suggest CBT brings about changes in fronto-limbic systems, potentially normalising abnormal activity. Writers have commented on how functional imaging studies of depression particularly implicate change in regions regarded as crucial components of a well-established model of information processing in the forebrain (1). This model recognises two distinct but interacting systems: a ventral 'affective' circuit involving the amygdala, anterior hippocampus, ventral striatum, insular cortex, ventral (subgenual) part of the ACC and ventral and orbital PFC; and a dorsal 'cognitive' circuit, involving the hippocampus, dorsal (pregenual) part of the ACC and dorsolateral PFC ((1,34). It is proposed the ventral system is important for identification of the emotional significance of a stimulus and production of affective states and autonomic regulation related to emotionally significant situations, while the dorsal system is important for executive function, including selective attention, planning, and effortful regulation of affective states; essentially the 'cognitive control' functions described by Miller and Cohen (10). DeRubeis *et al.* incorporated an understanding of such distinct (but intertwined) circuits into a proposed hypothesis of how CBT works. They emphasised differences from antidepressant medication effects by suggesting the former works in a 'top-down' manner while the latter works in a 'bottom-up' way (33). In essence, that CBT might allow a resetting of tonic prefrontal activity to yield greater capacity for 'top-down' emotion regulation when it is needed (such as when skills taught in CBT are engaged); conversely antidepressants might increase subcortical cingulate metabolism tonically, creating a 'bottom-up' effect whereby relevant limbic regions are inhibited during medication administration. This is of course not incompatible with a model of both modalities having 'normalising' and 'compensatory' effects. To speculate, CBT could normalise or lead to compensatory changes in the dorsal network which subsequently impact on subcortical regions, whereas pharmacotherapy could conversely promote normalising or compensatory subcortical changes which over time normalise cortical abnormalities.

This model for understanding the mechanism of action of CBT in depression has much appeal. It is parsimonious, but also fits with the idea that the benefits experienced with CBT treatment derive from cognitive restructuring and improved ability to rationally appraise automatic thoughts; essentially bolstered cognitive control of emotionally salient automatic thoughts. The reality is however that the reviewed data provide at best only partial support for this model. In the case of the DLPFC for example, a brain region believed to play a crucial role in cognitive control, changes in activity post-CBT were only seen in the study of Goldapple *et al.* (21). By contrast changes in DLPFC have been reported following successful treatment with antidepressants, ECT and even placebo (1). CBT-associated changes were also reported in several of the reviewed studies in the OFC and amygdala, these of course being parts of the proposed 'affective' circuit, function of which is purportedly influenced by medication rather than CBT. Decreased resting state activity in the dorsal ACC (cognitive circuit) and increased resting state activity in the ventral ACC (affective circuit) following CBT (20,21) can be explained by CBT resetting tonic prefrontal activity (i.e. reduced resting state activity) resulting

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in greater capacity for 'top-down' emotion regulation when needed. If they are 'opposing' networks however, why task-related activity in both the dorsal and ventral ACC would be increased during the processing of negative facial expressions is much harder to explain within this model (27).

It may be that some of the apparent inconsistencies discussed can be explained by factors such as heterogeneity in study design, inconsistency in region definition and the limited spatial resolution inherent in current functional imaging methodologies. Even accounting for these factors however, the reality is that the existing imaging data are not fully supportive of the existing models purporting to explain how CBT brings about its effects. Clarification of this will clearly require further study, with inclusion of appropriate comparator groups essential if effects specific to treatment with CBT are to be identified. Design of such studies will be challenging, separating the effects specific to CBT from those of spontaneous recovery or the non-specific effects of being in a therapeutic relationship being hampered by the ethical implications of delaying treatment in a suffering and potentially high-risk group. The question of whether CBT and antidepressants bring about recovery through distinguishable mechanisms is intriguing and potentially informative. As suggested above however, it is also conceivable that even though these treatment modalities do have different neurobiological mechanisms of action early in treatment, as recovery progresses these differences diminish. Consequently, if the effects of the two treatments modalities are to be distinguished, this may necessitate repeat scans during treatment, following remission, and beyond. As it is thought that patients treated with CBT are less vulnerable to relapse than those who were treated with antidepressants (35), it would be particularly interesting to examine if differences in brain function are detectable post-remission. Could differences specific to CBT treatment be particularly crucial to protection from relapse?

In conclusion, though limited in number and variable in methodology, the reviewed studies do suggest that CBT is associated with functional brain changes. Whether it results in structural brain changes, which has been demonstrated when used to treat conditions such as chronic fatigue syndrome, remains unexplored. The data summarised demonstrate CBT is having 'biological' effects. Further work, applying the expanding variety of imaging methodologies of increasing sophistication and resolution, may enable elucidation of the effects of CBT in ever more localised brain regions. This could expand our understanding of how all treatment modalities actually work, and potentially elucidate if specific psychological treatments do indeed have unique effects. Further randomised studies certainly seem essential in disentangling if antidepressant and psychological treatments have distinct modes of action, and characterising what these specific effects are.

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Conflicts of Interest

There are no conflicts of interest.

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