

Volume I
Research Component

**The Neural Correlates of Psychotherapy:
Functional Magnetic Resonance Imaging Investigations of the Effects of
Cognitive Behavioural Therapy for Anxiety on Human Neural Function**

by

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A Thesis Submitted to the University of Birmingham in Partial Fulfilment of the
Requirements for the Degree of Doctor in Clinical Psychology

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Overview

This thesis was submitted in partial fulfilment of the requirements of the degree of Doctor in Clinical Psychology at the University of Birmingham. It comprises two volumes. Volume I consists of the research component of the degree, Volume II of the clinical component.

Volume I is concerned with the effects of psychotherapy on the human brain. It contains a literature review, a research paper and a public dissemination document. The literature review is a critical evaluation of brain imaging studies that attempted to identify how neural processing changes in patients after having received cognitive behavioural therapy for an anxiety disorder. The research paper reports the finding of a randomised controlled trial that investigated how the brain's threat processing mechanisms changed after patients received cognitive behavioural therapy for their panic disorder. The public dissemination document contains a brief summary of the work written in a style that is (hopefully) accessible and (at least somewhat) informative to non-expert audiences.

Volume II contains five clinical practice reports (CPRs). CPR1 is a case formulation of a gentleman with obsessive-compulsive symptoms. Two conceptually different formulations of his presentation are presented. One is based on cognitive-behavioural principles, the other is formulated within a psychodynamic framework. CPR2 is a single-case experimental design that attempted to evaluate whether CBT led to a statistically robust improvement for a lady with panic disorder. CPR3 presents a case study of an ex-military serviceman who received CBT for posttraumatic stress disorder with a particular focus on the technique of nightmare rescripting. CPR4 reports the findings of an evaluation of a provider of neurorehabilitation services against how well it adhered to national guidelines on screening and interventions for depression. CPR5 was an oral

presentation of the case of a fourteen-year-old girl who received CBT for obsessive-compulsive disorder. Its abstract is reproduced in the present volume.

Names, initials and other identifiers of patients and service settings were altered in order to ensure confidentiality.

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CHAPTER 1

Literature Review

A Critical Review of Functional Brain Imaging Studies on the Neural Effects of Cognitive Behavioural Therapy in Anxiety Disorders

Abstract

Background: Cognitive behavioural therapy (CBT) is the first line treatment for anxiety disorders recommended by clinical guidelines. However, little is known about how CBT works at a neural level. Aim: To critically review functional magnetic resonance studies of the neural effects of CBT for anxiety disorders. Method: A systematic search of the major scientific literature databases identified thirteen studies of relevance. Results: The anxiety disorders studied were spider phobia, social phobia, posttraumatic stress disorder and panic disorder. CBT was shown to be effective in reducing symptoms in all studies. All studies identified neural activation changes in brain regions located within the brain's fear processing network. Specific findings were variable, however, and no consistent neural response signature was found across or within disorder categories. The highest degree of agreement existed about the amygdala, insula and anterior cingulate cortex: When their activation changed as a function of CBT it was typically reduced after treatment.

Conclusions: Agreement exists that CBT for anxiety results in changed neural processing of threat related information. This is an emerging field of research, however, and significant methodological shortcomings will need to be overcome in the future in order to obtain more consistent findings that will prove reliable, replicable and robustly interpretable.

Introduction

Anxiety disorders are amongst the most prevalent mental health difficulties across cultures and societies. (Baxter et al., 2013; Kessler et al., 2005). They frequently take a chronic course and, as a consequence, have a significant impact on sufferers' quality of life (Rapaport et al., 2005). The cost of interventions and loss in productivity presents a substantial socioeconomic burden (Whiteford et al., 2013).

Cognitive behavioural therapy (CBT) is the first line treatment recommended by clinical guidelines for a range of conditions across the spectrum of anxiety disorders (NICE, 2005a, 2005b, 2011, 2013). Whilst the majority of recipients of CBT show some clinical improvement, a considerable number of patients responds only with partial symptom resolution (Barlow et al., 2004) and relapse rates remain high (Cuijpers et al., 2013; Roth et al., 2006), particularly in the longer term (Durham et al., 2005).

Based on the work by DeRubeis & Feeley (1990) and Jacobson et al. (1996) numerous authors have argued for the empirical identification of the specific active components within CBT to determine the most effective treatment ingredients (Ahn & Wampold, 2001; DeRubeis et al., 2005; Marks, 2002; Wampold, 2005). Such efforts have only had some success. So-called nonspecific factors, such as the therapeutic alliance, often explain more outcome variance than specific therapeutic ingredients (Chatoor et al., 1979). The possibility needs to be considered that individual patient characteristics or an interaction of patient factors, therapist attributes and therapy ingredients may be more predictive of therapeutic change.

Given the large body of neuroanatomical evidence on the aetiology and maintenance of fear and anxiety (Bishop, 2007; Britton et al., 2011; Delgado et al., 2006;

Kim et al., 2011; Ray & Zald, 2012) the study of the neural correlates of effective therapy may hold promise. A better understanding of the neurocognitive mediators of effective psychotherapy could be instrumental in allowing us to refine treatments better. Reliable probes of these may ultimately serve as biomarkers to aid the evidence based selection of personalised medical, psychological and integrated treatment pathways (Cortese, 2007; Hamburg & Collins, 2010; Lesko, 2007).

Of all the neural imaging methods functional magnetic resonance imaging (fMRI) is the most promising for this purpose. It measures a physiological marker of regional blood flow, a correlate of neural transmission (Logothetis, 2002, 2003; Logothetis & Wandell, 2004) noninvasively and without the use of ionising radiation. Its comparatively high spatial and temporal resolution, widespread availability, relative ease of administration and good safety record position it uniquely within the mix of neuroscience methods (Walsh & Cowey, 2000). Since its conception in the early 1990s it has therefore become the most successful human brain mapping tool (Raichle, 2009).

This review provides a systematic overview of all studies published to date that have used fMRI to identify the neural correlates of symptom improvement as a function of CBT for anxiety disorders. Whilst several articles have been published that summarise functional imaging investigations of psychotherapy (Linden, 2006; Messina et al., 2013; Porto et al., 2009; Roffman et al., 2005) the present review is novel in that it focuses on fMRI, anxiety disorders and CBT alone. Its aims are, firstly, to describe the neural changes associated with CBT for anxiety, secondly, to highlight methodological limitations in the published research and, thirdly, to identify research questions that in the future may be helpful in furthering our understanding of how exactly effective psychotherapy works at a neural level and whether such knowledge may be helpful in devising treatments, or

selecting therapeutic treatment ingredients, that may increase efficacy and reduce non-response and relapse.

Methods

Search Strategy

The remit of this paper is to review English language publications of experiments and randomised controlled trials that quantify the effect of CBT for anxiety disorders on neural markers in adults. To identify these, a search of the databases Embase, Medline and PsycINFO was conducted. The search strategy combined semantic permutations of the concepts “fMRI”, “CBT” and “anxiety disorders”. The latter was defined to include those mental disorders which have been shown to be treatable effectively with CBT, i.e. specific phobias, panic disorder, social phobia, generalised anxiety disorder (GAD), hypochondriasis and posttraumatic stress disorder (PTSD) (Clark & Beck, 2011; Wells, 2013). In the prevailing diagnostic system, DSM–5, these generally overlap with the definition of anxiety disorders (American Psychiatric Association, 2013). An exception is PTSD. Even though since last year it has been comprised in a separate category of disorders it nevertheless shares much of its hypothesised neurobiological underpinnings with the remainder of the anxiety disorders (Shvil, Rusch, Sullivan, & Neria, 2013). In the new edition of DSM, obsessive-compulsive disorder (OCD) is also no longer comprised within the anxiety disorders. Whilst this has sparked considerable debate (Bystritsky et al., 2013; Nemeroff et al., 2013; Stein et al., 2010) its neurobiology is indeed very distinct from the anxiety disorders and positions it much closer to tic and movement disorders (Bartz & Hollander, 2006; Münchau et al., 2002). OCD will therefore not form part of this review.

The database search strategy is presented in Table 1. The literature search was conducted on April 15th, 2014 and limited to papers published since 1987, prior to the conception of fMRI. It yielded 319 results.

Table 1. Search strategy used to interrogate the databases Embase, Medline and PsycINFO for original studies researching the neural effects of cognitive-behavioural therapy in anxiety disorders using functional magnetic resonance imaging.

Query	Search term	Hits	Query	Search term	Hits
#1	functional	1777236	#18	anxiety	449207
#2	magnetic	1394266	#19	phobia	29663
#3	resonance	1423027	#20	phobic	16553
#4	imaging	1624660	#21	panic	44822
#5	#1 and #2 and #3 and #4	137677	#22	social	1516189
#6	fmri	68554	#23	#18 and #22	90070
#7	#5 or #6	150261	#24	#19 or #20	39581
#8	cognitive	783323	#25	#22 and #24	20803
#9	behaviour	324813	#26	#24 or #25	39581
#10	behavior	2050799	#27	posttraumatic	93990
#11	behavioural	134300	#28	stress	1340050
#12	behavioral	574966	#29	#27 and #28	71447
#13	#9 or #10 or #11 or #12	2592774	#30	health	4430838
#14	therapy	3993705	#31	#18 and #30	108771
#15	psychotherapy	202440	#32	hypochondriasis	6565
#16	#14 or #15	4101391	#33	#31 or #32	114396
#17	#8 and #13 and #16	82336	#34	#18 or #19 or #20 or #26 or #29 or #33	550934
			#35	#7 and #17 and #34	319

Inclusion Criteria

For a search result to be included in the final literature review it had to fulfil the following inclusion criteria: It needed to be an original research report published in English in a peer reviewed journal reporting experimental research using fMRI to identify the neural effects of CBT in an adult study population. After removal of duplicates (72 exclusions), non-English articles (14 exclusions), review articles (85 exclusions), conference abstracts (52 exclusions), books (2 exclusions) and editorials (5 exclusions) 89 articles of possible interest remained. Abstracts were read to eliminate 74 articles which

either did not report research on CBT for anxiety or were using paediatric populations. Three studies (Bryant et al., 2008; Doehrmann et al., 2013; Falconer et al., 2013) were excluded because they used fMRI solely to predict subjects' responses to CBT without a post-therapy brain scan to examine the correlates of therapeutic change. Perusal of the references cited in the remaining twelve papers revealed one more article of interest (Hauner, Mineka, Voss, & Paller, 2012), giving a total of thirteen studies as target for the present review. Figure 1 shows a flowchart of inclusion and elimination of research reports for the present review.

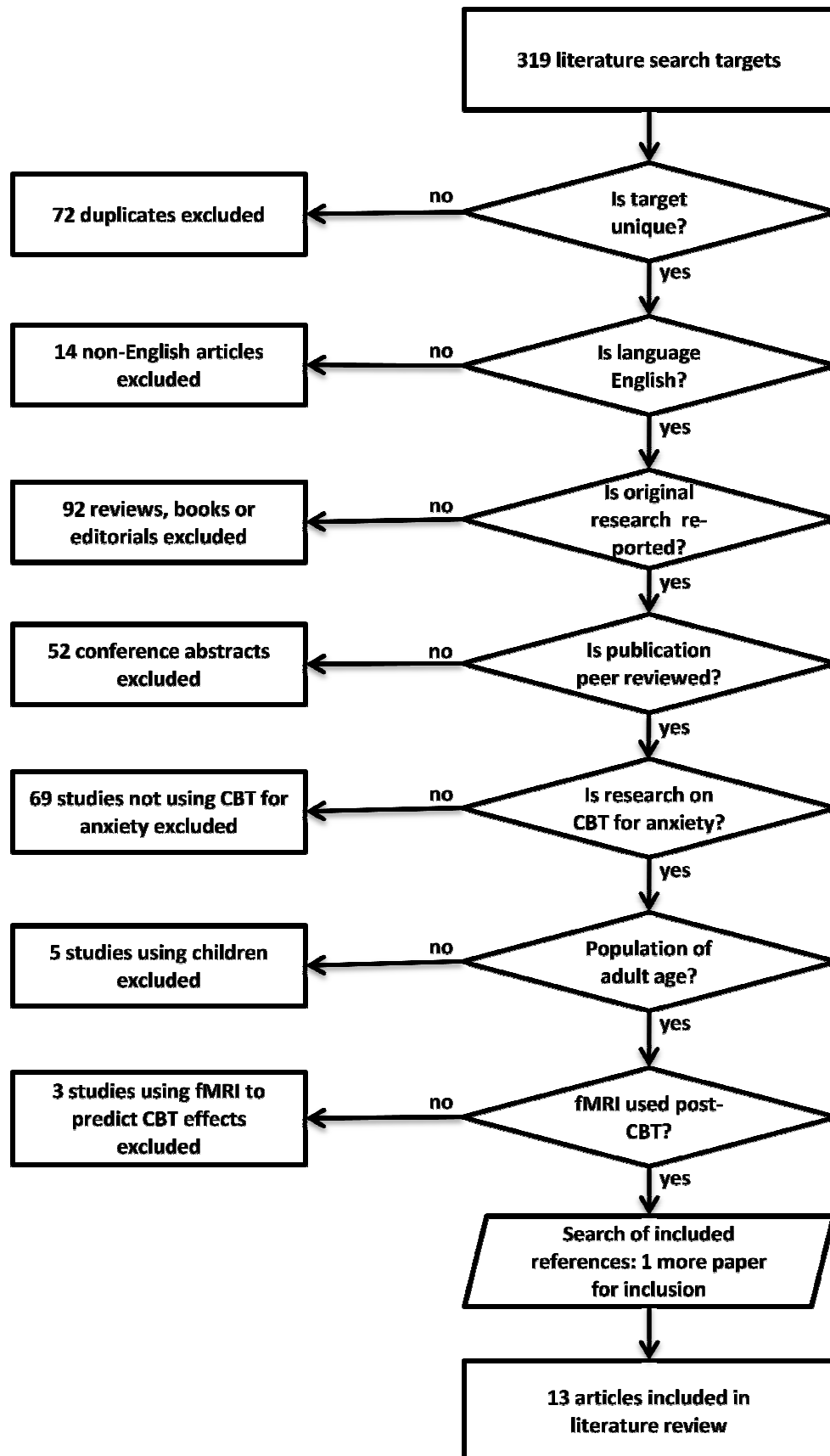


Figure 1. Process of selection of relevant target articles for inclusion in the review.

Extracted Variables

Articles were classified according to the specific anxiety disorder of interest and, within these, are reviewed in order of their date of publication. Functional imaging findings of post- versus pre-therapy brain scans were extracted and evaluated in light of the experimental design and control procedures applied, sample sizes, suitability of the functional neural activation paradigms employed, consistency with a priori hypotheses and the plausibility of the authors' integration of their results with the relevant background literature

Quality Criteria

Even though all of the reviewed articles employed a cognitive-behavioural intervention to reduce anxiety, they did so in order to study whether and how neural processes change as a function of successful therapy. This contrasts with studies that aim to assess the efficacy of healthcare interventions. Only the latter type intends to evaluate whether a clinical intervention works or whether its efficacy is better than that of other known interventions. It is this type of study that is typically referred to as a "clinical trial" and questions of clinical efficacy are most reliably addressed using the methodological design of a randomised controlled (clinical) trial (Moher et al., 2010). None of the studies reviewed in this chapter attempted to evaluate the clinical efficacy of therapeutic interventions for anxiety but studies using interventions to influence neural or other systems would also do well to use the methodological principles of experimental control, randomisation and blinding to permit unequivocal and unbiased attribution of any observations of change to the clinical intervention employed.

Quality frameworks such as the CONSORT statement (Schulz et al., 2010) have been developed to permit an objective appraisal of the quality with which clinical efficacy trials have been designed, conducted and analysed. Even though their principal remit is to reduce a biased reporting of clinical efficacy they can also be helpful in ensuring that non-efficacy trials are reported to a high standard. Whilst some quality criteria do not apply to non-efficacy trials the majority of criteria is appropriate because the research philosophies underlying the different types of studies share considerable commonalities. For this reason the experimental studies included in this review have been appraised against the criteria of the CONSORT checklist reproduced in Table 2 below.

Using this checklist papers were rated against whether each item had been reported adequately as commanded by the guidelines, partially so or not at all. At times certain items were identified as not applicable to individual studies (e.g. the requirement for identification as randomised trial when no randomisation had taken place or the requirements on how binary outcomes should be reported when no such outcomes existed). For each paper a CONSORT adherence score was computed by summing the number of items adhered to and dividing them by the number of applicable items and expressed as a percentage as

$$100 * \frac{\text{number of items reported adequately}}{(\text{total number of items}) - (\text{number of items scored as N/A})}.$$

Table 2. CONSORT (Schulz et al., 2010) checklist items used to appraise the quality of the reporting standards in the studies reviewed.

Section/topic	Item no.	Checklist item
Title and abstract	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group

fMRI Studies of CBT in Anxiety Disorders: A Critical Review

Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

Results

Table 3. Demographic and methodological design characteristics of the studies reviewed.

Reference	Sample	Mean age	Design	Phobia	Therapy	Time of brain scans	Whole brain or ROI
Paquette et al. (2003)	12 f phobic, 13 HC	24.8 phobic, 28.6 HC	HC vs TG, non-random	spiders	Gradual exposure based CBT, six per group, 3h/week, 4 weeks	pre- & post-CBT	whole & ROI
Straube et al. (2006)	28 f phobic (13 WG, 12 TG), 14HC	22.07	HC vs phobic (randomised into TG & WG)	spiders	Exposure-based CBT, 2-3 per group, 4-5h/day, 2 days	TG & WG, pre- & post-CBT; HC, once	ROI
Goossens et al. (2007)	16 f phobic, 12 f & 2 m HC	24	HC vs TG, non-random	spiders	Modeling & exposure based CBT, 3-5 per group, 4-5h, single session	phobic, pre- & post-CBT; HC, once	whole & ROI
Schienle et al. (2007)	12 f TG, 14 f WG, 25 f HC	27.2 TG, 24.3 WG, 24.6. HC	HC vs phobic (randomised into TG & WG)	spiders	Modeling & exposure based CBT, <=4 per group, 4h, single session	pre- & post-CBT or wait	whole & ROI
Schienle et al. (2009)	10 f phobic, 8 f HC	29.1 TG, 24 HC	HC vs TG, non-random	spiders	Modeling & exposure based CBT, <=4 per group, 4h, single session	pre- & 6 months post-CBT or wait	ROI
Hauner et al. (2012)	9f & 3 m phobic	22.3	TG vs WG, randomised	spiders	Modeling & exposure based CBT, 2h, single session	pre- & post CBT, 6-month follow-up	whole & ROI
Kircher et al. (2013)	29 f & 23 m phobic, 29 f & 13 m HC	35.42 TG, 34.33 HC	HC vs TG, non-random	panic	Manualised exposure-based CBT, 12 sessions, twice weekly	pre- & 6 months post-CBT or wait	whole & ROI
Lueken et al. (2013)	33 f & 16 m phobic	35.27	post-therapy split into responders and non-responders, non-random	panic	Manualised exposure-based CBT, 12 sessions, twice weekly	pre- & post-CBT	whole & ROI
Farrow et al. (2005)	4 f & 9 m phobic	42	TG only	PTSD	CBT not otherwise specified but modified to	pre- & post-CBT	whole & ROI

					include forgiveness		
Felmingham et al. (2007)	5 f & 3 m	36.8	TG only	PTSD	CBT focused on imaginal exposure & cognitive restructuring, 8 weekly sessions	pre- & 6 months post-CBT	whole & ROI
Goldin et al. (2013)	60 phobic (31 TG, 29 WG)		TG vs WG, randomised	social	manualised CBT, 16 individual sessions over 4 months	pre- & post-CBT or wait	ROI & connectivity
Klumpp et al. (2013)	9f & 5 m phobic, 8f & 6 m HC	28.07 phobic 23.29 HC	HC vs TG, non-random	social	Manualised CBT focusing on exposure & restructuring, 1h/week, 12 weeks	pre- & post-CBT or wait	whole & ROI
Månsson et al. (2013)	20 phobic	32.27	CBT vs ABM control randomised	social	therapist-guided internet-based CBT, 9 weeks vs. ABM	pre- & post-CBT or control task	whole & ROI

f, female; m, male; HC, healthy control participants; TG, treatment group; WG wait list group; CBT, cognitive-behavioural therapy; ROI, region of interest; PTSD, posttraumatic stress disorder; ABM, attention bias modification

Table 3 shows a description of the sample characteristics and design parameters of the studies reviewed. Sample sizes ranged between 8 and 94 participants with group sizes accordingly smaller. The majority of studies tested participants of both genders although some recruited female participants only. Eleven of the thirteen brain imaging studies reviewed used a control group or a control condition of some sort and, when patient controls were used allocation to groups was always randomised. CBT varied widely and was not always described in sufficient details to determine to what extent it overlaps with the treatment characteristics recommended in clinical guidelines. The therapy paradigms were diverse with respect to the duration of treatment, whether it was delivered individually or in groups, face to face or over the Internet. In all but one (Farrow et al., 2005) of the studies therapy incorporated an element of exposure to feared stimuli or cognitions. The majority used a form of symptom or threat provocation during subjects'

brain scans. Table 4 contains an overview of the main design characteristics and a summary of the key findings of the studies reviewed.

Table 4. Key changes in neural activation and deactivation response to symptom provocation and related challenges as a function of completed psychotherapy. Abbreviations and symbols: ↑, increased BOLD activation; ↓, decreased BOLD activation; PFC, prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; US, unconditioned stimulus.

Reference	Diagnosis	Behavioural paradigm	Neural response changes after therapy
Paquette et al. (2003)	Spider phobia	Symptom provocation using videos of spiders	↓dorsolateral PFC ↓parahippocampal gyrus
Straube et al. (2006)	Spider phobia	Symptom provocation using videos of spiders	↓ insula ↓ ACC
Goossens et al. (2007)	Spider phobia	Symptom provocation using images of spiders	↓amygdala (event-related RSVP) ↓ACC ↓insula
Schienle et al. (2007)	Spider phobia	Symptom provocation using images of spiders	↑OFC
Schienle et al. (2009)	Spider phobia	Symptom provocation using images of spiders	↑medial OFC ↓insula ↓lateral OFC
Hauner et al. (2012)	Spider phobia	Symptom provocation using images of spiders	↑DLPFC ↑superior parietal lobule ↓amygdala ↓insula ↓ACC ↓ventromedial PFC
Kircher et al. (2013)	Panic disorder	Aversive conditioning, US white noise burst	↓inferior frontal gyrus
Lueken et al. (2013)	Panic disorder	As above (reanalysis to predict treatment response)	Not analysed
Farrow et al. (2005)	PTSD	Empathy judgements of social narratives	↑posterior cingulate gyrus ↑medial frontal gyrus ↑posterior middle temporal gyrus
Felmingham et al. (2007)	PTSD	Briefly presented masked fearful facial expressions	↑rostral ACC ↓amygdala
Goldin et al. (2013)	Social phobia	Reappraise vs. dwell on negative self referential statements	↑dorsolateral and dorsomedial PFC during reappraisal, inverse relationship with amygdala
Klumpp et al. (2013)	Social phobia	Fearful and angry facial expressions	↓dorsomedial PFC ↓medial frontal gyrus ↓dorsal ACC
Månsson et al. (2013)	Social phobia	Fearful, angry and surprised facial expressions	↓amygdala ↓cerebellum ↓somatosensory cortex ↓basal ganglia ↓thalamus ↓PFC ↑OFC

Quality Appraisal

When judging the papers against the CONSORT criteria, several of these were found to not apply, or to only partially do so. Of the 37 items 4 were judged as applying to none of the studies reviewed. These included item 7b (interim analyses and stopping guidelines) and item 17 b (reporting of binary outcomes). An additional 10 items only applied to some (between 3 and 11) of the studies reviewed: E.g. item 1 (identification as randomised trial in the title) was not a fair quality criterion for studies that could not use randomisation. 24 items were, however, deemed to be ap[applicable to all studies. Table 5 shows how the studies fared when rated against the CONSORT criteria.

Table 5. Results of the quality judgement of studies reviewed against the CONSORT (Schulz, 2010) guidelines. Items were scored as fully (y), partially (p) or not complied with (n). Items marked n/a were deemed not applicable. The quality score in the bottom row expresses the percentage of items a study report showed full compliance with, not taking into account criteria classed as not applicable.

Checklist Item	Paquette et al. (2003)	Straube et al. (2006)	Goossens et al. (2007)	Schienze et al. (2007)	Schienze et al. (2009)	Hauner et al. (2012)	Kircher et al. (2013)	Lueken et al. (2013)	Farrow et al. (2005)	Felmingham et al. (2007)	Goldin et al. (2013)	Klump et al. (2013)	Mansson et al. (2013)
1a	n/a	n	n/a	n	n/a	n	n/a	n/a	n/a	n/a	y	n/a	n
1b	n	n	p	n	n	n	y	y	n	n	y	n	n
2a	y	y	y	y	y	y	y	y	y	y	y	y	y
2b	y	p	p	y	p	p	y	y	y	y	y	y	y
3a	y	y	y	y	y	y	y	y	y	y	y	y	y
3b	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
4a	y	y	y	y	y	y	y	y	y	y	y	y	y
4b	n	n	n	n	n	n	y	y	n	n	n	n	y
5	y	y	y	y	y	p	y	y	n	p	y	y	y
6a	y	y	p	p	y	p	p	y	n	y	y	y	y
6b	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
7a	n	n	n	n	n	n	n	n	n	n	n	n	n
7b	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
8a	n/a	n	n	n	n	n	n/a	n/a	n/a	n/a	n	n/a	y
8b	n/a	n	n	n	n	n	n/a	n/a	n/a	n/a	n	n/a	y
9	n/a	n	n	n	n	n	n/a	n/a	n/a	n/a	n	n/a	y
10	n/a	n	n	n	n	n	n/a	n/a	n/a	n/a	n	n/a	p

11a	n	n	n	n	n	n	n	n	n	n	n	n	n
11b	n/a	n/a	n/a	n/a	n/a	n/a	n	n	n/a	n/a	n/a	n/a	n/a
12a	y	y	p	y	p	y	y	y	y	y	y	y	y
12b	n/a	n/a	n/a	n/a	n/a	n/a	y	y	n/a	n/a	n/a	n/a	n/a
13a	y	y	y	y	y	y	y	n	y	y	y	y	y
13b	n/a	y	y	y	y	y	n/a	n	n/a	n/a	n/a	n/a	y
14a	n	n	n	n	n	n	n	n	n	n	n	n	n
14b	n/a	n	n	n	n	n	n	n/a	n/a	n	n	n	n
15	n	n	n	y	y	n	y	y	n	n	n	y	y
16	y	y	y	y	y	y	y	n	y	y	y	y	y
17a	n	n	n	n	n	n	y	n	n	n	n	n	n
17b	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
18	n/a	n/a	n/a	n/a	n/a	n/a	y	y	n/a	n/a	n/a	n/a	n/a
19	n	n	n	n	n	n	n	n	n	n	n	n	n
20	n	y	y	y	y	y	y	y	y	y	y	y	y
21	n	n	n	n	n	n	y	y	y	n	y	y	y
22	y	y	y	y	y	y	y	y	y	p	y	y	y
23	n	n	n	n	n	n	n	y	n	n	y	n	n
24	n	n	n	n	n	n	n	n	n	n	n	n	n
25	y	n	n	y	y	y	y	y	y	y	y	y	y
% adherence	47.8	36.7	31.0	43.3	41.4	33.3	66.7	63.0	47.8	41.7	55.2	58.3	63.3

General strengths identified by the quality appraisal were that all studies provided satisfactory levels of background to justify their scientific rationale (item 2a), described their design sufficiently well (item 3a) and report inclusion criteria for their participants (item 4a). A generic weakness was, however that none of the studies reviewed provided a satisfactory rationale for how the sample size was determined (item 7a), whether and how any blinding was implemented (item 11a), when exactly testing took place (item 14a) and whether any adverse effects or harms were reported that may have been attributable to an intervention (item 19).

As described above an adherence score was calculated by relating adhered-to items to the total number of applicable items for each paper reviewed. Adherence ranged between 31% (Goossens et al., 2007) and 66.7% (Kircher et al., 2013), the paper that also used the largest sample size. Figure 2 shows the frequency distribution of papers'

adherence to CONSORT reporting standards. The studies with the highest adherence scores were those by Kircher et al. (2013), Månsson et al. (2013) and Lueken et al. (2013). Studies with the lowest scores were those by Straube et al. (2006), Hauner et al. (2012) and Goossens et al. (2007). The mid-field with adherence scores ranging between 41.4% and 58.3% was comprised of studies by Klumpp et al. (2013), Goldin et al. (2013), Farrow et al. (2005), Paquette et al. (2003), Schienle et al. (2007), Felmingham et al. (2007) and Schienle et al. (2009).

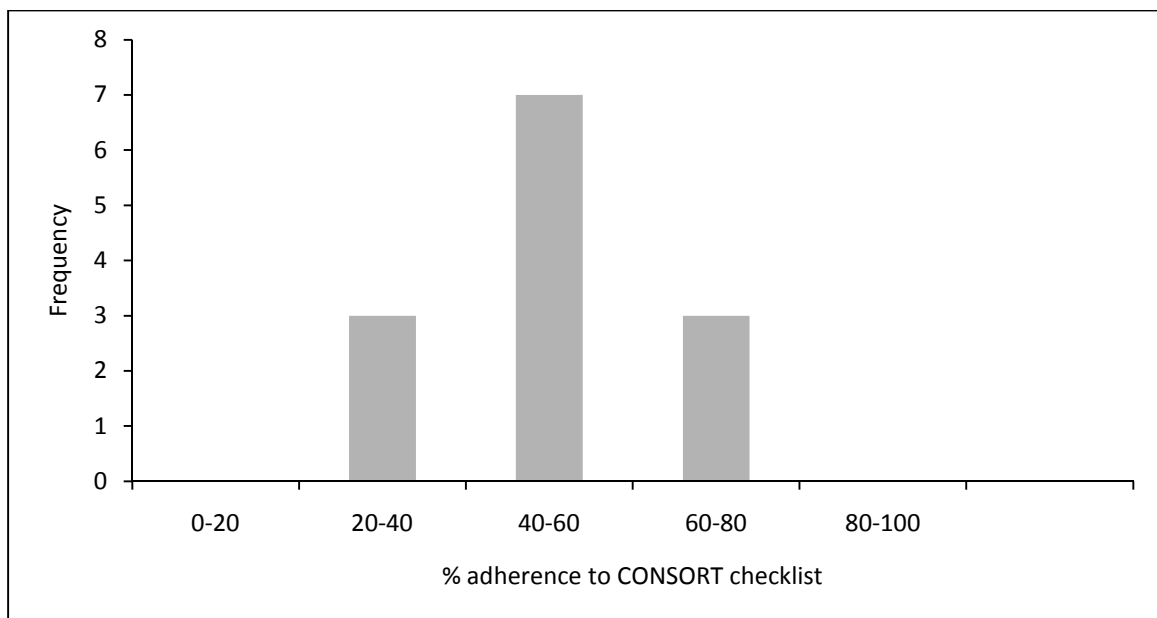


Figure 2. Frequency distribution of adherence to CONSORT quality criteria by the thirteen reviewed papers.

Specific Phobia

To date six studies have used fMRI to investigate the effects of CBT on specific phobia. In all of these the fear of interest was a phobia of spiders, presumably due to its high prevalence (Boyd et al., 1990; Magee et al., 1996), ease of creating valid symptom provocation procedures in the environment of a brain scanner (Johanson et al., 1998) and due to the availability of effective and efficient treatment paradigms (Öst, 1989, 1996; Zlomke & Davis, 2008).

The first fMRI study of the neural effects of CBT for arachnophobia was published by Paquette et al. (2003). They recruited twelve adult participants who were phobic of spiders and were given four weekly group therapy sessions lasting three hours each. Functional imaging contrasted neural responses to symptom provocation, using videos of spiders, with responses to non-fear inducing videos of butterflies. Patients' brain activations were further compared to those obtained from non-spider phobic control subjects.

Results showed that, before therapy and compared to controls, phobic patients' brains responded to spiders with bilateral activation of the parahippocampal gyrus (BA 36), which the authors interpret as an activation of the contextual fear memory system (Bechara et al., 1995). Dorsolateral prefrontal cortex (BA 10) showed a right lateralised activation which may be a correlate of the patients' use of volitional cognitive strategies to cope with, and reduce, the degree of fear experienced. This fits with the authors' observation that patients attempted to control their fear response by conscious control of their breathing. An earlier positron-emission computed tomography study reported a similar result (Johanson et al., 1998).

A third cluster of activation existed in secondary and higher order ventral visual processing areas. These are part of the attention network and plausibly reflect the deployment of visual attention and (hyper-) vigilance towards the phobic material, especially prioritising rapid recognition and identification of threat (Goodale, 2011). However, this was a large cluster and the specificity of this effect to subdivision of the extrastriate visual system is unclear. This kind of information would be useful to further dissect the specific role of neural networks in top-down attention deployment or bottom-up visual salience processing (Miller & Buschman, 2013) in future studies.

The authors found no activation of the amygdala. This is consistent with earlier neuroimaging studies of specific phobias (Fredrikson et al., 1993; Johanson et al., 1998; Mountz et al., 1989; Rauch et al., 1995) and may reflect a preferential role of the amygdala in the acquisition of a phobia, rather than the maintenance of fear in response to a phobic situation (LeDoux, 1993; Rauch et al., 2003). An alternative view is that amygdala activation is not seen when scanning phobic subjects because it habituates rapidly to repeated or prolonged stimulation with phobic material (Dilger et al., 2003; Straube et al., 2006).

CBT was highly effective in this study. After four sessions all patients were able to touch a spider without reporting cognitive or physiological symptoms of fear (Paquette et al., 2003). The corresponding neural correlates are likely a normalisation of activity levels in dorsolateral prefrontal cortex (BA 10) and both parahippocampal gyri (BA 36): after the original fear had extinguished, exposure to a previously phobic stimulus no longer required the same degree of cognitive effort to cope with this situation. Whilst it may reflect a reduced tendency for 'dysfunctional' thinking (Beck, 1979) such as cognitive misattributions (Gorman et al., 2000), it may also result from the reduced salience of the phobic object through extinction and, therefore, a concomitant reduction of vigilance to the feared object and efforts to engage in coping or avoidance strategies.

The main methodological limitation of this paper is that the healthy control subjects were only scanned once, whereas the patients were scanned before and after therapy. It can thus not be ruled out that the changes seen in patients are not related to CBT per se but reflect nonspecific changes, such as habituation to brain scanning procedures, which themselves may be more anxiety provoking in subjects with high levels of anxiety

(Hunt et al., 2011; Lueken et al., 2011; McGonigle et al., 2000). For the same reason it would have been desirable to have an untreated or placebo-treated patient control group.

Straube et al. (2006) improved on the design of Paquette et al. (2003) by adding a group of spider phobic patients who were scanned at the same time points as the treatment group but did not receive therapy. This controls for possible nonspecific effects, such as habituation to the experimental procedure in the brain scanner, that may have occurred concurrently with psychotherapy. Twelve spider phobic patients underwent two sessions of group CBT which lasted several hours on consecutive days and was highly effective. Thirteen patients were allocated to a waiting-list control group. Treatment group patients were scanned at two time points, immediately before psychotherapy and about two weeks after. Waiting-list control patients were scanned at identical time intervals but without receiving treatment. A third group of healthy control subjects was scanned once only. During brain scans participants viewed videos of a spider, which were fear inducing in untreated patients. Neural activations in response to these were contrasted with those to non-fear inducing control videos.

The authors found that, prior to therapy, threat processing in patients led to elevated activation in the insula and the anterior cingulate cortex (ACC). After therapy these responses fell to near normal levels. The insula is a brain region that is involved in sensing the body's homeostatic state and deviations from it. It is closely coupled with the autonomic nervous system (Critchley et al., 2001) and has increasingly been linked with threat processing and emotional awareness (Grupe & Nitschke, 2013).

Overactivation in the ACC, in particular its dorsal portion, normalised as a consequence of therapy. Like the insula, the dorsal ACC had been linked with sympathetic

nervous system arousal (Critchley et al., 2003) and, more recently, has been suggested to play a key role in appraisal, regulation and suppression of negative emotion (Etkin et al., 2011), making it a plausible neural candidate area to exhibit markers of therapy related cognitive changes.

Goossens et al. (2007) expressed their surprise that neither Paquette et al. (Paquette et al., 2003) nor Straube et al. (2006) found a change in amygdala activation as a correlate of therapy. They speculated that this may have been due to the activation paradigms used. Breiter et al. (1996) reported that the amygdala habituated rapidly to visual stimulation. Thus the stimulation paradigms in the previous work (presentation of fear-inducing stimuli in longer-lasting blocks) may have followed a suboptimal time course. To allow for such rapid habituation of amygdala activity, Goossens et al. (2007) used an event-related paradigm in which a more rapidly changing time course could be measured relative to the presentation of phobic images of spiders compared to control images of snakes. Sixteen spider phobic subjects were scanned before and two weeks after a highly effective single therapy session based on the approach by Öst (1989). Fourteen healthy control subjects were scanned once only. Regions of interest were the amygdala, ACC and insula.

Compared with controls, phobics had significantly elevated activation of their left amygdala when viewing spiders prior to therapy. After CBT this normalised and was no different from activations in response to viewing snakes – a pattern exhibited by healthy controls. Previously elevated activity in the ACC and the left insula also reduced to control levels, in line with the findings by Straube et al. (2006).

The normalisation of fear-related elevated amygdala responses after CBT is congruent with the well recognised role of the amygdala within the fear network (LeDoux,

1999). Since the authors scanned their control subjects only once the effects of CBT on the observed neural changes cannot be determined with certainty. Whilst a normalisation of fear network responses is plausible it is possible that this occurred as a consequence of therapy-nonspecific learning and habituation effects.

Schienle et al. (2007) also noted with interest that none of the first two studies identified the amygdala as area of therapy-related change since it is a core structure of the fear network (LeDoux, 1999). They thus sought to replicate the study by Straube et al. (2006) using a largely identical methodology which included random allocation of 26 spider phobic patients to a waiting-list or CBT group, pre and post-therapy brain scans for all patients and a single scan in a control group of 25 non-phobic volunteers. In addition, the authors wanted to investigate the specificity of what appeared to be the neural correlate of therapy related changes in processing of previously phobic material in the earlier studies. For this purpose patients were scanned during symptom provocation but also whilst viewing aversive but non-phobic material.

Therapy consisted of a single session of group CBT lasting four hours and was based on the principles by Öst (1996). It was highly effective in that all previously phobic patients could subsequently hold a spider in their hand. Compared to control participants, symptom provocation in phobic participants prior to therapy led to increases in activation of the amygdala and of visual association cortex. Medial orbitofrontal cortex was less activated in patients. The main neural effect of CBT was that orbitofrontal activation increased significantly which the authors interpret as consistent with an increased use of cognitive strategies, such as restructuring, in order to differently evaluate the valence of the – previously phobic – stimulus material. It should be noted that the authors found no consistent change in amygdala activation post therapy that reached statistical significance.

The authors had a strong a priori hypothesis relating to the effects of their manipulations on signal change in the amygdala. It would have been desirable if the authors had quantified the effect size they may have expected in order to determine whether sufficient statistical power existed to plausibly identify it with the sample size used.

Six months after their original study the same group performed a further brain scan on ten patients of their original therapy group and compared their measures with eight non-phobic control participants (Schienle et al., 2009). Results showed that the therapeutic gains had endured: previously treated participants did not differ statistically from control subjects on measures of phobia severity and behavioural avoidance. When contrasting brain activations six months after CBT with those obtained prior to therapy, the neural correlate of this lasting symptom improvement was a reduced activation of the insular and the lateral orbitofrontal cortex and an increase of activity in medial orbitofrontal cortex. The authors argue that the orbitofrontal increase is a likely reflection of the patients' enduring cognitive change and propose further that it may reflect a reward signal as the patients pride themselves in no longer experiencing fear in response to spiders. It is unfortunate that the authors did not report an analysis of how orbitofrontal activation at follow-up compared with that immediately post therapy. Inspection of the t-values suggests that, had an appropriate repeated-measures comparison been computed, a further increase of orbitofrontal activation since the post-therapy scan may well have been revealed and it would have been interesting to read the authors' interpretation, particularly within the context of their reward magnitude hypothesis.

Hauner et al. (2012) published the most recent fMRI investigation of the effects of CBT in spider phobia. Twelve spider phobics were randomised to either receive treatment or remain on the waiting list. All subjects were scanned at three time points: at baseline,

following therapy or a wait of identical duration and six months after. Brain responses to phobic stimuli (spiders) and neutral stimuli (moths) were compared.

At baseline phobics' brains showed elevated activation in the right amygdala, both insular and cingulate cortices. Therapy was highly successful: at the end all patients handled a tarantula without significant distress. The corresponding neural changes consisted of an increase of activity in, both, the right dorsolateral prefrontal cortex and the superior parietal lobule during exposure to spider images. The authors interpret this as reflecting the role of the dorsolateral prefrontal cortex in emotional self regulation and cognitive reappraisal in line with Herwig et al.'s (2007) suggestion that increased activity in prefrontal cortex down regulates fear-related activity in the amygdala. The parietal activation was proposed to reflect enhanced visual attention (Goodale, 2011). The increased activation at baseline in the amygdala, insula, cingulate as well as ventromedial prefrontal cortex all reduced as a function of psychotherapy.

Six months after therapy the treatment gains were maintained and so were the normalised activity levels in all previously elevated regions. Dorsolateral prefrontal cortex, however, no longer exhibited the increased activity seen immediately after therapy. The authors suggested that when altered behavioural and cognitive strategies were novel, cognitive regulation of fear may have played an important role in allowing newly treated patients to approach previously phobic material. Emotion regulation of this type has been proposed to involve an inhibitory influence by dorsolateral prefrontal cortex over amygdala activity (Hartley & Phelps, 2010). As these strategies consolidate and become second nature raised prefrontal cortical resources may no longer be required to maintain therapy success.

In summary, whilst all six studies on specific phobia tested arachnophobic patients and all utilised symptom provocation, the results were varied. The most consistent finding concerned the insula: two thirds of the papers reported an activation reduction after therapy. Half of the studies found a post-therapy reduction of amygdala activation and half found the same in the ACC. Findings on pre- and orbitofrontal cortex were mixed: whilst three reports identified CBT related changes in these areas some found increases and others decreases in activation leaving a slightly inconsistent picture.

Panic Disorder

Two studies have thus far been published that examine the neural response to CBT in panic disorder using fMRI. They report data from a large German multicenter randomised controlled trial of CBT for panic disorder (Gloster et al., 2009; 2011). Whilst both present data from the same functional imaging investigation they attempt to answer different questions and accordingly employ different statistical methods.

Kircher et al. (2013) used a classical conditioning paradigm to investigate the neural correlates of patients' responses to CBT. Large samples of patients and healthy controls (each consisting of 42 participants) were scanned whilst learning to associate a conditioned stimulus with an unpleasant burst of loud white noise. Patients were scanned before and after a six week, twelve session, course of CBT, which was very effective in alleviating panic symptoms and agoraphobic avoidance. Controls had their two scans at corresponding time intervals. The main finding was that, compared to controls, patients exhibited a significantly higher activation in the left inferior frontal gyrus during early aversive conditioning trials. This activation had reduced to normal levels when the conditioning trials were repeated during the scan after completion of CBT. The authors interpret this as showing that CBT reduces patients' tendency to engage in unhelpful

cognitive styles, such as vigilance for threat cues, catastrophising and expectancy of harm (Bishop, 2008; Hofmann, 2008). Following CBT, activation related to aversive conditioning in patients had also reduced in the amygdala, the ACC, the insula and prefrontal areas but these did not reach statistical significance.

The authors also analysed the functional connectivity of patients' inferior frontal gyrus using the clinical outcomes as covariates. This revealed that, before the commencement of CBT, the left inferior frontal gyrus and left amygdala were correlated more positively the more agoraphobic patients were. After therapy a larger degree of symptomatic improvement corresponded with increased connectivity between patients' left inferior frontal gyrus and bilateral and medial frontal cortex as well as cingulate cortex but no longer the amygdala. A reduced need for cognitive regulation of limbic activity could arise from reduced bottom-up elicitation of affect rather than increased top-down control.

The interpretation of the results by Kircher et al. (2013) is compromised because no suitable patient control group was included. Any observed differences between pre- and posttreatment scans in patients and healthy controls may not solely be due to the effects of CBT. It is likely that non-anxious controls habituated differently to a fear conditioning task and also to brain scans which themselves are known to be anxiety inducing (Hunt et al., 2011; Lueken et al., 2011; McGonigle et al., 2000). The current research design confounds these aspects and it needs to be considered that the observed effects could solely stem from factors not specific to successful psychotherapy of panic disorder. Future work would benefit from inclusion of a control group of patients with panic disorder of comparable severity who undergo the repeated brain scans and conditioning experiments whilst not working on improving their clinical condition.

Another criticism relates to the validity of the cognitive-emotional probe used during functional MRI scanning. Whilst the authors refer to this paradigm as “fear conditioning” (Kircher et al., 2013, p 93), it is unclear how frightened the subjects ended up when hearing the conditioned stimulus repeatedly. Whilst it must undeniably have been somewhat unpleasant to endure loud bursts of white noise repeatedly, the emotional consequences may well have been of quite a different phenomenological quality to the dread panic sufferers experience during a panic attack or its build-up during the prodrome (American Psychiatric Association, 2013). In support of this view is the original publication of the conditioning paradigm used: Its authors stopped short of labelling the procedure fear conditioning and only referred to it as “aversive conditioning” (Reinhardt et al., 2010, p. 443). A test more closely related to the phenomenology of panic disorder would have been one that induces the unprovoked, sudden and intense sense of dread and imminent catastrophe that typically accompanies panic attacks. This is of course difficult to accomplish in a brain scanner. However, identifying the neural correlates of classical conditioning to loud white noise bursts may not further our understanding of the brain mechanisms involved in the pathogenesis and maintenance of panic disorder.

Lueken et al. (2013) presented a different analysis of the functional imaging data from the same large trial (Gloster et al., 2011). Of the 42 patients on whom functional imaging data were available, 33 were subselected and split into two groups based on the degree of symptom reduction they experienced after CBT. Whilst both groups showed a statistically significant improvement the authors nevertheless labelled them treatment “responders” and “nonresponders”, respectively (Lueken et al., 2013, p. 1346).

Results showed that the best neural predictor of patients’ non-response to future CBT was increased activation in the right ACC, the hippocampus and the amygdala when,

within the classical conditioning paradigm, patients were processing a stimulus that was not followed by an unpleasant burst of white noise (*i.e.*, a safety signal). The authors suggest that such an elevation of activity in fear-processing structures even when a non-threatening stimulus is presented may signify a highly hypervigilant attentive state, biasing detection towards danger and impairing an ability to discriminate between safety and threat.

The authors' main remit for this reanalysis of the original dataset was to see whether any neural measures could serve as reliable predictors for the outcome of therapy. This is a highly relevant question to answer. In order to detect strong relationships between variables it is important to maximise their variances as otherwise the covariance, and thus correlation, between the two can appear too low (Howell, 2010). The present dataset is hampered in that all patients responded to therapy remarkably well. Even the 'nonresponders' showed considerable, and statistically significant, improvement on the Clinical Global Impressions Scale (Guy, 1976), the Hamilton Anxiety Rating Scale (Shear et al., 2001), the Panic and Agoraphobia Scale (Bandelow, 1995), the Anxiety Sensitivity Index (Reiss et al., 1986) and even on the Beck Depression Inventory (Beck et al., 1996). In that context it is interesting to note that the neural activation pattern typical for treatment nonresponders resolved after CBT which was of course rather successful in alleviating at least some of the symptoms.

The authors appear to have done a substantial amount of statistical transformation and analyses in order to identify a neural pattern that predicted treatment response with some statistical significance. To put this in perspective, a look at the authors' data shows that the statistically most robust relationship was not between treatment response and a neural measure but patients' baseline score on the Panic and Agoraphobia Scale

(Bandelow, 1995) instead. In other words it seems that by far the best predictor of clinical outcome remains the severity of patients' initial presentation: the worse they are the more likely they are to leave therapy with residual problems remaining.

It is worth noting that both the reports by Kircher et al. (2013) and Lueken et al. (2013) based their analyses on different number of patients even though they only constitute different statistical analyses of the same underlying dataset of the large randomised controlled trial by Gloster et al. (2011). Unfortunately no clear rationale for this discrepancy was presented.

In summary, both studies on panic disorder reported the same dataset but focused on different statistical analyses. They exhibit a number of methodological inconsistencies and different subsamples were selected for inclusion in the two analyses without clear rationales for the decisions behind this. The validity of the aversive conditioning paradigm for the understanding of aberrant neural processes in the development and maintenance of panic disorder is also unclear. The main findings were that, after CBT patients showed less recruitment of lateral PFC, presumably because of a lowered tendency to engage in unhelpful safety seeking behaviours and maladaptive cognitive strategies such as avoidance. Similarly, the more patients recruited neural areas involved in (hyper-) vigilance prior to therapy, the less likely they were to benefit from CBT. Unfortunately no waiting list control group was included in the design of both papers. Therefore any effects seen in treated patients may merely reflect different degrees of adjusting and habituating to the scanner environment and experimental procedure, rather than differences brought about specifically by CBT.

Posttraumatic Stress Disorder

Two reports have to date been published that aim to identify the neural factors involved in CBT for PTSD using fMRI. The first, a paper by Farrow et al. (Farrow et al., 2005), differs from all other studies reviewed here in that no symptom provocation or anxiety induction was studied. Instead the authors use experimental paradigms from the field of social cognition and theory of mind. No brain structures within the fear network were selected for a region-of-interest analysis. Instead the authors focused on candidate areas within the domain of social cognition, based on their previous neuroimaging work in a non-clinical population (Farrow et al., 2001).

Thirteen road traffic accident survivors with PTSD were offered between four and ten sessions of CBT which was not further specified apart from that it included a “forgiveness component” (Farrow et al., 2005, p. 47). After therapy PTSD symptoms had improved significantly. Before and after therapy subjects had an fMRI scan during which they read brief social scenarios on which they made judgements regarding the forgiveability of actions presented and the degree to which they empathised with them. This was contrasted with a social reasoning task.

Prior to therapy empathy judgements (when compared to social reasoning) led to increased activations in right medial frontal and left posterior cingulate gyrus, extending into the precuneus. After therapy, left middle temporal gyrus showed increased activations during empathy judgements when contrasted with pre-therapy baseline. Forgiveability judgements increased baseline activations in left medial frontal and posterior cingulate gyrus. After therapy the forgiveability vs. social reasoning contrast revealed increased activation in posterior cingulate, medial frontal and left posterior middle temporal gyrus.

Unfortunately no data were presented to show how the content of subjects' social-moral judgements changed over the course of forgiveness-based CBT.

A degree of caution in interpreting the therapy-related findings may be prudent because the authors' results in the narrative of their paper is different from those shown in a table. The authors offer the tentative interpretation that their results may demonstrate a therapy-related change in semantic processing when making social judgements. However, their principal conclusion is merely "that it is feasible to (... measure the effects of therapy ...) on the brain's functional response to cognitive tasks" (Farrow et al., 2005, p. 51) – an assumption they must surely already have held when their experiment was in the planning stage.

It is unfortunate that no control subjects – whether healthy or traumatised – were included in the design. This precludes the discrimination of therapy-related from nonspecific effects, such as the passage of time. Since the authors present no rationale for their way of modifying CBT to include a forgiveness component there is no certainty that the treatment was evidence based and had proven efficacy. Because no control group was tested the clinical changes seen may not only be due to factors separate from therapy but could indeed have happened despite of it.

In their brief paper Felmingham et al. (2007) present an fMRI investigation of eight patients who developed PTSD after surviving an accident or interpersonal violence. Functional MRI scans were conducted before and after an eight week course of trauma focussed CBT. During scans patients viewed blocks of fearful and neutral facial expressions that were presented very briefly before being masked. Data analysis centred on

the ACC and the amygdala as regions of interest. Therapy was effective and led to substantial improvements of PTSD symptoms in all patients.

The authors found increased bilateral activation of the rostral ACC after therapy when viewing fearful facial expressions. They also found two statistically significant and strong correlations. Firstly, the degree of activation of the right ACC covaried substantially with the degree of symptom improvement after therapy. Secondly, the more fear processing related amygdala activation reduced after therapy, the better patients recovered from their PTSD symptoms. This is an encouraging finding as the theory base so strongly predicts that recovery from an anxiety disorder should also manifest itself in altered threat detection and fear processing by the amygdala (Bishop, 2007, 2008; LeDoux, 1999).

The absence of a control group limits the value of this paper. Any changes the authors attribute causally to therapy could also be related to habituation, or any other factors that changed during the eight weeks between the baseline and post-therapy brain scans. Nor were the authors able to find the therapy related increase of ACC involvement in threat processing they had predicted. Given the small sample size this is not entirely unexpected and this report should largely be considered a pilot study.

In summary none of the two papers on PTSD employed a robust design. Farrow et al. (2005) had no control group or condition and report insufficient information on their test procedure to render their results interpretable within the remit of this review. Felmingham et al (2007) tested only eight patients but found that neural activation was lower in the amygdala and had increased in the ACC, with both effects corresponding to the degree of symptomatic improvement post therapy.

Social Phobia

Three papers exist, all published in 2013, that used fMRI to understand the mechanisms of CBT for social anxiety. Goldin et al. (2013) scanned the brains of 60 patients with social anxiety disorder before and after sixteen sessions of individual CBT. During scanning, patients viewed displays of negative self beliefs with individual personal relevance. They were instructed to either cognitively reappraise the statements to make the belief less upsetting or to react to them by dwelling on the truth value of the statement. Activated brain regions were identified using a region of interest analysis.

The task was successful in significantly affecting negative emotion ratings. Therapy was effective in that both reappraise as well as react strategies led to reduced negative emotions after CBT than after having waited for treatment. During react trials CBT raised activations in the medial prefrontal cortex. During reappraisal CBT was associated with increased activity in dorsomedial and left dorsolateral prefrontal cortex. No main effects or interactions were found in the amygdala in either of the two tasks. However, a functional connectivity analysis in patients after CBT showed an inverse relationship between activations of the dorsomedial prefrontal cortex and the left amygdala.

The authors interpret their results as reflecting more effective frontal cortical top-down regulation of amygdala based emotional appraisal (*e.g.*, Ochsner & Gross, 2005) after successful therapy. It must be stressed, however, that the inverse relationship between activation of the amygdala and dorsomedial prefrontal cortex was only obtained when the authors selected a seed region in the latter. This location was chosen post hoc, rather than hypothesis driven. A more stringent probe of functional amygdala connectivity would have been to plant the seed for the analysis there. Nevertheless the authors used the largest

sample size of all studies reviewed so far and the use of a wait list control group lends good support to its interpretability.

Klumpp et al. (2013) gave a twelve week course of CBT to fourteen patients with social phobia. Before and after therapy patients had an fMRI scan in which presentation of happy faces was contrasted with fearful or angry facial expressions. A control group of healthy volunteers was also scanned twice using the same paradigm.

Therapy led to a statistically significant reduction of social phobia in patients. In a first step the authors analysed the neural predictors of therapy success. Those patients who benefitted most from therapy had greater baseline activation of higher order visual processing areas, dorsomedial prefrontal cortex and dorsal ACC in response to threatening facial expressions. Increased processing of threatening social stimuli in brain areas involved in recognition, evaluation, appraisal and generation of a fear response correlated with success of therapy here.

Analysing the neural correlates of CBT, the authors found that elevated baseline activity to angry versus happy faces in dorsomedial prefrontal cortex, middle frontal gyrus and insula reduced significantly in patients but not in controls. The authors interpreted this as evidence that reduced cognitive biases towards recognition and processing of threat signals are associated with enhanced symptom reduction. It should be noted that no differential activation of the amygdala was found.

The interpretability of the results, especially of the latter effects, is jeopardised by the lack of a suitable control group. The authors confound being a patient who suffers from social phobia with being in receipt of treatment and experiencing symptom improvement. Any observed effects could be due to either of those factors.

The third paper on social phobia is by Månsson et al. (2013), this time looking at CBT delivered via the Internet. 26 patients, of whom 20 provided brain data, were randomised to either receive CBT or attention bias modification training as a control condition. Internet based CBT consisted of the nine-week therapist guided intervention developed by Andersson et al. (2006) which was shown to have good and sustained efficacy (Hedman et al., 2011). Attention bias modification is based on the concept that cognitive biases, such as the directing of attention towards threat, cause and maintain negative affect in anxiety disorders (MacLeod et al., 1986). Reducing such biases, typically through computerised tasks using cued visual attention paradigms, has been shown to lower the likelihood of experiencing anxiety and its perceived intensity (Clarke et al., 2014; Macleod, 2012; MacLeod & Mathews, 2012). The attention bias modification group received Internet based training to direct their attention away from disgusted facial expressions (Carlbring et al., 2012) twice weekly for four weeks.

Both CBT and attention bias modification training were effective in lowering symptoms of social anxiety although CBT led to a larger improvement. The fMRI activation paradigm consisted of a task in which angry, fearful or surprised faces had to be processed. At baseline the task induced significant bilateral activation of the amygdala. After the treatments this had reduced significantly more in subjects who had received CBT compared to those who had attention bias modification. Similar CBT related decreases were seen in the cerebellum, somatosensory cortex, basal ganglia and the thalamus. A multiple regression analysis was used to further explore the normalisation of left amygdala activation in the CBT group. This showed that it was negatively correlated with activity in the medial orbitofrontal cortex and positively correlated with that in right ventro- and dorsolateral prefrontal cortices.

The authors were successful in finding their hypothesized normalisation of anxiety-related amygdala activation after CBT. This normalisation, together with the associated orbitofrontal activation may reflect enhanced top-down control of emotional responses, although the authors conceded that the concurrent deactivation of right prefrontal cortex was counterintuitive given its role in cognitive control and emotion regulation (Ochsner & Gross, 2005). It is, however, congruent with similar findings by Paquette et al. (Paquette et al., 2003) and Straube et al. (2006) in spider phobics reviewed above.

A methodological strength of the current study is the inclusion of an active control group. In theory this would permit to identify the neural correlates more specific to CBT itself. Unfortunately the treatments differed in their efficacy, so the findings may relate to different degrees of symptom resolution, rather than different cognitive strategies employed. The main limitation of the current study is that no wait-list control group was included. This would have been helpful in quantifying the degree of spontaneous, therapy unrelated symptomatic improvement over time and given an indication about the degree of efficacy of attention bias modification. At present it is difficult to disentangle the effects of the passage of time alone. In addition the two treatments differed not only in therapeutic content but also in duration, so any effects observed may be related to that.

The three papers on the neural effects of CBT in social phobia reviewed here comprise the one with the largest sample size of patients and the only report that provided CBT over the Internet. The two studies that employed suitable methodological controls found some evidence that, after CBT, amygdala and PFC are less activated – unless patients were actively engaging in a cognitive reframing procedure, in which case recruitment of PFC was increased.

Discussion

This paper has reviewed thirteen functional magnetic resonance imaging studies that attempted to identify the neural correlates of successful CBT in patients with an anxiety disorder. Twelve of the thirteen studies reported original data, one (Lueken et al., 2013) was a reanalysis of an extant dataset also reviewed here (Kircher et al., 2013). The overarching finding of this review is that no consistent pattern of results exists across the various studies.

The quality appraisal using CONSORT criteria has also highlighted that most studies would have benefitted from being designed and reported in a more methodical manner, aiding replication, interpretability and generaliseability of findings. The CONSORT checklist was designed for trials of clinical efficacy. The present studies did not aim to establish whether CBT works and therefore using such quality criteria may be a slightly unfair benchmark. Nevertheless adherence to a systematic method of designing and reporting trials within the fields of experimental medicine or psychology criteria is possible in principle and would reduce the risk for reports, or at least interpretations of them, to be biased.

Although by far from consistent, the highest degree of concordance across studies exists about the amygdala, insula and ACC: Whenever their activation changed as a function of psychotherapy it was always (or, in the case of the ACC, predominantly) reduced after CBT. Table 2 demonstrates that for the amygdala this was the case in four of the thirteen studies, in particular in spider phobia (Goossens et al., 2007; Hauner et al., 2012), PTSD (Felmingham et al., 2007) and social phobia (Månsson et al., 2013). Reduced insula activation was also found by four studies, exclusively in spider phobia (Goossens et al., 2007; Hauner et al., 2012; Schienle et al., 2007; Straube, Glauer, et al., 2006). The

ACC showed reduced involvement after therapy in three studies of spider phobia (Goossens et al., 2007; Hauner et al., 2012; Straube, Glauer, et al., 2006) and one of social phobia (Klumpp et al., 2013). In contrast, one study found that it was more recruited during the processing of masked fearful facial expressions after therapy for PTSD (Felmingham et al., 2007). That said, it should be noted that the most consistent commonality across the studies reviewed here was that reduced activation in these brain regions was *not* reliably found.

Why was an effect of CBT not seen in the amygdala more frequently? Some might argue that this should have been expected, given the central position of the amygdala within the brain's fear network (Bishop, 2007, 2008; LeDoux, 1999). Unfortunately imaging the amygdala by fMRI is complicated by its comparatively small size and its proximity to the air filled paranasal sinuses. Magnetic field homogeneity is disrupted near boundaries between dense body tissue and air and BOLD signal to noise ratio is reduced there (Merboldt et al., 2001).

Another concern is, however, whether the studies reviewed used the right neurocognitive probes to preferentially activate the amygdala in a way that is measurable using fMRI. The amygdala is a neural structure that habituates rapidly to stimulation, perhaps too quickly to be generating signal of sufficient intensity to be identified with fMRI scanning sequences (Dilger et al., 2003). The majority of studies used repeated slow presentation of visual stimuli, often not reporting whether they were perceived as threatening when viewed inside the bore of a large magnet in a hospital laboratory.

Of the studies that did find reduced amygdala activation as a function of CBT, only half could also identify a concurrent increase of frontal cortical activation. Whilst Månsson

et al. (2013) found a post-therapy increase of orbitofrontal activation in social phobics, prefrontal cortex showed the inverse response pattern. In the insula the picture looks no more consistent. Schienle et al. (2007), who studied spider phobics, found that medial orbitofrontal cortex showed higher activation after CBT whereas lateral orbitofrontal cortex demonstrated reduced activation. Only Hauner et al. (2012) found that reduced activation of the insula corresponded with an increase in dorsolateral prefrontal activation after therapy.

CBT involves the teaching of conscious cognitive strategies, such as thought challenging and reattribution. Therefore a popular and intuitively plausible view is that, at a neural level, CBT should work by increasing frontal cortical control over phylogenetically older subcortical limbic structures that may operate without conscious awareness, in particular the amygdala and insula (Beauregard, 2007; Ochsner & Gross, 2005; Ochsner et al., 2012). In other words, some have argued that successful CBT for anxiety should be mirrored in reduced activation of amygdala/insula and concurrent upregulation of prefrontal cortex which inhibits the former structures.

Technical, methodological and statistical limitations may account for the lack of consistency in observing reduced amygdala activation or increased frontal cortical top-down modulation of deeper limbic structures as a function of symptomatic improvement. Based on the present body of evidence we can therefore not conclude with confidence that such neural mechanisms are not influenced by CBT. It has recently been suggested, however, that increased frontal cortical top-down control may indeed not be the way in which CBT for anxiety acts at a neural level: Reinecke & Harmer (in press) proposed that the therapy-related reduction of frontal cortical activation seen across a range of studies

could reflect a reduction of otherwise fear-maintaining cognitive biases such as hypervigilance and safety behaviours centred around avoidance.

There is considerable consistency in the involvement of the ACC during the regulation of emotional arousal. Bush et al. (2000) suggested that the ACC includes specific processing modules for sensory, motor, cognitive and emotional information and integrates input from various sources including motivation, evaluation of error and representations from cognitive and emotional networks. They proposed that it acts by influencing activity in other brain regions and modulating cognitive, motor, endocrine and visceral responses. Accordingly, the ACC may be particularly sensitive to therapeutic effects that utilise top-down control of elicited emotional reactions (emotion regulation) but, in turn, might be less sensitive to therapeutic strategies targeted at reducing the bottom-up salience of the anxiety producing object (emotion elicitation).

The majority of studies in this nascent literature was shown to have considerable methodological limitations, a view that was confirmed by the quality appraisal. Almost all studies used very low sample sizes, many with less than ten subjects in each experimental group. That said it is difficult to criticise this shortcoming constructively. Because significance testing in functional MRI does not involve a single outcome variable but three-dimensional brain activation maps, often using complex factorial time-series designs it is notoriously difficult to carry out power calculations (Hayasaka et al., 2007). No consensus on how this should be done exists and statistical fMRI analysis packages do not contain options to perform power calculations. Initial solutions have now been proposed that allow for power calculations in some very standard fMRI designs (Joyce & Hayasaka, 2012; Mumford, 2012). Whilst such procedures will undoubtedly be of substantial value to

improve fMRI research in the future their inception was too recent to have been of benefit to the studies reviewed here.

In addition to flaws with the study design, statistical weaknesses in the way data were analysed were also very prevalent amongst the papers reviewed. Frequently the significance level was insufficiently adjusted for multiple inferential statistical comparisons, leading to type-I-error inflation. Combined with the file drawer problem (van Assen et al., 2014; Vevea & Woods, 2005) this leaves one wondering whether any of the results of the thirteen papers reviewed are veridical (Ioannidis, 2005). Replication of the studies, especially by independent research groups, is thus essential to help separate true and consistent findings from spurious, one-off type-I-errors.

In conclusion, the present review has been unable to identify the neural correlates of CBT for anxiety. No single set of unifying findings could be identified that stands out as representative, for example that therapy increases prefrontal cortical top-down control over limbic fear centres such as the amygdala. Factors that will most likely contribute to such a lack of consistency are the high degree of heterogeneity across the studies reviewed: The samples used showed large degrees of clinical and demographic heterogeneity and so did, in particular, the psychotherapeutic treatments used. Studies' methodological design was also very varied, in particular regarding the implementation of experimental control procedures and the sample sizes deemed suitable to identify treatment effects. The review is further limited by the fact that it mainly assembled information in what has been compared to "vote-counting" (Hedges & Olkin, 1980). Ideally a meta-analytical approach would have been employed. However, this would have required a more consistent and comprehensive reporting of research methodology and results in the first place. A

paradigm shift towards assured quality in research reports is hopefully underway enabling easier comparison of clinical trials as well as experimental medicine research findings.

It has, however, highlighted the need for future research. Both imaging neuroscience and psychotherapy research are still in their infancy, however (Marks, 2002). With the development of better neuroimaging paradigms and the further advance of dismantling studies that identify the effective ingredients in psychotherapy we will hopefully become able to integrate the two fields to help us understand how different components of psychotherapy work and the factors involved in their ability to reduce distress. Having a better understanding of what it is that makes good psychotherapy work, how to make it even more effective and, perhaps most importantly, allow us to better predict who will respond best to what type of intervention would be beneficial in deciding how to allocate scarce clinical resources and where to spend research funding. Whether functional MRI will become a routine part of clinical screening remains to be seen. It is currently too time and resource expensive to be viable to become a standard clinical assessment tool. However, the further development of quicker tests, such as structural MRI or electrophysiological measures such as electroencephalogram or evoked potentials may be developed to give test results of good enough predictive validity to be useful in everyday clinical decision making about whom to offer what type of intervention to combat anxiety disorders.

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CHAPTER 2

Empirical Paper

A Randomized Controlled Trial of the Neural Effects of Cognitive Behavioural Therapy for Panic Disorder

Abstract

Background: Cognitive behavioural therapy (CBT) is an effective treatment for panic disorder. However, little is known about whether and how neural processing of threat changes following CBT. Aim: To identify the effects of CBT for panic disorder on brain mechanisms involved in threat processing using a wait-list control group. Method: In a randomised controlled trial 28 participants with panic disorder were allocated to receive brief CBT or to wait for treatment for the same amount of time. After treatment or waiting participants had a functional magnetic resonance scan of their brain while they were viewing aversive and threatening pictures. Neural activations were measured in two conditions – when participants maintained their negative affect or used cognitive reappraisal strategies to reduce affect. Results: Brief CBT was highly effective in reducing clinical symptoms of anxiety. Neuroimaging identified that CBT reduced responsivity of dorsolateral and dorsomedial prefrontal cortex to threatening images. CBT reduced threat-related activation in the amygdala only when participants maintained the affect induced by the aversive pictures and not when they employed cognitive reappraisal strategies. Conclusions: Fronto-limbic responsivity to threat is reduced by brief CBT in panic disorder. These results highlight relevant neurobiological mechanisms of CBT which may be important for future treatment development and treatment combination approaches.

Introduction

Panic disorder is one of the most prevalent anxiety disorders (Kessler et al., 2006). Its hallmark is the occurrence of unexpected panic attacks – sudden-onset episodes of intense fear during which the sufferer believes that a physical, mental or social catastrophe is imminent (American Psychiatric Association, 2013). Panic disorder is not only highly distressing for those who experience it but also presents a significant socioeconomic burden because morbidity, chronicity and associated disability are high (Yonkers et al., 2003).

The psychological factors involved in the development and maintenance of panic disorder are well understood (Clark, 1986) and effective treatments have been developed (Gelder et al., 1993). Clinical guidelines now recommend cognitive-behavioural therapy (CBT) as a first line treatment above pharmacological or other interventions (NICE, 2011). However, a significant proportion of those treated fails to respond to CBT or relapses after discharge from therapy (McHugh et al., 2009; Otto et al., 2000). Furthermore, only a minority of people with panic disorder has good access to CBT. Understanding the mechanisms underlying successful treatment of panic disorder may help to develop faster acting and more specific therapy programmes, devise better combination approaches (using pharmacological as well as psychological strategies) and identify individual differences which predict the likelihood of treatment efficacy before its resource intensive application.

The amygdala, a subcortical nucleus in the pole of the temporal lobe, has long been identified as an essential neural substrate in the recognition of threat and the generation and maintenance of fear (Klüver & Bucy, 1937; LeDoux, 1999; Rolls, 2007). Gorman et al. (Gorman, Kent, Sullivan, & Coplan, 2000) reviewed a large body of animal and human

neuroscience research and proposed that panic attacks are mediated by a similar fear network in the brain that is involved in fear conditioning. They suggested that this network consists of the amygdala and its interactions with the hippocampus and medial prefrontal cortex. Physical reactions like those seen in conditioned fear responses were proposed to be mediated by the hypothalamus and brainstem sites that receive afferents from the amygdala. Bishop (2007, 2008) reviewed cognitive research into the neural substrates of anxiety based on a range of human neuroimaging studies that were mainly conducted on PTSD as well as in healthy individuals with high levels of state or trait anxiety. She concluded that the amygdala acts as a threat detector whose stereotyped and automatic action is brought under top-down control by the prefrontal cortex. In untreated anxiety, this circuit seems imbalanced, with excessive amygdala responsivity to threat not being sufficiently regulated by higher cortical areas. Thus, interactions between the amygdala and the prefrontal cortex appear to play a central role in the generation, maintenance and control of anxiety.

Pharmacological treatments used for anxiety have been shown to modulate prefrontal-amygdala circuits during threat processing. For example, selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines, which are used in the management of anxiety, reduced amygdala responses during the presentation of negative facial expressions of emotion in healthy volunteers (Del-Ben et al., 2012; Harmer et al., 2006; Murphy et al., 2009). SSRI treatment also resolved the imbalance in prefrontal cortex (PFC) – amygdala responses seen in people with social anxiety disorder during the processing of negative facial cues (Phan et al., 2013). However, comparatively little is currently known on whether successful CBT for panic disorder influences the neural processing of threat and fear.

During the past decade a number of neuroimaging studies investigated the neural correlates of psychotherapy for panic disorder. Using positron emission tomography (PET) to measure resting state brain glucose metabolism, Sakai et al. (2006) found that successful CBT was related to a modulation of glucose uptake in the hippocampus, medial prefrontal cortex and anterior cingulate cortex during rest. Unfortunately no control group was used and thus the effects of CBT cannot be differentiated from nonspecific effects.

Using fMRI, Kircher et al. (2013) reported that people with panic disorder exhibited a significantly higher activation in the left inferior frontal gyrus during aversive classical conditioning trials, which normalised after CBT. Lueken et al. (2013) reanalysed the same data set but focussed on differences between responders and nonresponders to CBT. They found that non-response to future CBT was best predicted by increased activation in the right ACC, the hippocampus and the amygdala when, within the same classical conditioning paradigm, participants were processing a stimulus that was not followed by an unpleasant burst of white noise (i.e., a safety signal). These results suggest potential effects of CBT on neural circuits engaged during threat processing in people with panic disorder. However, the conclusions which can be reached are seriously compromised by the absence of an equally symptomatic control group that would have allowed to determine the effects of repeated testing in this paradigm or the influence of nonspecific therapy effects. The relevance of the aversive conditioning paradigm to panic disorder is also questionable and clearer results may be seen with a paradigm more closely related to the nature of threat bias seen in panic disorder.

A recent fMRI study explored the neural correlates of emotional regulation during the presentation of aversive and physically threatening images in people with panic disorder compared to healthy controls (Reinecke et al., in press). Two conditions were

compared: the normal emotional experience to the stimuli versus the response when participants applied cognitive reappraisal strategies. During the normal experience of threatening pictures, people with panic disorder showed increased activation of the amygdala, dorsomedial and dorsolateral PFC. These differences were resolved when participants were reappraising the content of the images. These findings are consistent with the idea that the amygdala may be over-sensitive in people with panic disorder. But they also raise additional insights into the neural architecture of panic. Instead of showing impaired recruitment of prefrontal cortex, participants with panic disorder showed elevated responses there. This implies that they were able to engage neural circuits involved in emotion regulation but that this engagement did not resolve the amygdala hyperarousal. Reinecke & Harmer (in press) suggested that this may signify the use of unhelpful safety behaviours in attempts to control the emotional response. However, when people with panic had been taught helpful reappraisal strategies they were able to modulate the response in limbic areas, perhaps implying that PFC circuits may indeed be functioning well in people with panic once they are given effective cognitive tools.

Reinecke et al (in press) have shown that untreated people with panic disorder can make good use of effective cognitive strategies once these are provided, but until then unhelpful strategies may be applied instead. The present study aimed to expand on these results by using the same emotion regulation paradigm to assess the clinical as well as neural effects of a short course of CBT compared to a waiting list control group in people with panic disorder. The neural effects were assessed using a whole brain analysis as well as a region of interest around the amygdala, based on the results of Reinecke et al (in press).

Our primary hypothesis was that CBT would reduce engagement of the amygdala during threat processing, particularly during the maintain emotion condition. This hypothesis was based both on the effects of pharmacological interventions used in anxiety disorders (Harmer et al. 2006) as well as on evidence for overactivation of this area in panic disorder (Reinecke et al., in press). Similarly, as a secondary hypothesis, we predicted that short-term CBT would be effective in reducing overactivation of the dorsomedial and dorsolateral PFC during the maintenance of emotion. In the reappraisal condition we expected to find fewer effects of treatment given that previously no differences in neural processing was found in such a task when comparing untreated people with and without panic disorder (Reinecke et al, in press). It was also hypothesized that the brief CBT would show clinical efficacy by alleviating panic disorder symptoms in those participants randomised into the treatment group.

Materials and Methods

Study Design

The present study used a parallel trial design. Half of all participants were assigned to a CBT treatment group (TG) and half to a waiting group (WG) not receiving any interventions until after the experimental procedures.

Participant recruitment

Potential volunteers were informed about the study via advertisements (in local newspapers, radio broadcasts, on facebook.com, on dailyinfo.com, posters around town and in GP practices) In addition, patients waiting to access the Lupina Service, a group of graduate psychologist volunteers trained in delivering CBT for panic disorder based at the Warneford Hospital, Oxford, were invited to enrol in the study. Oxfordshire GPs were sent information about the study.

Interested participants were asked to complete an online screening of around 10 minutes duration. This included the Panic Disorder Severity Scale (PDSS) to assess the severity of panic symptoms as well as the Hospital Anxiety and Depression Scale (HADS). In excess of 300 people completed this. To be considered for inclusion in the study, volunteers had to be aged between 18 and 70 years, be sufficiently fluent in English to understand the task and instructions, have a PDSS score of six or higher and have experienced at least two full panic attacks or limited symptoms attacks during the preceding four weeks. Volunteers were unable to enrol in the study if they were left-handed (to minimise variability due to differences in brain lateralisation), pregnant, had contraindications to MRI (such as metal implants) or a lifetime history of epilepsy, heart or respiratory problems (to ensure participant safety), alcoholism, psychotic or bipolar

disorder (to reduce variability due to clinical complexity), substance abuse (to ensure participant safety and to reduce variability due to clinical complexity), treatment with antidepressant medication during the last 6 months (to maximise possible specificity of the treatment offered here) and having previously received CBT (since this may have masked potentially subtle effects of the very brief treatment offered here).

62 eligible volunteers were interviewed by a qualified clinical psychologist using the clinician version of the Structured Clinical Interview for DSM-IV Axis I Disorders, SCID-CV (First et al., 1996). A diagnosis of panic disorder could be established in 28 volunteers who were enrolled in the study.

Occasional use of benzodiazepine or beta-blocker medication, which was defined as prescribed to patients as pro re nata (PRN) to help with symptoms only when they felt panicky, was not an exclusion criterion but patients refrained from these drugs 48 hours before treatment and scanning sessions. Five members of the TG and two of the WG were benzodiazepine users, one member of the WG and none of the TG took beta blockers. Ethical approval was obtained from the local research ethics committee (National Research Ethics Service, Oxfordshire REC A, reference number 09/H0604/55). All participants gave written informed consent.

Collection of behavioural data took place at the Neurosciences section of the Department of Psychiatry, Warneford Hospital, Oxford and functional imaging data were acquired at the University of Oxford Centre for Clinical Magnetic Resonance Research, John Radcliffe Hospital, Oxford.

Interventions

Cognitive-Behavioural Therapy

Participants in the TG and, after the waiting period had passed, those of the WG were given individual CBT that was provided by graduate volunteer, research and trainee clinical psychologists who had been trained in Clark's protocol for brief cognitive therapy for panic disorder (Clark et al., 1999). This treatment programme has been shown to be as effective as standard CBT which would typically last between twelve and fifteen sessions (Clark et al., 1994; Gelder et al., 1993). It is based on the assumption that panic disorder develops as a consequence of neutral sensations (e.g., increased heart rate) being misperceived as threatening (e.g., having a heart attack), and safety strategies (e.g., leaving the situation, calling a friend) being developed to reduce the perceived danger. Safety behaviours are reinforced because they reduce anxiety but at the same time preclude the experience of corrective experiences (e.g., realising that they would not have died of a heart attack if they had remained in a crowded supermarket after physical symptoms began).

Therapy consisted of weekly sessions of 60 minutes' duration and was delivered over the course of four weeks. It was based on and adapted from the protocol by Clark et al. (1999). A typical session plan was as follows.

Assessment session: Presenting problems, brief personal history, therapy goals, development of a therapeutic alliance, a typical panic attack, avoidance and safety behaviours. Homework: Psychoeducation by reading a booklet on panic disorder provided by the local Oxford Cognitive Therapy Centre (OCTC) that covered the cognitive approach to panic disorder and the vicious cycle of panic (Clark, 1986).

Therapy session 1 : Collaborative development of a maintenance formulation based on the cognitive model of panic (Clark, 1986) using a typical or recent panic attack. Identification of idiosyncratic safety behaviours, avoidance strategies. Socratic dialogue on how these serve as perpetuating factors. Catastrophic beliefs about (the typically physical) symptoms of panic. Evidence for and against these beliefs. Homework: Keep panic diary with emphasis on recording catastrophic thoughts and associated belief ratings when experiencing panic symptoms.

Therapy session 2: Review of thought records. Collaborative development of idiosyncratic panic circle (maintenance formulation) using these. Discourse on catastrophic versus harmless alternative explanations for panic symptoms. Socratic dialogue aimed at understanding how avoidance and safety behaviours act as barrier to discovering whether the feared catastrophe could occur in reality or if the outcome could instead be harmless. Homework: Keep panic diary with particular emphasis on fears of symptoms and how these could be tested.

Therapy session 3: Review of panic diary and key feared symptoms. Discourse on the specific role of avoidance and safety behaviours. Derivation of how it could be tested out whether these symptoms have awful consequences or not. Introduction of the notion of guided discovery and socialisation to exposure as therapeutic mechanism. In-session provocation of (a) highly-feared symptom(s), typically by hyperventilating or vigorous aerobic exercising. Homework: Keep panic diary, seek out triggers to panic attacks (also using symptom provocation techniques), resist urge to use avoidance/safety behaviours.

Therapy session 4: Review of homework. Further practice using symptom provocation. Summary of personal development over course of therapy. Completion of a

relapse prevention/management plan, focusing on the maintenance of exposure and identification of unhelpful use of safety behaviours and avoidance.

Clinical supervision was provided by a chartered clinical psychologist and accredited cognitive-behavioural psychotherapist from the Oxford Cognitive Therapy Centre.

Outcomes

The primary outcome of this study was the neural activation patterns in response to viewing negative-affect inducing pictures whilst maintaining that affect versus managing it by cognitively reappraising the content of the pictures. It was assessed using an fMRI scan of the participants' brains. Even though this study was not aimed at verifying the efficacy of the therapeutic intervention, clinical symptoms can nevertheless serve as a useful secondary outcome

Primary outcome: fMRI measures

Participants were brain scanned after four sessions of brief CBT (TG) or after waiting the same amount of time (WG). 40 coloured images of negative valence from the International Affective Picture Series (IAPS, Lang et al., 2008) were presented in 8 blocks of 5 images, one after another, for 5s each. They depicted characteristic panic-related catastrophic expectations, such as accidents, funerals and medical procedures. IAPS picture numbers used were as follows: Block 1, 9600, 2053, 3022, 6350, 9592; Block 2, 9622, 9912, 6212, 6360, 6300; Block 3, 1300, 9800, 6838, 6560, 6940; Block 4, 6312, 9250, 1050, 9920, 2691; Block 5, 9910, 6821, 3030, 3230, 6510; Block 6, 1930, 6570, 6370, 9911, 8480; Block 7, 2100, 6550, 9921, 9001, 1201; Block 8, 6540, 2751, 2141, 2120, 6211. The normative sample in the study by Lang et al. (2008) had given mean

valence ratings for these images of 2.8 ± 1.7 and mean arousal ratings of 6.0 ± 2.2 on 9-point Likert scales ranging from 1 (unpleasant or low arousal, respectively) to 9 (pleasant or high arousal, respectively). Valence and arousal ratings as well as scene content were matched between the two experimental conditions, Maintain and Reappraisal.

The order of picture blocks remained constant across participants. Experimental conditions alternated between blocks and were pseudo-randomised so that half of the subjects per group started with a Maintain and half with a Reappraisal block. In Maintain blocks, participants were instructed to respond naturally to the images without attempting to consciously regulate or alter the emotional state they experienced. In Reappraisal blocks, they were instructed to down-regulate the provoked negative affect by using strategies of cognitive reappraisal (e.g., reframing or rationalising). These strategies had been trained before the scan. Experimental conditions were cued prior to each block by presenting the word MAINTAIN or REAPPRAISE on the screen for 4s. To evaluate effectiveness of the reappraisal task a 4-point rating scale (1= neutral, 4= negative) was presented for 4s at the end of each picture block, and participants indicated the intensity of negative affect they experienced across the past block using a keypad. Figure 1 shows a schematic sketch of a typical timeline of stimuli experienced by a participant in the brain scanner.

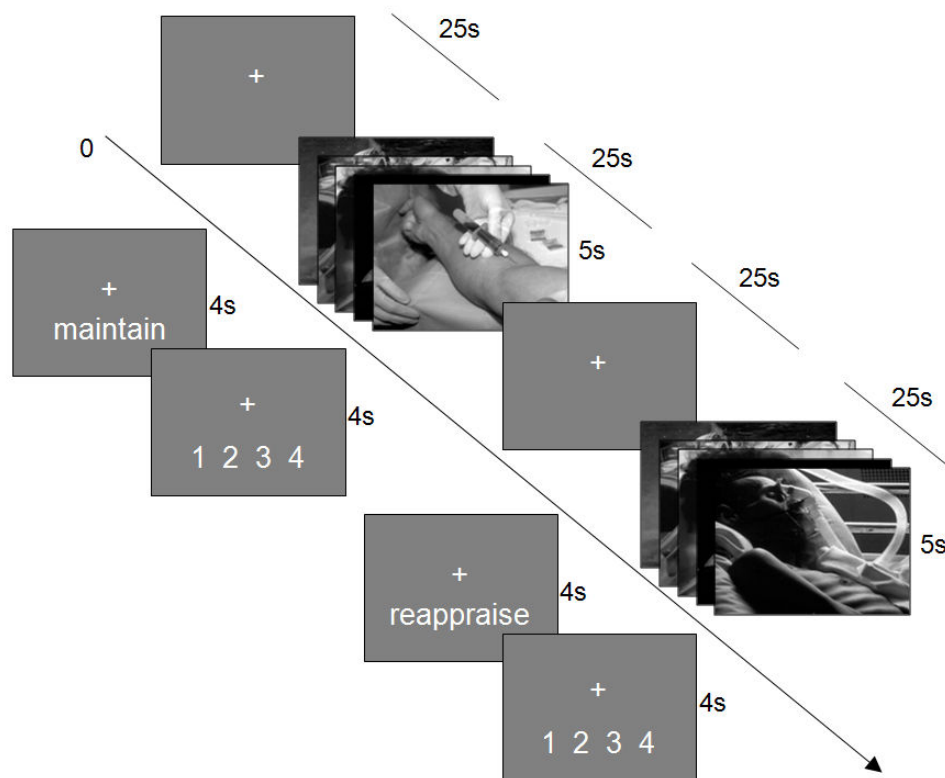


Figure 1. A sample timeline of visual stimuli. Sequences of affective pictures lasted 25s and alternated with baseline periods during which a fixation target was presented on a grey screen, also for 25s. Picture blocks consisted of successive presentations of five affective pictures and were preceded by a word cue that instructed participants whether to maintain their emotional experience or regulate it by cognitively reappraising the content of the pictures. At the end of each picture block participants rated how negative their affect had been on a scale ranging from 1 to 4. Maintain and reappraisal blocks alternated until a total of eight blocks was completed.

Prior to the fMRI scan, and using IAPS images different from those presented during the experiment, participants were trained to apply reappraisal strategies effectively. It was emphasized not to look away from the images and not to generate thoughts unrelated to the images as a means of distraction. The experimenter introduced emotion regulation strategies by presenting two sample images and modelling verbal reappraisal, such as positive reframing (e.g., interpreting the scene of a middle-aged woman in a

hospital waiting room as her waiting either to hear whether her husband could be saved or to visit her newborn grandchild) or rationalising (e.g., interpreting the tears of a child as signs of tiredness instead of grief). Participants then practised reinterpreting three images aloud. Reappraisal training took place immediately prior to the brain scans. It lasted between 5 and 10 minutes. It was separate from techniques taught in CBT in that explicit cognitive reappraisal of distressing pictorial material had not been practised by the TG during their therapy sessions. Another pre-scan practice consisted of presenting complete example Maintain and Reappraisal blocks together with fixation baselines and valence rating tasks until participants were familiar with the task and had no more questions.

MR Image Acquisition

Images were obtained using a 3T Siemens Sonata MRI scanner. T2*-weighted functional data were acquired for a whole-brain field-of-view (64x64x40 matrix), with a voxel resolution of 3mm³, repetition time (TR) of 3.0s, echo time (TE) of 30ms and a flip angle of 90 degrees. Field maps were acquired using a dual echo 2D gradient echo sequence with echoes at 5.19ms and 7.65ms, respectively, and a repetition time of 500ms. High-resolution T1-weighted structural MR images were acquired for subject alignment using an MPRAGE sequence with the following parameters with a 174x192x192 matrix, a voxel resolution of 1mm³, a TR of 2.04s, a TE of 4.7ms and an inversion time (TI) of 900ms.

Secondary outcome: Clinical scores

At baseline as well as after four sessions of brief CBT (TG) or waiting (WG), participants completed the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), the Body Sensations Questionnaire (BSQ; (Chambless, Craig, Bright, & Gallagher, 1984)

and the Agoraphobic Cognitions Questionnaire (ACQ; Chambless et al., 1984). The HADS has 14 items, is quick to complete, frequently used in clinical research and has good reliability (Crawford, Henry, Crombie, & Taylor, 2001). Both the BSQ and the ACQ are detailed screening checklists of typical physical symptoms and cognitive biases experienced in panic disorder. They have been reported to have good validity and reliability and have frequently been used in clinical trials of treatments for panic disorder (Chambless et al., 1984; D M Clark et al., 1999; Ehlers et al., 2003).

Sample size

Because significance testing in functional MRI does not involve a single outcome variable but three-dimensional brain activation maps, sample size calculations based on expected effect sizes pose substantial statistical problems (Hayasaka et al., 2007). When the study was designed no statistically validated method of determining the sample size existed. Therefore the following rationale was applied. Functional imaging work by the same group had shown that antidepressant medication can alter the neural response signatures associated with cognitive processing of threat (Harmer et al., 2006). There twelve participants in either of two experimental groups was sufficient to produce reliable fMRI signal change in the amygdala. Antidepressant medication not only reduces amygdala response to threat but is also used to treat panic disorder. We therefore anticipated that CBT may have a similar effect, justifying a similar sample size. To allow for greater variability of the mechanisms of action of a talking treatment we decided to test a total sample of 28 participants.

Randomisation, matching and blinding

Participants enrolled in the study were numbered consecutively (1, 2, 3, etc). Before the start of the study they were randomly allocated to the groups in blocks of four such that, e.g., of participants 1-4 two would be allocated to the TG and two to the WG. Whenever too many participants of one gender accumulated in one group compared to the other, a participant would automatically be swapped to the opposite group, ensuring groups were matched for gender. Randomisation, allocation and implementation were carried out by a senior postdoctoral research assistant. No mechanisms were employed to blind participants as they would of course always know whether they had waited or received therapy. fMRI pre-processing occurred without knowledge of participant group membership. Further data analysis employed coded participant numbers with no link to individual identifiers.

Statistical methods

Analysis of fMRI data

Pre-processing

Functional MRI scans require a degree of pre-processing to maximise signal-to-noise and to ensure correct anatomical alignment of activation signals with actual brain tissue. Over the duration of a scan participants move their head slightly. To account for this a motion correction was applied (Jenkinson et al., 2002) in which images were spatially realigned. In a next step any image voxels that did not consist of brain tissue (e.g. the skull) were removed from the images (Smith, 2002). Spatial smoothing reduces local noise and increases statistical power. This was done using a Gaussian kernel of 5.0mm full width at half maximum. Subsequently the entire 4-dimensional dataset was normalised for its

overall intensity values. Activation data were then co-registered onto the anatomical template of the Montreal Neurological Institute (MNI) standard brain template 152 (Brett, Johnsrude, & Owen, 2002). For technical reasons the spatial distribution of the magnetic fields inside a brain scanner is not homogenous. Further, MRI signal varies over time, again due to the physical properties of an MRI scanner. Slow signal drifts arising from this were reduced using high pass temporal filtering (by Gaussian-weighted least-squares straight line fitting with a standard deviation of 50.0s). Spatial field inhomogeneities were accounted for using the field map correction function

Image Analysis

Functional imaging data consist not of a single data point per measurement but of a three-dimensional array of BOLD signal contrast values in a time series of numerous measurements per second across experimental conditions. A standard way of analysing such data is to model the experimental procedure an individual participant experienced over the time he or she spent in the scanner. Software packages generate a hypothesised time course of brain activation signal change depending on the experimental design. This expected time series is then fitted to individual data to determine whether and where in the brain significant activation differences across experimental conditions and other covariates of interest are seen.

In contrast to behavioural research paradigms, fMRI data analysis is performed using mass-univariate approaches. Statistical inferences are made at the level of voxels or clusters of voxels and involve separate independent statistical tests. Such extensive inferential statistical testing comes at the expense of type-I-error inflation and requires control. One way to do so is to apply cluster-extent based thresholding (Woo, Krishnan, & Wager, 2014). This method detects statistically significant clusters on the basis of the

number of contiguous voxels whose voxel-wise inferential statistic values lie above a pre-determined primary threshold. In contrast to voxel-wise approaches, such as Bonferroni correction, cluster-based approaches have comparatively higher sensitivity and do not make the a-priori assumption that adjacent voxels are independent from one another. Since, by virtue of their spatial proximity, they are in fact autocorrelated, assuming independence would over-correct for type-I-error inflation and reduce statistical power more than needed.

Functional imaging data were analysed using the FEAT toolbox of the FMRIB Software Library 6.0. (Jenkinson et al., 2012). In this software, a primary cluster detection threshold of $Z=2.3$ is the default setting and is frequently used as a standard in fMRI research (Woo et al., 2014). Z-statistic brain activation maps were thus thresholded at 2.3, equating to a threshold of $p < .05$.

Event-Related Analysis

. At the first level, data were analysed using a general linear model approach with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Two regressors of interest (Maintain and Reappraisal) and two regressors of no interest (instruction periods and rating periods) were included. Fixation blocks, presented between picture blocks, served as baseline reference. Contrast images were calculated for picture blocks in general, Maintain blocks, Reappraisal blocks, Maintain versus Reappraisal, and Reappraisal versus Maintain. These individual activation maps were then analysed at group level (TG, WG), using a mixed-effects analysis across the whole brain (Beckmann et al., 2003).

Region of Interest Analysis

Recently Reinecke et al. (in press) identified the amygdala as hyperactive in incidental (Maintain) versus volitional (Reappraisal) emotion regulation in panic disorder.

Based on these results a region of interest (ROI) analysis was computed. The ROIs were defined by spherical masks with a radius of 10mm that were centred around the peak voxel of a left amygdala region (MNI coordinates -14, -6, -8) as well as its right-hemisphere counterpart.

Significant whole-brain or ROI interactions were explored by extracting percent blood oxygenation level-dependent (BOLD) signal changes within these areas and entering them into Group (TG, WG) x Task (Maintain, Reappraisal) split-plot ANOVAs with t-tests for follow-up where appropriate.

Analysis of clinical scores

Questionnaire composite scores for each participant were entered into separate Group x Time split-plot ANOVAs for each measure. Significant interactions or main effects were followed up by way of post-hoc comparisons using paired or independent t-tests as appropriate.

Analysis of efficacy of reappraisal training

Participants' ratings of negative affect experienced when viewing the affective pictures were analysed in a Group (TG, WG) x Task (Maintain, Reappraisal) split-plot ANOVA.

Results

Baseline status

Table 1 shows the demographic composition of both samples. Independent samples t- or X^2 -tests showed that TG and WG did not differ from each other (all $p \geq .48$).

Participants completed the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), the Body Sensations Questionnaire (BSQ; Chambless et al., 1984) and the Agoraphobic Cognitions Questionnaire (ACQ; Chambless et al., 1984).

Table 1. Demographic and clinical composition of the experimental groups at baseline (mean \pm SEM; p-values from independent samples t- or X^2 -tests; NART, National Adult Reading Test; PDA, panic disorder with agoraphobia; PD, panic disorder without agoraphobia; SP, social phobia; SPP, specific phobia).

	<i>Treatment Group</i>	<i>Waiting Group</i>	<i>p</i>
Age	34.8 \pm 3.9	37.2 \pm 3.0	.63
Gender	8 female/ 6 male	10 female/ 4 male	.70
Years of education	15.2 \pm 0.7	15.8 \pm 0.7	.56
Verbal IQ (NART)	118.0 \pm 1.3	116.6 \pm 1.5	.48
Primary diagnosis	10 PDA/ 4 PD	8 PDA/ 6 PD	.70
Comorbid diagnoses	2 SP/ 2 SPP	1 SP/ 3 SPP	.77

Table 2 contains the clinical symptom measures taken and shows that these did not differ between the groups at baseline (all $p \geq .51$). On the HADS, both groups scored within the ‘moderate’ range for anxiety and within the ‘mild’ range for depression (Zigmond & Snaith, 1994). Scores for both the BSQ and the ACQ exceeded those of a normative clinical population (Bibb, 1988).

Table 2. Clinical symptom severity of the experimental groups at baseline (mean \pm SEM; p-values from independent samples t-tests; HADS, Hospital Anxiety and Depression Scale; BSQ, Body Sensations Questionnaire; ACQ, Agoraphobic Cognitions Questionnaire)

	<i>Treatment Group</i>	<i>Waiting Group</i>	<i>p</i>
HADS - anxiety	14.4 \pm 1.1	13.4 \pm 1.0	.51
HADS - depression	8.4 \pm 1.2	9.1 \pm 1.0	.62
BSQ	3.4 \pm 0.1	3.4 \pm 0.2	.75

ACQ	2.5 ± 0.2	2.3 ± 0.2	.54
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Clinical Scores: effects of intervention

Group x Time split-plot ANOVAs revealed significant interactions for all clinical scores (HADS –anxiety: $F = 212.16$, $df = 1,26$, $p < .001$; HADS –depression: $F = 95.16$, $df = 1,26$, $p < .001$; ACQ: $F = 3.77$, $df = 1,26$, $p < .001$; BSQ: $F = 8.73$, $df = 1,26$, $p < .001$). These interactions were further explored using follow-up t-tests. As above, at baseline no differences existed between groups (all $p > .51$, see Table 2). Table 3 shows that over the four-week course of CBT there was a significant reduction of anxiety and depression (HADS), fear of physical sensations (BSQ), and agoraphobic cognitions (ACQ) in TG (paired-samples t-tests, all $p \leq .001$) but not in WG (paired-samples t-tests, all $p > .3$). After CBT, or the according wait, TG had significantly reduced clinical symptom scores when compared to WG using independent t-tests (all $p < .001$). After therapy, both TG HADS scores had reduced to within the normal range (Zigmond & Snaith, 1994) and those of the BSQ and ACQ were at, or slightly below, the mean levels of a normative non-clinical community sample (Bibb, 1988).

Table 3. Clinical symptom severity of the experimental groups at baseline and after treatment or after a four-week waiting period (mean ± SEM; p-values in normal typeface from paired t-tests, comparing clinical scores pre- vs. post CBT or wait; p-values in bold typeface from independent samples t-tests, comparing groups after CBT or wait; HADS, Hospital Anxiety and Depression Scale; BSQ, Body Sensations Questionnaire; ACQ, Agoraphobic Cognitions Questionnaire).

	<i>Treatment Group</i>			<i>Waiting Group</i>			<i>p</i>
	<i>Baseline</i>	<i>After CBT</i>	<i>p</i>	<i>Baseline</i>	<i>After wait</i>	<i>p</i>	
HADS - anxiety	14.4 ± 1.1	6.1 ± 1.1	<.001	13.4 ± 1.0	12.9 ± 0.9	.47	<.001

HADS - depression	8.4 ± 1.2	2.6 ± 0.7	<.001	9.1 ± 1.0	8.6 ± 1.0	.36	<.001
BSQ	3.4 ± 0.1	1.8 ± 0.2	<.001	3.4 ± 0.2	3.3 ± 0.2	.61	<.001
ACQ	2.5 ± 0.2	1.5 ± 0.1	.001	2.3 ± 0.2	2.4 ± 0.2	.72	<.001

Efficacy of reappraisal task

Due to technical difficulties negative affect ratings could not be obtained in two of the 14 TG participants. In the TG, mean (\pm SEM) negative affect ratings when viewing IAPS pictures were 2.68 (0.25) when maintaining affect and 1.60 (0.24) during reappraisal. Corresponding values for the WG were 2.56 (0.25) in maintain and 1.85 (0.20) when reappraising. ANOVA detected no interaction between group and task ($F < 1$, $df = 1, 24$, n.s.), nor were groups found to differ from one another ($F < 1$, $df = 1; 24$, n.s.). However, a main effect of task was found, showing a highly significant reduction of negative affect when reappraising the pictorial content ($F = 16.1$; $df = 1; 24$, $p < .001$).

Whole-Brain Analysis

Main effect of task (Reappraisal versus Maintain, across both groups combined). In line with previous work (Reinecke et al., in press), reappraising the threat associated with the IAPS stimuli was associated with increased activation in bilateral areas of dorsal ACC, dorsomedial PFC, dorsolateral PFC, ventrolateral PFC, orbitofrontal cortex, and insula (18201 voxels, MNI coordinates -4, 24, 44, $Z = 5.15$), bilateral cerebellum extending into occipital fusiform gyrus (left: 406 voxels, MNI coordinates -54, -60, -32, $Z = 3.39$; right: 1557 voxels, MNI coordinates 32, -62, -52, $Z = 4.53$), and bilateral angular gyrus (left: 355 voxels, MNI coordinates -48, -40, 30, $Z = 3.86$; right: 507 voxels, MNI coordinates 54, -48, 48, $Z = 4.07$).

Main effect of group (picture blocks versus baseline). Compared to WG, TG showed significantly reduced activation in bilateral dorsomedial PFC and left dorsolateral PFC during the eight picture blocks versus the fixation screen baseline (540 voxels, MNI coordinates -2, 36, 60, $Z=4.59$; main sub-regions within this cluster: MNI coordinates -36, 38, 42, $Z=3.52$, MNI coordinates 2, 46, 50, $Z=3.46$) (Figure 2).



Figure 2. Main effect of Group: Compared to the waiting list group (WG), participants in the treatment group (TG) showed significantly reduced activation in left and right dorsomedial PFC and left dorsolateral PFC during picture blocks (versus fixation baseline blocks). Error bars show SEM.

Group x task interaction (Maintain versus Reappraisal). Figure 3 depicts a significant Group x Task interaction in the left middle and superior temporal gyrus cluster (356 voxels, MNI coordinates -58, -4, -10, $Z=4.53$). Post-hoc analyses on BOLD signal change extracted from this cluster indicated that this interaction was driven by inverse differences in activation across groups during Maintain and Reappraisal Blocks (ANOVA Task x Group $F = 39.40$, $df = 1,26$, $p < .001$), with TG showing significantly reduced

activation compared to WG in Maintain blocks ($t = 3.24$, $df = 26$, $p = .003$) and relatively increased activation in Reappraisal blocks ($t = 2.42$, $df = 26$, $p < .05$).

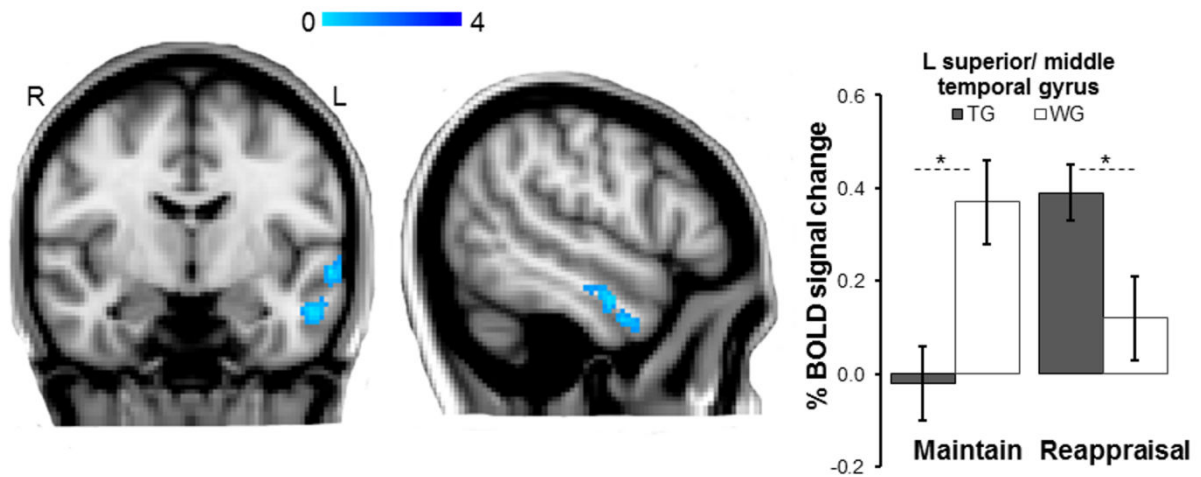


Figure 3. Group x Task interaction: Maintaining negative affect (versus reappraisal) was associated with attenuated signal response in treated compared to untreated participants in the left superior-middle temporal gyrus. Images thresholded at $Z > 2.3$, $p < 0.05$, corrected. Error bars show SEM.

Amygdala Region of Interest Analysis

A hemisphere x Group x Task ANOVA on BOLD percent signal change extracted for the left (Maintain: TG $.06 \pm .34$, WG $.37 \pm .46$; Reappraisal: TG $.28 \pm .28$, WG $.15 \pm .31$) and right amygdala (Maintain: TG $.03 \pm .36$, WG $.33 \pm .58$; Reappraisal: TG $.27 \pm .53$, WG $.12 \pm .25$) spheres showed no significant laterality effect. Pooled across hemispheres a significant Group x Task interaction was found ($F = 6.45$, $df = 1,26$, $p < 0.05$). As Figure 4 demonstrates, this effect was driven by TG showing reduced activation compared to WG in Maintain blocks ($p < 0.05$), but not in Reappraisal blocks ($p = .29$).

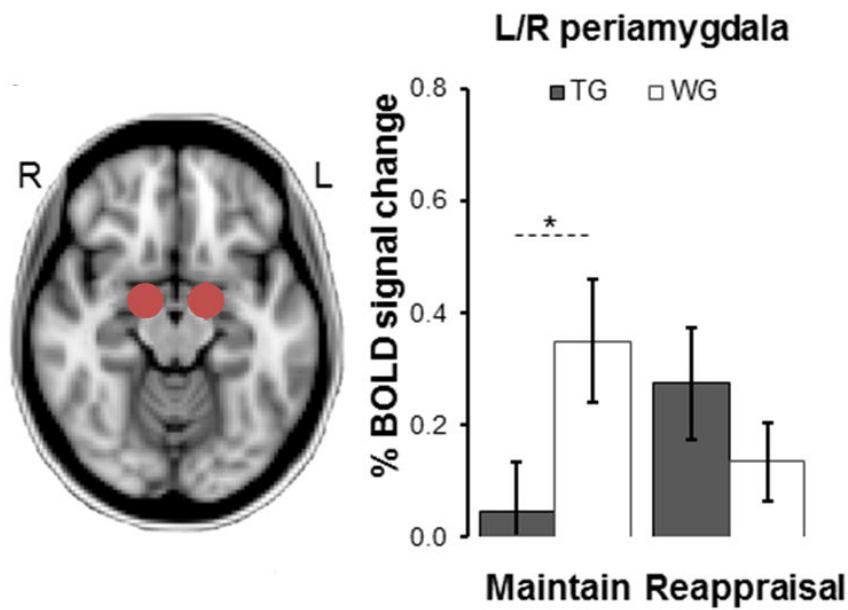


Figure 4. Region of interest analysis in left and right amygdala regions of interest: Participants showed reduced bilateral amygdala activation during Maintain blocks when they had completed treatment (TG) but not when they had been on the waiting list (WG). Error bars show SEM.

Discussion

In this study four sessions of CBT were highly effective and led to significant improvements in panic severity, anxiety and mood compared to the waiting list control group. Emotion regulation was associated with increased engagement of prefrontal cortex. Participants receiving CBT showed reduced amygdala response during normal emotional viewing of aversive pictures as well as reduced responses in the dorsolateral and dorsomedial PFC during aversive picture presentation. These results support the view that aberrant neural processing of threat in panic disorder may have been normalised following CBT.

A Brief CBT Programme

Clinical guidelines recommend that the optimal duration of CBT for panic disorder should range from seven to twelve hours (NICE, 2011). The present study used a relatively brief programme of four sessions of CBT, which was also shown to be highly effective, in line with our hypothesis as well as affirming the results of Clark et al. (1999). Recent work suggests that even a single session of CBT can reduce symptoms measured after four weeks – although not immediately after therapy (Reinecke et al., 2013). These findings suggest that the effects of CBT develop over time and it is possible that when the right treatment paradigms are deployed maximal clinical efficacy may be achieved with a much lower frequency and intensity of interventions than previously thought. It would therefore be interesting to carry out a longer term follow up with the participants treated here to see whether the therapy benefits seen after four weeks may have endured or possibly even increased over time.

The Neural Effects of CBT

The amygdala and dorsomedial PFC. The amygdala plays a central role in the detection and response to threat and is believed to be involved in the pathophysiology of a number of different anxiety disorders (Bishop, 2007, 2008; LeDoux, 1999; Rolls, 2007). Previous work in panic disorder supports the hypothesis that the amygdala is hyper-responsive during threat processing compared to healthy controls (Reinecke et al., in press). These effects are consistent with increased sensitivity to benign threat cues in the disorder. The current study further suggests, in line with our primary hypothesis, that amygdala hyper-arousal is normalised following a brief course of CBT compared to a matched sample of participants in a waiting list condition. This effect is similar to that seen with pharmacological treatment used for anxiety disorders suggesting a potential overlap in the neural mechanisms of action (Harmer et al., 2011). It is also consistent with behavioural evidence for an early reduction in vigilance to threat seen after only a single session of CBT (Andrea Reinecke et al., 2013). Attentional bias to threat is believed to rely on amygdala based circuits and in this study, reduced vigilance to threat was predictive of later improvements in symptoms of panic and agoraphobia. Therefore it is possible that changes in the processing of threat might be an important mechanism underlying therapeutic gains.

The dorsomedial PFC has efferent connections to the amygdala: Robinson et al. (2012) suggested that threat relevant biases are amplified via this excitatory projection and that it may drive and amplify amygdala responses to threat. Dorsomedial PFC activity and its connectivity with the amygdala is increased in anxiety and during the anticipation of aversive shocks (Robinson et al., 2012). Previously Reinecke et al. (in press) also found increased response in the dorsomedial PFC in panic disorder compared to controls. The

present findings suggest, in partial support of our hypothesis, that the activity of this amplification circuit is reduced following a brief course of CBT. Together with the effects in the amygdala, these results support the hypothesis that CBT reduces an otherwise enhanced threat related responsivity in neural circuits known to play a role in the automatic detection of and response to danger cues. However, contrary to our hypothesis this was a general effect seen across threat picture presentation and was not restricted to the maintain emotion condition. This suggests that CBT can potentially increase the effects over and above re-appraisal training focused on this task.

Dorsolateral PFC. Anxiety has been associated with deficient engagement of prefrontal cortex during the regulation of aversive cues. A number of theoretical papers have suggested that anxiety disorders occur when the PFC-amygdala circuit fails to operate successfully and the amygdala response to danger is left unattenuated (for reviews, see Bishop, 2007, 2008). This would be expected to lead to an over-response to danger cues, even when these cues were harmless, ambiguous or irrelevant.

In a previous study on panic disorder it was found, however, that parts of this regulatory network, including the dorsolateral PFC, were engaged during viewing of threat, but that this was not sufficient to reduce amygdala responses (Reinecke et al., in press). Such a pattern could have occurred for a number of reasons. Firstly, enhanced engagement of PFC may be seen in panic disorder compared to healthy controls if a stimulus is not threatening enough to engage this circuitry in the healthy control group, i.e., if the threat does not appear to require regulation in this group but does so in the anxious group. Secondly, an enhanced prefrontal response may relate to the increased use of unhelpful safety strategies in people with panic disorder, which the healthy control group does not need to deploy: Hofmann et al. (2012) suggested that PFC activation was a correlate of

(maladaptive) cognitive avoidance of triggers that had raised limbic activation. A third view could be that, whilst the PFC shows increased activation in people with panic disorder, its connectivity with the amygdala may function insufficiently, thus functionally uncoupling the two.

The present results suggest that effective CBT reduces the elevations in dorsolateral PFC activation in people with panic disorder, again in partial support of our hypothesis. This implies that the circuit is not ‘broken’ but can be used effectively if appropriate treatment is given. This is in line with findings that CBT can reduce activity of dorsolateral (Paquette et al., 2003; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006) and ventromedial (Klumpp, Fitzgerald, & Phan, 2013; Månsson et al., 2013) PFC during processing of threat. The recent observation by Reinecke et al. (in press) that these responses can also be normalised by simply providing a single helpful reappraisal strategy during threat processing is in line with this interpretation. The high degree of efficacy of CBT in panic disorder is consistent with the observations that cognitive regulation strategies and learning about threat can be very helpful. As such, we may need to further understand the neural basis of this disorder; whether it is different from other anxiety disorders and how we may be able to capitalise on these effects. Again these effects were seen across maintain and re-appraisal blocks of aversive picture stimuli suggesting that CBT can still affect the processing of threat processing over and above the use of re-appraisal strategies.

Normal viewing versus emotional regulation. The difference in amygdala response during aversive picture presentation following CBT was only seen when participants were instructed to look at the pictures as they would naturally and were absent when they used reappraisal strategies that reduced their threatening nature. We also

observed a specific effect of CBT during maintain vs. reappraise conditions in the superior and middle temporal gyrus, potentially part of the extended limbic response to threatening cues (Leitman et al., 2008; Miyahara, Harada, Ruffman, Sadato, & Iidaka, 2013). This observation was outside our key hypotheses but may lend further support to the argument that people experiencing panic disorder can regulate limbic responses to threat when they have been given helpful reappraisal skills but are much less able to do so when their threat processing continues as normal. CBT may thus allow recipients to use more helpful strategies even under the ‘normal’ viewing condition.

By contrast, the effects in the dorsomedial and dorsolateral PFC were seen irrespective of viewing condition (i.e., whilst maintaining affect as well as when reappraising) suggesting more elaborate effects of therapy which go beyond the use of brief reappraisal strategies. These results may suggest reduced representation of threat value following therapy and perhaps reduced application of unhelpful safety behaviours during threat processing. Again, these effects suggest that neural mechanisms of threat processing in panic disorder can be modulated by a psychological intervention. While some of these effects resemble the changes seen with pharmacotherapy, there are potential differences in the response of PFC circuits. In particular, SSRI treatment increased the response of the PFC during the processing of negative facial expressions in people with social phobia (Phan et al., 2013). It is of course difficult to compare results across studies, anxiety disorders and paradigms, but if replicated in a within-subjects randomised study, it may be an interesting difference, perhaps allowing better stratification of those in need or treatment combination in the future.

Limitations

Since the control group in the present study was untreated, we cannot with certainty attribute the changes seen to the CBT per se that was offered to the treatment group. Nonspecific factors, such as spending time with a therapist, getting a professional's attention or simply making a committed effort to try and work on one's problem may have contributed to the clinical improvement seen in the treatment group, rather than the CBT itself. To account for such nonspecific factors and be able to relate clinical improvements to a specific intervention or, better, specific, 'active ingredients' of the intervention, a suitable 'sham' or control treatment would have needed to be offered.

Another limitation concerns the maintain versus reappraisal task used here. Although reappraisal of distressing pictorial content was not practised explicitly in the treatment group's CBT, changing how one thinks about triggers to distress is a core component of CBT. Thus the task that served as a cognitive probe in the brain scanner and the experimental treatment using CBT are potentially confounded. To identify such a possible confound the study design would ideally have included an additional control task less correlated with one of the group's treatments. That said, however, the results may alleviate this concern somewhat because only a main effect of task, across both groups of participants, was obtained.

Within the cognitive-behavioural framework panic, like other anxiety disorders, is conceptualised as arising from and being maintained by unhelpful, perhaps aberrant, cognitive processes (Clark, 1986). A debate exists whether functional neuroimaging has much value in helping us understand how cognitive processes operate. Some have claimed that functional localisation adds insufficiently to cognitive theory and our understanding of how the mind, whether functioning healthily or pathologically, operates (see, e.g. Coltheart,

2013). Others, however, have argued that functional neuroimaging does possess value within cognitive psychology and that it can add unique and important information to inform cognitive theories (Mather, Cacioppo, & Kanwisher, 2013). In a recent opinion paper Holmes et al. (2014) make a strong case for neuroscience within mental health science. They argue that neuroscience adds value, firstly, by improving our understanding of the mechanisms of how existing psychological interventions work, secondly by beginning to have the potential to optimize psychological treatments and, in the near future, perhaps even generating new interventions in which psychological therapy may even be combined with optogenetic methods to therapeutically interfere with the way the brain would operate otherwise. Whilst the jury between these viewpoints is still out there consensus is growing that neurobiological measures should not only inform our understanding of mental disorders but that they should even become part of a new way of classifying them: In 2008 the United States National Institute of Mental Health made such research a strategic priority (Casey et al., 2013).

Future Directions

The current study suggests that CBT exerts effects on the neural response to threat in people with panic disorder even after a brief period of application. Future studies should assess whether these effects can be replicated in a study using an active control condition which controls for nonspecific therapy effects. It would also be important to compare the effects of CBT to other interventions such as SSRIs to pinpoint potential for overlap or joint mechanisms of action. Recently interest has arisen in using pharmacological strategies to amplify the effects of CBT by enhancing the neural mechanisms of learning (Bontempo et al., 2012; Norberg et al., 2008). Neuroimaging markers may help improve the specificity of such combination treatments. Ultimately we may have to accept that not

everyone who suffers from panic disorder benefits from CBT. Studies like the present one may one day result in a method that helps to better predict what treatment is likely to work best for whom. Such information may then allow us to maximise clinical efficacy by matching those who are most likely to respond to a particular intervention to it and offer suitable alternatives to those who have been empirically shown to reap more benefits from those. This would not only be desirable from a treatment planning viewpoint but also help to deploy research funding where it is most at need, in particular to aid the discovery and further refinement of treatment strategies for those who can currently not benefit sufficiently from extant and mainstream treatment provision.

Conclusions

Brief CBT for panic disorder was highly effective when compared to a wait list control group and may be a cost effective alternative to standard interventions. CBT showed key effects on the neural response to threat in people with panic disorder including modulation of the amygdala in response to threat cues. The pattern of results suggests that prefrontal cortical circuits may be intact in people with panic disorder and that they can be used effectively when helpful cognitive strategies are trained. Without treatment these circuits may operate in a dysfunctional manner in panic disorder, reinforcing maladaptive safety strategies which prevent learning in the long term. Further studies are needed to compare and contrast the effects of CBT with other interventions and assess how we may be able to use these results to guide the application of successful therapy in the future.

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CHAPTER 3

Public Dissemination Document

Introduction

Anxiety disorders, such as extreme shyness or an extreme fear of suffering a panic attack, are very frequent and present a heavy burden not only on the sufferers but also on society (Baxter, Scott, Vos, & Whiteford, 2013; Kessler et al., 2006; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Rapaport, Clary, Fayyad, & Endicott, 2005; Whiteford et al., 2013). Traditionally anxiety disorders would be treated by medication but side effects are strong and a large number of patients tend to relapse. In recent years effective psychotherapeutic interventions have been developed. Cognitive behavioural therapy (CBT) for anxiety is now recommended as an effective alternative to medication (NICE, 2005a, 2005b, 2011, 2013). Nevertheless a significant number of patients respond insufficiently to therapy and relapse rates remain high after CBT too (Barlow, Allen, & Choate, 2004; Cuijpers et al., 2013; Durham et al., 2005; Roth, Fonagy, Parry, Target, & Woods, 2006).

An important aspect of CBT is to teach patients to change the way they interpret situations that could be perceived as threatening. Specific brain mechanisms have evolved to enable us to detect, and respond to, danger and threat cues in our environment (Bishop, 2007, 2008). If we were to better understand how CBT works at a brain level we may be able to allow us to modify components of therapy to make it even more effective. Recent decades have seen a surge in brain research techniques. An excellent way of studying the human brain is a brain scanning method called functional magnetic resonance imaging (fMRI; Raichle, 2009). Because it allows to identify which areas in the brain are involved when subjects are carrying out a specific task it is very suitable to study how the brain's processing of threat cues changes as a function of CBT for anxiety.

Literature Review

Chapter I of this thesis reviews the scientific literature on the neural mechanisms of CBT. Specifically it identified thirteen scientific studies that used fMRI to determine how the brain's processing of threat changes after patients had received CBT for anxiety disorders. The majority of reports studied this questions in patients suffering from spider phobia. Three reports used patients with social phobia and two reports each studied panic disorder and posttraumatic stress disorder, respectively.

All studies found that CBT was very effective in reducing patients' symptoms of anxiety. They were also consistent in identifying that the brain's threat processing network exhibits changes as a consequence of successful therapy. However, only little concordance existed across studies about which specific areas within this network are influenced by CBT. When studies reached agreement on some brain areas there was typically little consistency regarding the direction of the neural changes, i.e. whether a specific brain area was more or less active after CBT.

It is encouraging that the studies identified the threat network as a target of therapy, since that is where CBT would most plausibly be expected to act. However, the principal conclusion of the review is that most studies suffered from significant methodological shortcomings to render their results difficult to integrate cohesively. It is early days and using neuroscientific principles in psychotherapy research is an evolving and promising field of research.

Empirical Paper

Chapter II of this thesis presents a brain imaging experiment carried out at the University of Oxford. 28 volunteers with a fear of panic attacks were randomly split into

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two halves. One received a five session course of CBT for panic disorder, after which they had an fMRI scan of their brains while they were presented with aversive and threatening pictures. The other half had no therapy initially and waited for four weeks until they had a brain scan using identical pictures. For ethical reasons the untreated group received equivalent CBT after their waiting period. During brain imaging the participants carried out two different tasks: for half of the time they suppressed their emotional reactions using mental strategies, whereas for the other half they maintained their emotional response by viewing the pictures as they would without applying any mental strategies to reinterpret their content or context.

As expected, the volunteers who had completed their treatment experienced less anxiety than the control participants. Their brains showed reduced activation of areas involved in processing threat, particularly when they tried to maintain the emotional state elicited by viewing aversive pictures.

These findings confirm the previously reported observation that a brief course of CBT can be a very effective intervention for panic disorder (Clark et al., 1999). It may be a more cost effective alternative to the standard recommendation of twelve to sixteen sessions of therapy (NICE, 2011). Successful symptom reduction by CBT appears to be related to lowered responsivity of brain areas involved in the detection and processing of threat-related information and in the creation and maintenance of fear. These findings may help with the future refinement of CBT for panic disorder, such as by supplementing a talking therapy with pharmacological agents that enhance patients' ability to learn skills they encounter in therapy (Bontempo, Panza, & Bloch, 2012)

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Appendix 1

Instructions to Authors from Behavioural Brain Research

Source: <http://www.elsevier.com/journals/behavioural-brain-research/0166-4328/guide-for-authors> (accessed on 06/07/2014)

Appendix 2

Author's own contributions to the research chapter

This study was conceived and presented in a grant and ethics application by a senior postdoctoral researcher prior to my involvement with the research group. The data acquisition, analysis and interpretation parts of the study were going to be offered as a research project for a clinical psychology trainee. I was involved in the design and implementation of the functional imaging methods and carried out CBT in more than two third (19) of all study participants for a total of 95 clinical hours. The remainder of participants was offered CBT by team research psychologists and volunteer psychologists within the Lupina service, Warneford Hospital, Oxford. Clinical supervision was provided by a consultant clinical psychologist of the Oxford Cognitive Therapy Centre. I analysed the behavioural, clinical and functional neuroimaging data. I independently interpreted the results and authored the thesis chapter. Research supervision was provided by a senior postdoctoral research assistant.

Appendices

4

Appendix 4

Participant recruitment: advertising texts

NEWSPAPERS AND ONLINE FORUMS



UNIVERSITY OF OXFORD
DEPARTMENT OF PSYCHIATRY

TERRIFIED OR PANICKY?

Are you terrified of a pounding heart, chest pain, breathlessness, dizziness – and your GP does not have a medical explanation? Have you ever experienced these symptoms or had a **Panic Attack**? Participants are needed for a study investigating how anxiety can influence the processing of emotional information. Please complete a first screening questionnaire on:

<https://weblearn.ox.ac.uk/site/users/psyc0395/panic4/quest/>

We will contact you afterwards for an appointment.

REC 09/H0604/55

FACEBOOK

TERRIFIED OR PANICKY?

Panic attacks? Participate in Oxford University study. Time and travel costs reimbursed.

<https://weblearn.ox.ac.uk/site/users/psyc0395/panic4/quest/>

REC 09/H0604/55

Appendix 5

Participant information sheet



UNIVERSITY OF OXFORD
DEPARTMENT OF PSYCHIATRY

WARNEFORD HOSPITAL
OXFORD
OX3 7JX

PARTICIPANT INFORMATION SHEET
Neural effects of CBT in panic disorder

REC 09/H0604/55
Version 2: 29/04/2009

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take a moment to read the following information carefully and discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part. Thank you for reading this.

PART 1: ABOUT THIS STUDY AND PARTICIPATION

What is the purpose of this study?

We are interested in how cognitive-behavioural therapy (CBT) affects emotional information processing in people who experience panic attacks. In particular, we would like to measure the activity of your brain while you are reacting to different types of emotional information. We would like to test two groups of people with panic attacks: one who receives CBT between our two test sessions, and one who receives CBT after the second test session.

In the study, we will use Functional Magnetic Resonance Imaging (fMRI). This technique identifies changes in blood flow in different parts of the brain that are active when people perform simple cognitive tasks. fMRI uses the same methods that are used for MRI brain scanning and provides detailed pictures of the brain. Both methods use strong magnetic fields for imaging. Specifically, we are interested in whether experience with panic affects the way in which the brain processes emotional information (such as positive and negative words). Improved knowledge of these psychological processes will help contribute to the improvement of treatment for people who experience distressing panic attacks and anxiety disorders.

Why have I been chosen?

We would like 30 people to take part who have experienced panicky symptoms and/ or panic attacks.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given (or can print) this information sheet to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

The first part of the study involves completing an online questionnaire (<https://weblearn.ox.ac.uk/site/users/psyc0395/panic4/quest/>) that asks about your current and previous experiences of panic. We estimate that this will take about 10 minutes to complete. Only people whose questionnaire scores match the study criteria will then be invited to participate in the next part of the study.

This second part will involve two visits within 4 weeks and a CBT treatment course. The CBT treatment will consist of a brief "taster CBT course". This course will involve a total of 4 CBT sessions of 1 to 2 hrs each over the 4 following weeks. These sessions will take place at the Warneford hospital site and will be offered by the Lupina Service, which forms part of the OBMH primary care Counselling & Psychology Service. The service is specialised in intensive individual CBT for panic disorder and agoraphobia and is staffed by trained psychology graduate therapists. You will either receive treatment during the 4 weeks between the two sessions, or after the second session. The allocation to one of these options will be randomized. At the beginning of the first visit, you will be given a copy of this information

sheet and a consent form to sign and keep. You will be asked to come to the Department of Psychiatry in the Warneford Hospital for a standard psychiatric interview which will take 1 to 1 ½ hrs. In addition, we will give you some questionnaires asking about your personality, current mood and feelings. At the end of the CBT course we will ask you to come to the scanning centre at the John Radcliffe hospital on a prearranged day. We will ask you to answer some more questions about your mood and to take part in the fMRI scan.

The scan will take about 60-90 mins and we will ask you to respond to simple cognitive tasks displayed on a screen that you can see whilst in the scanner via a button box placed in your right hand. After the scan, we will ask you to complete some more tasks on a computer laptop. The total time of your visit at the John Radcliffe hospital including the scanning is approximately 2 to 2 ½ hours. It is essential that you can keep the appointment arranged for you as scanner time is highly sought after and cancellations must be made as soon as possible so that other researchers can use the time on the machine.

Previous work has also suggested that normal variations in a particular gene (5HTT polymorphism: which affects the chemical messenger serotonin) may influence how the brain responds to this kind of information. If you agree we would like to measure this using a quick and painless cheek swab which will be taken when you come for the screening interview. You will be asked in the consent form if you agree to the collection and analysis of this sample for this study.

Please note that completing the online questionnaire does not mean that you have to participate in the second part of the study if you are invited to do so, although we do hope that this will be possible if you are contacted.

What is Cognitive Behaviour Therapy (CBT)?

Cognitive behaviour therapy is a short-term form of psychotherapy based on the concept that the way we think about things affects how we feel emotionally. Thus, it aims at helping people to modify the way they think and the way they act. The underlying assumption is that learning processes play an important role in overcoming anxiety. Previous research suggests that this type of therapy is very effective in the treatment of anxiety disorders. In this study, we will only be able to offer a brief course of CBT. Full CBT treatment for panic disorder typically involves around 7-10 sessions, thus we do not expect that you will be free of all your symptoms after the brief course. Nevertheless, our previous work suggests that the majority of people make significant gains after 4 sessions of this type of treatment, thus you may experience a significant improvement in your symptoms at this point.

The MRI Scan

The scanner is a large cube shape and has a tube running through the middle, which is open at both ends. You will enter the scanner headfirst and your feet/lower legs will remain outside the tube. During the scan you will hear some loud noises (earplugs are provided). The Radiographer and Researcher will be able to see you throughout the scan and we will provide you with a call button which you can press at any time. MRI scans are safe, non-invasive and do not involve any ionising radiation (x-rays). As the scanner consists of a powerful magnet, it may attract certain metallic objects. Please, on the day of scan wear comfortable clothes without metal buttons or buckles. In the unlikely event of us seeing any structural abnormalities on your MRI scan, a member of our research team will discuss the implications with you and, with your permission, your GP may be notified. However, it is important to note that we do not carry out our scans for diagnostic purposes, and therefore these scans are not a substitute for a clinical appointment. Rather, our scans are intended for research purposes only. During the scan, we would also like to record your heart activity with a simple electrocardiogram (ECG). The ECG recording merely requires the attachment of electrodes to your chest and limbs with sticky tape.

Exclusion Criteria

General exclusion criteria include any medical condition such as epilepsy or severe heart or breathing problems. You will also not be able to take part if you have a family history of epilepsy, if you are on some types of regular medication (except the contraceptive pill), or if you might be pregnant.

fMRI scanning should not be performed if you are severely claustrophobic or if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry pieces of metal that have accidentally entered your body. Also, it is not possible to wear normal glasses in the scanner. However, we can provide scanner-safe glasses for most prescriptions. Before going into the scanner the radiographer at the John Radcliffe hospital will go through the procedure with you and ensure that you are safe to go into the scanner (i.e. make sure you do not have a pacemaker etc.).

Risks and benefits

There are no known risks of MRI for most people. However, the use of magnets means that the scan procedure is not suitable for people with pacemakers, mechanical heart valves, hip replacements or with other metal implants in their body. Also, as noted above, if you have ever sustained an eye injury involving metal or have any history of seizures you should not take part. If you are pregnant you should also not take part. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part. If you suffer from severe claustrophobia you may find lying still in the scanner unpleasant and it may be better not to take part.

Expenses and payments

In recognition of your time and help you will be paid £50 at the end of the study. In addition, you will receive a taster CBT course for your panic symptoms, and we hope that you will find this useful. We will also cover reasonable travel expenses to come to testing and treatment sessions.

PART 2: DATA PROTECTION AND INDEMNITY

What will happen if I do not want to carry on with the study?

Even after you have signed the consent form, you are absolutely free to withdraw from the study at any point without giving any reason. Any identifiable data will then be destroyed.

What would happen if there is a problem?

We believe that this is a very safe study. Compensation for harm arising from an accidental injury and occurring as a consequence of your participation in the study may be covered by the University of Oxford. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Oxford.

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential and must be kept securely in paper or electronic form for 10 years following its completion. It would have your name and address replaced by a code so that you could not be recognised from it. Responsible members of the University of Oxford or the Oxford Radcliffe Hospitals NHS Trust may be given access to anonymised data for monitoring and/or audit of the study to ensure we are complying with regulations.

What will happen to the results of the study?

Anonymised results may be published at conferences and in scientific journals. A summary of results will be sent to volunteers who requested this on the consent form or afterwards.

What will happen to my DNA samples?

Should you agree to have DNA samples taken these will be anonymised (labelled with an identifying number rather than personal identifiers) and stored in the laboratory freezer. We would also like to have your permission to store any remaining DNA. This will allow us to carry out similar work in the future on any genes that are subsequently identified to be

potentially involved in anxiety and investigate how people's individual variations in these genes can affect their response to the measures used in this study. Ethical approval will be obtained for all such future projects. If you do decide to take part in this part of the study, you can withdraw at any time without giving a reason for doing so, up to the point where samples are anonymised.

If you do not want to provide a DNA sample and/or do not wish us to store it just say so and we will note on your consent form that you will not be participating in this part of the study.

The results of our research may eventually allow us to identify functional effects of the different types of brain receptors. However, many other factors are also likely to be involved and individual results will be very difficult to interpret. For this reason, we do not inform individual participants of their results from this part of the study.

Who is organising and funding the research?

The University of Oxford is Sponsor of the research and it is being funded by the Medical Research Council.

Who has reviewed the study?

The study has received favourable ethical opinion from the Oxfordshire researcher Ethics Committee A (REC 09/H0604/55).