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An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is currently undergoing active investigation for use in the treatment of major depression. Recent research has indicated that current methods used to localize the site of stimulation in dorsolateral prefrontal cortex (DLPFC) are significantly inaccurate. However, little information is available on which to base a choice of stimulation site. The aim of the current study was to systematically examine imaging studies in depression to attempt to identify whether there is a pattern of imaging results that suggests an optimal site of stimulation localization. We analysed all imaging studies published prior to 2005 that examined patients with major depression. Studies reporting activation in DLPFC were identified. The DLPFC regions identified in these studies were analysed using the Talairach and Rajkowska–Goldman-Rakic coordinate systems. In addition, we conducted a quantitative meta-analysis of resting studies and studies of serotonin reuptake inhibitor antidepressant treatment. There was considerable heterogeneity in the results between studies. Changes in Brodmann area 9 were relatively consistently identified in resting, cognitive activation and treatment studies included in the meta-analysis. However, there was little consistency in the direction of these changes or the hemisphere in which they were identified. At this stage, the results of imaging studies published to date have limited capacity to inform the choice of optimal prefrontal cortical region for the use in rTMS treatment studies.

Keywords: Depression; Prefrontal cortex; fMRI; PET; Imaging

1. Introduction

Since the mid-1990s, a considerable number of trials have been conducted of repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression (e.g. George et al., 1995; Pascual-Leone et al., 1996; Padberg et al., 1999; George et al., 2000; Fitzgerald et al., 2003). The majority of these have focussed on rTMS applied to the

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left dorsolateral prefrontal cortex (DLPFC) and several meta-analyses have indicated that high frequency stimulation applied to the left DLPFC has effects in excess of sham stimulation (Holtzheimer et al., 2001; McNamara et al., 2001; Burt et al., 2002; Martin et al., 2003). Despite the majority of studies producing positive findings, considerable doubts have continued to be expressed about the clinical applicability of rTMS, predominately due to concerns about the magnitude of the clinical effects seen and the number of patients considered to meet clinical response criteria.

Based on the earliest studies conducted (George et al., 1995; Pascual-Leone et al., 1996), almost all studies to date have followed a standard procedure for the localization of the site of stimulation. This involves finding the scalp site that is optimal for the stimulation of a hand muscle, usually the abductor pollicis brevis (APB), and then measurement 5 cm anteriorly along the cortical surface ('5 cm method'). In the original studies of George et al. (1995) and Pascual-Leone et al. (1996), it was proposed that stimulation should be targeted to the DLPFC, either in general or to Brodmann area 46 (Pascual-Leone et al., 1996). The choice of area was based upon observations of the role of the DLPFC in the genesis of depression (lesion and imaging studies) and in normal mood regulation (Pascual-Leone et al., 1996).

However, there are potentially several reasons why this method may lead to sub-optimal therapeutic results. First, there are considerable concerns about the fidelity of the technique and its capacity to accurately ensure reliable placement of the coil over the DLPFC. In the only systematic evaluation of the technique published to date, Herwig et al. (2001) localized the position identified with this method using a neuro-navigational system and evaluated using structural MRI scans the actual anatomical location of the points identified. In 7 of 22 subjects studied, the '5 cm method' localized the site of potential stimulation in the DLPFC (specifically Brodmann area 9). In the other 15 subjects, the method located a site over more posterior regions, mostly over the premotor cortex.

Second, it is not clear where the ideal target for rTMS stimulation should be, the DLPFC has traditionally been considered to comprise Brodmann areas 9 and 46. However, Brodmann areas are identified on a cytoarchitectonic map that was originally derived from the examination of a different single brain than that used by Talairach and Tournoux. There are several other similar maps based on multiple brains and there are considerable differences in the localization of DLPFC between these maps (Rajkowska and Goldman-Rakic, 1995a,b). For example, Rajkowska and Goldman-Rakic (1995a,b) have produced a revised definition of areas 9 and 46 using modern cytoarchitectonic techniques based on the analysis of seven post mortem brains. The common area for these regions across all subjects was used to define conservative boundaries of areas 9 and 46 (we will refer to these as the R–GR coordinate system).

It is also not immediately obvious from imaging studies conducted in depressed patients where the optimal site to direct TMS stimulation should be. Whereas a number of early imaging studies reported abnormal PFC activity in depressed subjects (e.g. Videbech, 2000), some recent reports have produced conflicting results (e.g. Videbech et al., 2002). In addition, although many studies report findings in 'DLPFC' or 'area 9/46', they often fail to distinguish between DLPFC subregions. In some studies, this relates to a lack of anatomical resolution (e.g. with SPECT studies) or to the use of activation paradigms in fMRI studies that produce effects in only one of the two areas (Cabeza and Nyberg, 2000). There are likely to be significant differences in the functional roles of various DLPFC subregions reflecting both the cytoarchitectural differences (Rajkowska and Goldman-Rakic, 1995a,b) and different patterns of activation seen in normal subjects in imaging studies (Cabeza and Nyberg, 2000).

There are now a variety of methods that can produce accurate and reliable scalp-to-cortex co-registration and that can be used for DLPFC localization in rTMS depression studies. However, only one published clinical trial has used neuro-navigational methods in treatment targeting. In this study, patients were scanned with PET before treatment in an attempt to determine the optimal site of stimulation localization (Herwig et al., 2003). The aim of the current study was to systematically examine the depression imaging literature to identify whether there is a pattern of imaging results that suggests an optimal site of stimulation localization; especially whether the existing imaging literature implicates one subregion in the DLPFC in the pathogenesis of major depression. We conducted a systematic review of all imaging studies conducted in depressed subjects, identified all studies with reported Talairach coordinates and compared these to the Talairach as well as R–GR definitions of Brodmann areas 9 and 46. This study was also motivated by a desire to provide a comprehensive review of the relevance of DLPFC activation to the pathophysiology of major depression as identified by imaging studies.

2. Methods

A systematic review of imaging studies conducted in adult patients with major depressive disorder (studies exclusively of patients with bipolar disorder were

Table 1
Studies conducted at rest with identified coordinates in dorsolateral prefrontal cortex

First author, year	Coordinates			Hemisphere	Location described	BA	R–GR region	Comments
	x	*y*	*z*					
Bench et al., 1992	−38	34	20	L	DLPFC, 9, 46	9	46	
Bonte et al., 2001	28	46	40	R	Superior frontal	9	9	
	−36	42	32	L	Prefrontal cortex	9	9/46	
	44	36	12	R	Inferior frontal	46		
	−28	38	48	L	Superior frontal	9	9	
Drevets, 1992	47	41	10	L	Prefrontal cortex	46		Increased blood flow
Ito et al., 1996	−20	56	28	L	PFC	9		
	27	55	28	R	PFC	9	*	*Anterior border of 9
Kimbrell et al., 2002	38	30	−12	R	Inferior frontal	47		
	44	16	24	R	DLPFC	9		
Oda et al., 2003	−40	30	10	L	Frontal lobe	46		

BA = Brodmann area identified by atlas of Talairach and Tournoux (1988), R–GR = area identified by coordinate system of Rajkowska and Goldman-Rakic (1995a,b), PFC = prefrontal cortex, DLPFC = dorsolateral prefrontal cortex.

excluded) was conducted. Studies were identified by searches of the Medline database using the key words "depression", "imaging", "fMRI", "PET" and "SPECT" up to the end of 2004 and by manual searching of references. All identified articles were individually screened by one investigator for the presence of Talairach coordinates. For those studies reporting Talairach coordinates in prefrontal regions, the location of the reported changes was tabulated using both the atlas of Talairach and Tournoux (1988) and the system of Rajkowska and Goldman-Rakic (1995a,b), and independently checked by a second investigator. Any conflicts in this process were then resolved by consensus.

Studies were separated into the following five groups: (1) resting studies (i.e. studies conducted at rest); (2) emotion induction studies; (3) cognitive induction studies; (4) treatment studies (i.e. change in brain activity with treatment (pharmacological, ECT, psychotherapy or rTMS) and (5) other studies, including tryptophan depletion, sleep deprivation and vagal nerve stimulation paradigms.

In a second step, studies in groups 1 and 4 were subject to a quantitative meta-analysis. These groups were selected due to the presence of a number of studies with comparable methods. In regards to resting studies, studies were included where there was a comparison between blood flow/activation at rest between a group of currently depressed subjects and a healthy control group. This included six studies reporting a decrease in activity in patients in PFC and three studies reporting a increase. Due to the small numbers, only the former were subjected to analysis. In regards to the treatment studies, we identified a relatively homogeneous group of eight studies all investigating changes in blood flow/activation produced with treatment with a selective serotonin reuptake inhibitor (SSRI) (paroxetine, citalopram or fluoxetine). All studies compared scans before and after treatment, five reporting increased PFC activity and four decreased with treatment (one study reported both).

Meta-analysis of these studies was conducted with the activation likelihood estimation (ALE) method (Laird et al., 2005; Turkeltaub et al., 2002). All coordinates were described in Talairach space so transformation was not required. We used a Gaussian filter of 10-mm full-width half-maximum (FWHM) and a threshold for false discovery of $P<0.05$ (tested with a permutation test of 5000 permutations). All ALE data processing was performed using the BrainMap Search and View software (http://brainmap.org). ALE results were overlaid onto an anatomical template generated by spatially normalizing the International Consortium for Brain Mapping (ICBM) template to Talairach space (Kochunov et al., 2002). A minimum cluster size of 250 mm^3 was applied. Locations of the voxels with peak probabilities within clusters and the cluster sizes were identified.

3. Results

We identified a total of 184 imaging studies including subjects with some form of mood disorder. Of these, 56 were excluded as they did not include analysis of a group of patients with unipolar major depressive disorder or there was no comparison with a valid control group. This left 128 studies including a total of 2333 depressed subjects and 1424 controls.

3.1. Resting studies

There were a total of 44 studies included in which the focus of the study was scanning at rest. This included 15 positron emission tomography (PET) studies and 29 using

Table 2
Studies conducted during emotional activation paradigms

Reference	Paradigm		Group	Difference in activity	Coordinates			Hemisphere	Location described	BA area	R–GR region	Comments
					x	*y*	*z*					
Beauregard et al., 1998	Viewing of film clip	Sad vs. neutral	Depressed	Increase	−4	64	32	L	Medial frontal gyrus, 9	9		No difference in DLPFC activation reported in patient–control comparison
				Increase	4	50	26	R	Medial frontal gyrus, 9	9	9	
				Increase	18	58	32	R	Superior frontal gyrus, 9	9	9	
Elliott, 2002	Emotive words	Happy or sad vs. neutral	Depressed	Increase	54	39	21	R	DLPFC, 46	46	46	
			vs. control	Increase	48	45	24	R	DLPFC, 9	46	46	
Kumari, 2003	Captioned pictures	Neutral vs. sad	Depressed	Decrease	23	43	15	R	DLPFC, 9/46	9	46	Less activation with negative than neutral pictures in patient group
		Happy vs. sad	Depressed vs. control	Decrease	30	20	32	R	Middle frontal gyrus, 9	9		Positive>negative pictures, reduced in patients than in controls
Lawrence, 2004	Faces	Happy vs. neutral	Depressed vs. control	Decrease	47	15	21	R	DLPFC, 44	44		ROI including BA 44, 45 and 9
		Sad vs. neutral		Decrease	47	26	13	R	DLPFC, 44	45		ROI including BA 44, 45 and 9
				Decrease	−44	12	28	L	DLPFC, 44	9		ROI including BA 44 and 9
Liotti et al., 2002 [a]	Autobiographical memory scripts	Sad vs. rest	Depressed	Increase	50	20	4	R	Ventrolateral prefrontal, 47	47		Quantitative between-group comparisons not provided
			Depressed	Decrease	6	40	27	R	Medial prefrontal, 9	9	46	
Siegle, 2002	Emotive words	Sad	Depressed vs. control	Decrease	−52	13	39	L	DLPFC 8/9	9		Less activation for positive and negative words in patients, negatively correlated with amygdala activation

BA=Brodmann area identified by atlas of Talairach and Tournoux (1988), R–GR=area identified by coordinate system of Rajkowska and Goldman-Rakic (1995a,b), PFC=prefrontal cortex, DLPFC=dorsolateral prefrontal cortex, ROI=region of interest.
[a] Study with PET (all others fMRI).

single photon emission tomographic (SPECT) techniques. The studies included a total of 1024 currently depressed subjects, 35 patients scanned in remission (in 3 studies) and 21 subjects with depression and dysthymia (1 study). There were a total of 873 healthy control comparator subjects.

Of these studies, 25 reported significant findings in DLPFC but only six reported Talairach coordinates in PFC (4 PET, 3 SPECT) for a depressed patient–control comparison (Table 1). Five of these studies reported a decrease in activity in DLPFC and one study ($^{15}O_2$ PET) reported an increase in DLPFC blood flow in depressed patients versus controls (Drevets et al., 1992). One of these studies reported decreased blood flow ($^{15}O_2$ PET) in depressed subjects with reversible cognitive impairment

Table 3
Studies conducted during cognitive activation paradigms

Reference	Paradigm (image type)	Group	Difference in activity	Coordinates			Hemisphere	Location described	BA area	R–GR region	Comments
				x	*y*	*z*					
George et al., 1997	Emotional Stroop (PET)	Depressed, within group	Increase	−36	28	20	L	DLPFC	46	46	Activation in DLPFC in standard Stroop in the patients (no controls) but not statistically significant between group differences
Hugdahl, 2004	Mental arithmetic (fMRI)	Depressed, within group	Increase	48	15	27	R	Middle frontal gyrus	46	N/A	Activation in depressed group in arithmetic task minus vigilance task
		Depressed vs. controls	Increase	36	28	44	Bil	Middle frontal gyrus	9	9	
Okada, 2003	Verbal fluency (fMRI)	Depressed vs. controls	Decrease	−34	32	5	L	Left PFC, 46	45		
Elliott et al., 1997	Tower of London (PET)	Depressed vs. controls	Decrease	−42	30	32	L	DLPFC, 9	9	*46	*On/close to posterior border of 46
			Decrease	40	28	28	R	DLPFC, 9	9	*46	*On/close to posterior border of 46

BA=area identified by Brodmann coordinate system/atlas of Talairach and Tournoux (1988), R–GR=area identified by coordinate system of Rajkowska and Goldman-Rakic (1995a,b), PFC=prefrontal cortex, DLPFC=dorsolateral prefrontal cortex, PET=positron emission tomography, fMRI=functional magnetic resonance imaging.

compared with controls (Dolan et al., 1992). Across the studies, abnormal activity/blood flow was identified in BA 9 on the left in one study, on the right in one study and bilaterally in two. Abnormalities in BA 46 were identified in two studies on the left (one increased and one decreased blood flow) and in one study on the right. Only two studies identified abnormalities in DLPFC using R–GR criteria, one in left BA 46 and one in bilateral BA 9.

Two additional treatment studies (see Table 4) reported baseline (before treatment) to control group comparisons. One of these reported increased (Brody et al., 2001) and the other decreased (Drevets et al., 2002) bilateral BA 9 metabolism.

3.2. Emotion induction studies

This group included a total of six studies (5 fMRI, 1 PET) with 46 currently depressed subjects, 10 patients in remission at the time of scanning and 53 controls. The studies used a mixture of emotion-induction techniques including the viewing of film clips, pictures and emotive words. All of the studies reported significant differences between activation in the PFC between depressed subjects and controls (Table 2). However, there was no clear pattern in the results of the studies with reports of increased and decreased DLPFC activation with the induction of both happy and sad affect. Decreased activation in patients versus controls was reported in several studies in BA 9 on both the right (Kumari et al., 2003; Lawrence et al., 2004) and the left (Siegle et al., 2002; Lawrence et al., 2004), with one study reporting increased right BA 46 activation (Elliott et al., 2002).

3.3. Cognitive activation studies

We identified a total of 11 studies (3 fMRI, 4 PET, 4 SPECT) in which brain activation during a cognitive task was studied. These studies included 142 patients and 151 controls. There was considerable heterogeneity in the cognitive tasks applied: three studies used a verbal fluency task, two studies used an arithmetic task and all other tasks were only used in one study (Wisconsin card sort, working memory, psychomotor task, planning and guessing tasks). Four studies reported changes in DLPFC (Table 3) and in only three of these were the findings in between-group analyses (Elliott et al., 1997; Okada et al., 2003; Hugdahl et al., 2004). Changes reported included decreased BA 9 activation during a planning task (Elliott et al., 1997) and increased BA 9 activation during a mental arithmetic task (Hugdahl et al., 2004).

3.4. Treatment studies

We identified a total of 15 studies (11 PET, 1 fMRI, 3 SPECT) including 242 patients. The majority of these

Table 4
Studies of brain changes associated with treatment

Reference	Paradigm (image type)	Treatment	Reported comparison	Difference in activity	Coordinates			Hemisphere	Location described	BA Area	R–GR region	Comments
					x	*y*	*z*					
Brody, 2001	PET (rest)	Paroxetine and IPT	Baseline comparison to controls	Increase	−44	24	30	L	DLPFC, 9/46	9		
					40	38	18	R	DLPFC, 9/46	9	46	
			Change with paroxetine	Decrease	−50	28	24	L	PFC	46		3 other PFC coordinates reported but not in DLPFC
					8	54	38	R	PFC	9		
			Change with IPT	Decrease	40	2	58	R	PFC	6		2 other PFC coordinates reported but not in DLPFC
			Change with treatment 2 groups pooled	Decrease	22	40	40	R	PFC	9	9	4 other PFC coordinates reported but not in DLPFC
Drevets, 2002	PET (rest)	Sertraline or other antidepressant	Baseline comparison to controls	Decrease	−15	55	26	L	DLPFC	9		No significant change with treatment in DLPFC
					5	49	36	R	DLPFC	9	9	
Fu et al., 2004	fMRI (response to sad faces)	Fluoxetine	Change with treatment	Increased dynamic range of response	−35	13	40	L	Middle frontal gyrus	8		No baseline differences from controls in DLPFC
					−31	19	32	L	Middle frontal gyrus	9	9	
Kennedy et al., 2001	PET (rest)	Paroxetine	Change with treatment	Increase	−38	14	38	L	DLPFC, 9	8		
					−36	24	36	L	DLPFC, 9	9		
Goldapple et al., 2004	PET (rest)	CBT or paroxetine	Change with CBT	Decrease	48	24	26	R	DLPFC, 9	9		
					50	8	22	R	DLPFC, 9	44		
					−52	18	24	L	DLPFC, 9	9		
					−48	44	10	L	Ventrolateral prefrontal, 45/46	46		*Anterior border of 46
					30	52	16	R	Ventrolateral prefrontal, 45/46	9/10	*46	
			Change with paroxetine	Increase	−34	14	42	L	DLPFC, 9	8		
					−22	26	40	L	DLPFC, 9	8	9	
Nofzinger et al., 2001	PET (rest)	Bupropion SR	Change in REM sleep metabolism	Decrease	−8	46	24	L	Medial frontal gyrus	*9		*Medial BA 9
Smith et al., 1999	PET (rest)	Sleep deprivation and paroxetine	Change with paroxetine	Decrease	−26	34	32	L	Superior frontal gyrus, 9	9	46	
					−18	34	36	L	Superior frontal gyrus, 9	9	9	
					−12	32	48	L	Superior frontal gyrus, 9	9	9	

Table 4 (*continued*)

Reference	Paradigm (image type)	Treatment	Reported comparison	Difference in activity	Coordinates			Hemisphere	Location described	BA Area	R–GR region	Comments
					x	*y*	*z*					
Shajahan et al., 2002	SPECT (verbal fluency)	rTMS	Change with treatment	Increase	−25	35	24	L	DLPFC	9	46	*Increased connectivity from this DLPFC site to caudate and globus pallidus
Nahas et al., 2001	SPECT (rest)	rTMS	Change with treatment	Increase	−48	26	34	L	Middle frontal gyrus	9	9	
Mayberg et al., 1999	PET (rest)	Fluoxetine (6 weeks)	Change with treatment	Increase	42	14	20	R	DLPFC	44		
					28	12	38	R	DLPFC, 9	8		
Mayberg et al., 2000	PET (rest)	Fluoxetine	Change with treatment after 6 weeks	Increase	−34	28	20	L	DLPFC, 46	46	*46	*Posterior border 46
					43	28	18	R	DLPFC, 46	46	*46	*Posterior border 46
					−38	22	26	L	DLPFC, 9	9		
					44	22	26	R	DLPFC, 9	9		
					−36	6	36	L	DLPFC, 9	9		
					36	2	34	R	DLPFC, 9	9		
Mayberg, 2002	PET (rest)	Fluoxetine vs. placebo	Change in fluoxetine responders	Increase	26	12	38	R	DLPFC	8		
					34	22	24	R	DLPFC	9		
					42	28	18	R	DLPFC	46		
			Change in placebo responders		40	16	22	R	DLPFC, 46	9/44		
Teneback et al., 1999	SPECT (rest)	rTMS	Baseline, correlated with depression severity	Negative correlation with depression severity	−42	32	2	L	DLPFC	45		
			Change in placebo group	Increase	−40	48	32	L	DLPFC	9		
				Decrease	48	16	24	R	Frontal lobe	46		
				Decrease	28	26	36	R	Frontal lobe	9		
Smith et al., 2002	PET (rest)	Citalopram	Change with treatment	Decrease	−22	44	16	L	Superior frontal cortex	9	46	
Yatham et al., 1999	PET—18F setoperone binding	Desipramine	Change with treatment	Decrease	−10	46	18	L	Medial frontal gyrus	9	46	

IPT = interpersonal psychotherapy, BA = area identified by Brodmann coordinate system/atlas of Talairach and Tournoux (1988), R–GR = area identified by coordinate system of Rajkowska and Goldman-Rakic (1995a,b), PFC = prefrontal cortex, DLPFC = dorsolateral prefrontal cortex, PET = positron emission tomography, fMRI = functional magnetic resonance imaging.

were studies of antidepressant medications (8 with SSRIs, 1 with desipramine, 1 with buproprion, 1 with a mixture of medications), three with rTMS and three with cognitive behavioural therapy.

There were seven reports of reduced activity with treatment (4 left-sided, 3 bilateral). Six studies reported increased activity (3 left, 1 right, 2 bilateral).

Of the studies reporting decreased activity, in *all* this was found in BA 9 (4 left side only, 3 bilateral) and only in one was this additionally reported in BA 46 (left). Of the studies reporting increased activity, this was also reported in *all* six studies in BA 9. Three of the studies also reported changes in BA 46 (2 right, 1 left).

3.5. Other studies

We identified four studies using amine depletion techniques and PET in depressed subjects. Tryptophan

Table 5

Comparison	Volume (mm^3)	Centre of cluster			Max ALE value	Site of maximum ALE value			Hemisphere/ Brodmann area
		x	*y*	*z*		*x*	*y*	*z*	
Resting—decreased in patients versus controls	928	30.45	48.51	33.68	0.00716	34	46	32	R9
	824	−7.13	29.9	11.7	0.008149	−6	30	12	L24
Treatment—increased activation	3440	−36.22	18.62	31.79	0.009926	−36	24	30	L9
	2888	41.31	23.79	20.77	0.013584	42	28	18	R46
	1392	28.52	10.16	37.37	0.012575	28	12	38	R8
	320	−22.12	26.16	40.27	0.006641	−22	26	40	L8
Treatment—decreased activation	1000	−21.66	34.05	34.09	0.007606	−22	34	34	L9
	656	40.79	38.58	−9.93	0.006698	44	38	−8	R47
	440	−11.99	32.01	47.95	0.006673	−12	32	48	L8
	384	7.89	53.72	32.72	0.006614	8	54	32	R9
	368	33.74	18.8	−11.04	0.00631	34	18	−12	R47
	336	35.63	49.36	15.92	0.006534	36	50	16	R10
	328	7.36	58.05	−11.34	0.006527	8	58	−12	R10
	312	−21.7	43.52	12.81	0.006491	−22	44	12	L9
	280	−49.55	28.64	21.06	0.00649	−50	28	20	L46

depletion was associated with decreased brain metabolism in middle frontal gyrus in patients experiencing relapse associated with tryptophan depletion (Bremner et al., 1997) but no changes in DLPFC were found in a second study (Neumeister et al., 2004) (coordinates not available). In a third study, activation in right BA 9 correlated with plasma tryptophan levels (16, 48, 44=BA 9) and depressive symptoms induced by tryptophan depletion (18, 44, 38=BA 9, R–GR 9). There is also a report of the affect of depletion of norepinephrine and dopamine with α-methylparatyrosine (AMPT) on metabolism in remitted subjects with major depressive disorder as assessed with PET (Bremner et al., 2003). Symptom relapse was associated with decreased DLPFC metabolism (no coordinates provided).

In a different pharmacological challenge paradigm, Fu et al. (2001) studied the response to clonidine challenge in depressed and non-depressed subjects with PET. Clonidine, an α_2-adrenoreceptor agonist resulted in decreased blood flow in the controls and increased blood flow in depressed subjects in right superior prefrontal cortex (group by clonidine interaction at 26, 58, 22 (BA 9/10) and 14, 32, 44 (BA 8)).

Oquendo et al. (2003) studied the response of depressed subjects with and without high lethality suicide attempts to fenfluramine challenge with PET. High lethality suicide attempt subjects demonstrated lower metabolic activity when administered placebo in an area including left BA 9 (−14, 48, 38) which extended over a greater region following fenfluramine administration.

Several studies have also analysed brain metabolism associated with sleep-related phenomena. Germain et al. (2004) reported that depressed subjects experience less of a decrease in regional metabolism from pre-sleep wakefulness to non-REM sleep including in left DLPFC (−32, 42, 32=R–GR 9). Ebert et al. (1994) reported a difference in baseline perfusion (SPECT) between responders and non-responders to sleep deprivation with greater fronto-orbital perfusion. No differences in DLPFC perfusion was reported by a more specific SPECT analysis in a latter study (Volk et al., 1997). In a PET study reported by Wu et al. (1999), there were also no differences in DLPFC between responders and non-responders, although non-responders did differ in activation from controls.

3.6. R–GR coordinate analyses

Across all groups of studies, only a subgroup of individual analyses identified areas of abnormal activity that mapped onto the R–GR definition of areas 9 and 46 (Tables 2–4). In resting studies, decreased activity was identified in these areas in only two studies, on in left 46 and one bilateral 9 (plus overlap with left 46). In regards to emotional activation studies, location in R–GR occurred in four of six studies: in all this was on the right (3 in area 46, 1 in area 9). In cognitive activation studies, two reported R–GR area differences from control subjects, one a bilateral increase in R–GR 9, and one a bilateral reduction in R–GR 46.

R–GR coordinates were most commonly identified in treatment studies. Decreased activity was reported in left 46 in three studies (1 included 9 and 46) and in right 9 and right 46 in one study each. One study reported increased activity in left 9, one in left 46 and one in bilateral 46. Both of the studies reporting unilateral left-sided increases were rTMS studies.

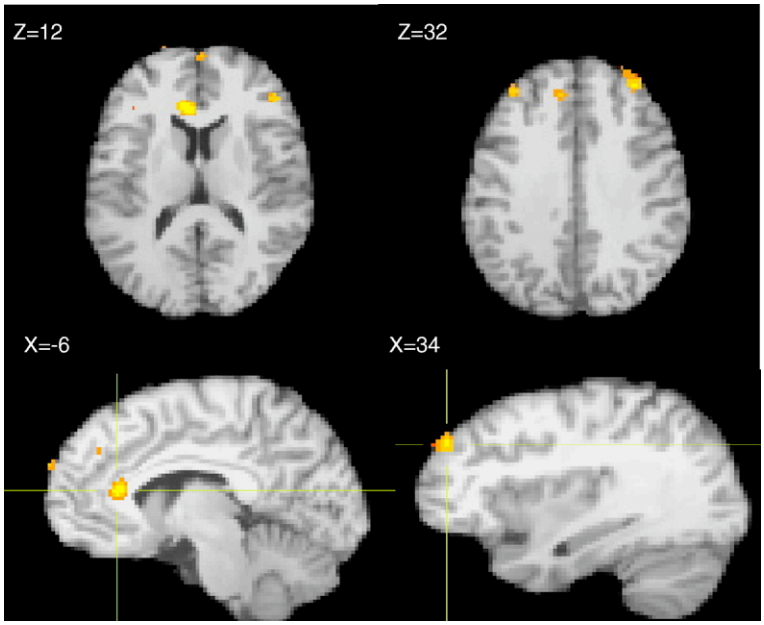

Fig. 1. Clusters identified of decreased activation at rest in patients compared with controls. The cross-hairs identify the significant clusters (bottom left: (−6, 30, 12), bottom right: (34, 46, 32)).

3.7. ALE analysis

Eighteen coordinates were entered into the ALE analysis of the resting studies. This analysis identified two clusters of greater than 250 mm^3 where patients showed reduced activation compared with controls. Two clusters were identified, one in right DLPFC in BA 9 and one in left subgenual anterior cingulate gyrus (BA 24) (Table 5, Fig. 1). Analysis of the treatment studies found five clusters where activation increased with treatment (16 coordinates entered) and nine clusters where activation decreased with treatment (12 coordinates entered) (Table 5, Fig. 2). Increased activation was seen in BA 9 on the left and in BA 46 on the right. Clusters of the decreased activation were seen in bilateral BA 9 and in left BA 46.

4. Discussion

The aim of this study was to establish whether there was a clear pattern of neuroimaging findings suggesting a

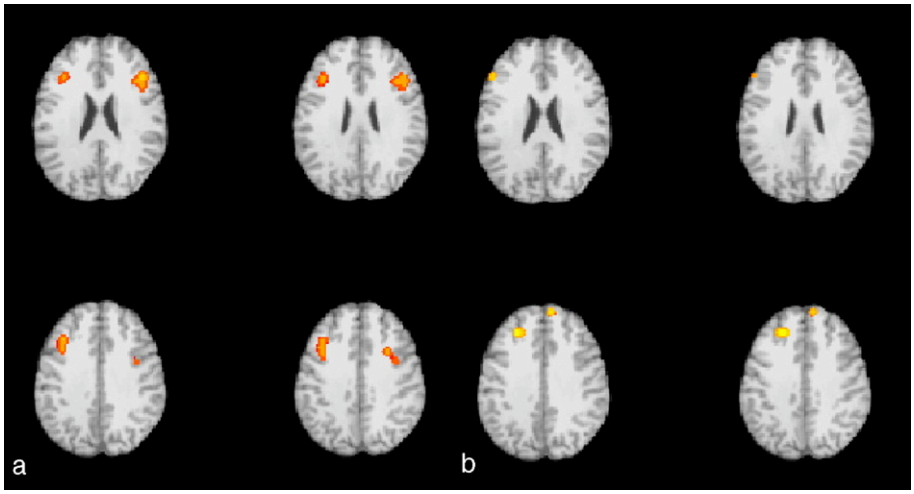

Fig. 2. ALE maps for treatment studies: (a) studies showing an increase of activation with treatment, (b) studies showing a decrease of activation with treatment (z=22, 24, 32, 34 for each set of images, left top to right bottom).

more refined potential target for stimulation in rTMS studies of depression. A study of this nature also had the capacity to inform our understanding of the involvement of the DLPFC in the pathogenesis of major depression. However, the results of the study clearly indicate that there is no consistent pattern of abnormalities in DLPFC activity identified in neuroimaging studies conducted to date. This may, in part, be due to the fact that there is considerable variation across studies both in regards to study type and between differing imaging paradigms. The results of studies vary in whether patients display increased or decreased activity/blood flow, whether this is in the left or right hemisphere and the site within the DLPFC. Conclusions from the descriptive analysis were confirmed by the limited ALE analyses we were able to perform, which also demonstrated heterogeneity in regards to the site of detected clusters, the polarity of effects and the identified hemisphere.

Despite the considerable variability seen, there was consistency in some areas. For example, the majority (6 of 8) of resting studies reported reduced activity and this was more common on the left side, although some studies reported right-sided and bilateral changes. In five of the eight studies, effects were predominately found in BA 9 with BA 46 changes in three reports. However, this was not clearly borne out by the ALE analysis. There were several clusters in left DLPFC but none reached our threshold of 250 mm^3. Perhaps the greatest degree of consistency was seen in the location of effects seen in the treatment studies. Here, most studies reported changes in BA 9, although almost an equal number of studies reported increased activation compared with studies reporting decreased activation. This pattern was confirmed in the ALE analysis. Although the reports were fewer in number, studies with cognitive activation paradigms also predominately reported effects in BA 9, although there was no consistency in the direction of the changes reported. There was considerably less consistency in regards to the studies of emotional activation, with reports of increased and decreased activation as well as effects in BA 9 and 46. In addition, unsurprisingly, there was no consistent pattern in the miscellaneous studies, although there was a trend for tryptophan depletion to be associated with reduced DLPFC activity.

The heterogeneity of these findings makes interpretation of the results of this study difficult. There is a range of potential reasons for the variability seen here. As well as the basic differences in the paradigms used, these include but are not limited to, significant differences in the imaging techniques applied, differences between depressed subjects in different studies and variation in imaging processing and analysis techniques. The type of imaging paradigm itself is critical. Resting studies have the capacity to identify fundamental differences between patient and control groups but can be influenced by confounding factors. For example, most studies match subject groups for age, sex and possibly education but do not control for variables such as personality characteristics that may have direct biological correlates that could potentially confound imaging results. Variables such as neuroticism have been shown to have a specific biological underpinning that may overlap with changes found in depression (Camp and Cannon-Albright, 2005). Although these effects can also potentially bias cognitive and emotional activation studies, these studies are more limited by the fact that they can only identify abnormalities in brain regions actually activated by the paradigm in question. For example, if an emotional activation task does not produce activation of the DLPFC, it is unlikely to show differences in this region even if these are present between the groups. Treatment studies avoid a number of these problems and, in particular, constrain non-illness-related confounds by limiting analyses to within-subject comparisons. The demonstration of change in a particular brain region with treatment provides some degree of confidence about the actual role of this brain region. However, the disadvantage of this sort of study is that one cannot be absolutely sure that changes are related to the presence of depression and are not just the direct effect of the treatment on the brain independent of the illness state.

Do the consistencies found in the articles studied provide any specific guidance that could be useful in the design of rTMS studies? If we are not concerned with considerations of the laterality and direction of effects in the reports, on the surface, the relative consistency of reports of changes in BA 9 across resting, treatment and cognitive studies would appear to suggest so. However, this is likely to be somewhat misleading. In the standard Brodmann outline of these regions (Brodmann, 1909), BA 9 is a larger area than BA 46, raising the possibility that the increase in reports here is purely by chance based on the size of the regions. In addition, BA 9 is a relatively long and elongated region without an obvious centre over which to place an rTMS coil, which will stimulate approximately 2 cm^2 in the cortex (Jalinous, 1991). Finally, when we analysed the results using the much more constrained R–GR criteria (Rajkowska and Goldman-Rakic, 1995a,b), this pattern was not clearly apparent. This may reflect the fact that regions 9 and 46 identified with the R–GR criteria are both smaller and more equal in size. It is also possible that despite the clear cytoarchitectural differences (Rajkowska and Goldman-Rakic, 1995a,b), there are not actually functional differences between these areas. Inspection of the results of an analysis of a large number of studies of normal cognition

indicates that there is very little differentiation between these areas in studies across a wide variety of paradigms (Cabeza and Nyberg, 2000).

In conclusion, there is marked heterogeneity in the large number of neuroimaging studies that have explored the brain regions identified as abnormally active in patients with depression. This is likely to reflect not only the variation in study type but may also result from the lack of a clearly localized DLPFC focus of abnormality in this condition. BA 9 appears the most promising area to target in rTMS studies, but choice of this region remains speculative and has only limited support from the data available to date. In addition, the results of imaging data do little to clarify the mechanism of action of rTMS treatment, be that treatment high-frequency left rTMS (e.g. George et al., 1995; Pascual-Leone et al., 1996), low frequency right-sided rTMS (Klein et al., 1999; Fitzgerald et al., 2003) or newer combinations of these approaches (Fitzgerald et al., 2006).

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References

Beauregard, M., Leroux, J.M., Bergman, S., Arzoumanian, Y., Beaudoin, G., Bourgouin, P., Stip, E., 1998. The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. Neuroreport 9, 3253–3258.

Bench, C.J., Friston, K.J., Brown, R.G., Scott, L.C., Frackowiak, R.S., Dolan, R.J., 1992. The anatomy of melancholia: focal abnormalities of cerebral blood flow in major depression. Psychological Medicine 22, 607–615.

Bonte, F.J., Trivedi, M.H., Devous Sr., M.D., Harris, T.S., Payne, J.K., Weinberg, W.A., Haley, R.W., 2001. Occipital brain perfusion deficits in children with major depressive disorder. Journal of Nuclear Medicine 42, 1059–1061.

Bremner, J.D., Innis, R.B., Salomon, R.M., Staib, L.H., Ng, C.K., Miller, H.L., Bronen, R.A., Krystal, J.H., Duncan, J., Rich, D., Price, L.H., Malison, R., Dey, H., Soufer, R., Charney, D.S., 1997. Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. Archives of General Psychiatry 54, 364–374.

Bremner, J.D., Vythilingam, M., Ng, C.K., Vermetten, E., Nazeer, A., Oren, D.A., Berman, R.M., Charney, D.S., 2003. Regional brain metabolic correlates of alpha-methylparatyrosine-induced depressive symptoms: implications for the neural circuitry of depression. JAMA 289, 3125–3134.

Brodmann, K. 1909. Vergleichende Localisationsiehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Barth, Leipzig.

Brody, A.L., Saxena, S., Stoessel, P., Gillies, L.A., Fairbanks, L.A., Alborzian, S., Phelps, M.E., Huang, S.C., Wu, H.M., Ho, M.L., Ho, M.K., Au, S.C., Maidment, K., Baxter Jr., L.R., 2001. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. Archives of General Psychiatry 58, 631–640.

Burt, T., Lisanby, S.H., Sackeim, H.A., 2002. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. International Journal of Neuropsychopharmacology 5, 73–103.

Cabeza, R., Nyberg, L., 2000. Imaging cognition: II. An empirical review of 275 PET and fMRI studies. Journal of Cognitive Neuroscience 12, 1–47.

Camp, N.J., Cannon-Albright, L.A., 2005. Dissecting the genetic etiology of major depressive disorder using linkage analysis. Trends in Molecular Medicine 11, 138–144.

Dolan, R.J., Bench, C.J., Brown, R.G., Scott, L.C., Friston, K.J., Frackowiak, R.S., 1992. Regional cerebral blood flow abnormalities in depressed patients with cognitive impairment. Journal of Neurology, Neurosurgery and Psychiatry 55, 768–773.

Drevets, W.C., Bogers, W., Raichle, M.E., 2002. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. European Neuropsychopharmacology 12, 527–544.

Drevets, W.C., Videen, T.O., Price, J.L., et al., 1992. A functional anatomical study of unipolar depression. Journal of Neuroscience 12, 3628–3641.

Ebert, D., Feistel, H., Barocka, A., Kaschka, W., 1994. Increased limbic blood flow and total sleep deprivation in major depression with melancholia. Psychiatry Research: Neuroimaging 55, 101–109.

Elliott, R., Baker, S.C., Rogers, R.D., O'Leary, D.A., Paykey, E.S., Frith, C.D., Dolan, R.J., Sahakian, B.J., 1997. Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography. Psychological Medicine 27, 931–942.

Elliott, R., Rubinsztein, J.S., Sahakian, B.J., Dolan, R.J., 2002. The neural basis of mood-congruent processing biases in depression. Archives of General Psychiatry 59, 597–604.

Fitzgerald, P.B., Benitez, J., De Castella, A.R., Daskalakis, Z.J., Brown, T., Kulkarni, J., 2006. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. American Journal of Psychiatry 163, 88–94.

Fitzgerald, P.B., Brown, T., Marston, N.A.U., Daskalakis, Z.J., Kulkarni, J., 2003. A double-blind placebo controlled trial of transcranial magnetic stimulation in the treatment of depression. Archives of General Psychiatry 60, 1002–1008.

Fu, C.H., Reed, L.J., Meyer, J.H., Kennedy, S., Houle, S., Eisfeld, B.S., Brown, G.M., 2001. Noradrenergic dysfunction in the prefrontal cortex in depression: an [^{15}O] H_2O PET study of the neuromodulatory effects of clonidine. Biological Psychiatry 49, 317–325.

Fu, C.H., Williams, S.C., Cleare, A.J., Brammer, M.J., Walsh, N.D., Kim, J., Andrew, C.M., Pich, E.M., Williams, P.M., Reed, L.J., Mitterschiffthaler, M.T., Suckling, J., Bullmore, E.T., 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Archives of General Psychiatry 61, 877–889.

George, M.S., Ketter, T.A., Parekh, P.I., Rosinsky, N., Ring, H.A., Pazzaglia, P.J., Marangell, L.B., Callahan, A.M., Post, R.M., 1997. Blunted left cingulate activation in mood disorder subjects during a response interference task (the Stroop). Journal of Neuropsychiatry and Clinical Neuroscience 9, 55–63.

George, M.S., Nahas, Z., Molloy, M., Speer, A.M., Oliver, N.C., Li, X.B., Arana, G.W., Risch, S.C., Ballenger, J.C., 2000. A controlled trial of daily left prefrontal cortex TMS for treating depression. Biological Psychiatry 48, 962–970.

George, M.S., Wassermann, E.M., Williams, W.A., Callahan, A., Ketter, T.A., Basser, P., Hallett, M., Post, R.M., 1995. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 6, 1853–1856.

Germain, A., Nofzinger, E.A., Kupfer, D.J., Buysse, D.J., 2004. Neurobiology of non-REM sleep in depression: further evidence for hypofrontality and thalamic dysregulation. American Journal of Psychiatry 161, 1856–1863.

Goldapple, K., Segal, Z., Garson, C., Lau, M., Bieling, P., Kennedy, S., Mayberg, H., 2004. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Archives of General Psychiatry 61, 34–41.

Herwig, U., Padberg, F., Unger, J., Spitzer, M., Schonfeldt-Lecuona, C., 2001. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biological Psychiatry 50, 58–61.

Herwig, U., Lampe, Y., Juengling, F.D., Wunderlich, A., Walter, H., Spitzer, M., Schonfeldt-Lecuona, C., 2003. Add-on rTMS for treatment of depression: a pilot study using stereotaxic coil-navigation according to PET data. Journal of Psychiatric Research 37, 267–275.

Holtzheimer III, P.E., Russo, J., Avery, D.H., 2001. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. Psychopharmacology Bulletin 35, 149–169.

Hugdahl, K., Gundersen, H., Brekke, C., Thomsen, T., Rimol, L.M., Ersland, L., Niemi, J., 2004. FMRI brain activation in a Finnish family with specific language impairment compared with a normal control group. Journal of Speech, Language and Hearing Research 47, 162–172.

Ito, H., Kawashima, R., Awata, S., Ono, S., Sato, K., Goto, R., Koyama, M., Sato, M., Fukuda, H., 1996. Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique [see comments]. Journal of Nuclear Medicine 37, 410–414.

Jalinous, R., 1991. Technical and practical aspects of magnetic nerve stimulation. Journal of Clinical Neurophysiology 8, 10–25.

Kennedy, S.H., Evans, K.R., Kruger, S., Mayberg, H.S., Meyer, J.H., McCann, S., Arifuzzman, A.I., Houle, S., Vaccarino, F.J., 2001. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. American Journal of Psychiatry 158, 899–905.

Kimbrell, T.A., Ketter, T.A., George, M.S., Little, J.T., Benson, B.E., Willis, M.W., Herscovitch, P., Post, R.M., 2002. Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. Biological Psychiatry 51, 237–252.

Klein, E., Kreinin, I., Chistyakov, A., Koren, D., Mecz, L., Marmur, S., D.B.-S., Feinsod, M., 1999. Therapeutic efficiency of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double blind controlled trial. Archives of General Psychiatry 56, 315–320.

Kochunov, P., Lancaster, J.L., Thompson, P., Toga, A.W., Brewer, P., Hardies, J., Fox, P.T., 2002. An optimized individual target brain in the Talairach coordinate system. Neuroimage 17, 922–927.

Kumari, V., Mitterschiffthaler, M.T., Teasdale, J.D., Malhi, G.S., Brown, R.G., Giampietro, V., Brammer, M.J., Poon, L., Simmons, A., Williams, S.C., Checkley, S.A., Sharma, T., 2003. Neural abnormalities during cognitive generation of affect in treatment-resistant depression. Biological Psychiatry 54, 777–791.

Laird, A.R., Fox, M., Price, C.J., Glahn, D.C., Uecker, A.M., Lancaster, J.L., Turkeltaub, P.E., Kochunov, P., Fox, P.T., 2005. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Human Brain Mapping 25, 155–164.

Lawrence, N.S., Williams, A.M., Surguladze, S., Giampietro, V., Brammer, M.J., Andrew, C., Frangou, S., Ecker, C., Phillips, M.L., 2004. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biological Psychiatry 55, 578–587.

Liotti, M., Mayberg, H.S., McGinnis, S., Brannan, S.L., Jerabek, P., 2002. Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression. American Journal of Psychiatry 159, 1830–1840.

Martin, J.L., Barbanoj, M.J., Schlaepfer, T.E., Thompson, E., Perez, V., Kulisevsky, J., 2003. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. British Journal of Psychiatry 182, 480–491.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. American Journal of Psychiatry 156, 675–682.

Mayberg, H.S., Brannan, S.K., Tekell, J.L., Silva, J.A., Mahurin, R.K., McGinnis, S., Jerabek, P.A., 2000. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biological Psychiatry 48, 830–843.

McNamara, B., Ray, J.L., Arthurs, O.J., Boniface, S., 2001. Transcranial magnetic stimulation for depression and other psychiatric disorders. Psychological Medicine 31, 1141–1146.

Nahas, Z., Teneback, C.C., Kozel, A., Speer, A.M., DeBrux, C., Molloy, M., Stallings, L., Spicer, K.M., Arana, G., Bohning, D.E., Risch, S.C., George, M.S., 2001. Brain effects of TMS delivered over prefrontal cortex in depressed adults: role of stimulation frequency and coil-cortex distance. Journal of Neuropsychiatry and Clinical Neuroscience 13, 459–470.

Neumeister, A., Nugent, A.C., Waldeck, T., Geraci, M., Schwarz, M., Bonne, O., Bain, E.E., Luckenbaugh, D.A., Herscovitch, P., Charney, D.S., Drevets, W.C., 2004. Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. Archives of General Psychiatry 61, 765–773.

Nofzinger, E.A., Berman, S., Fasiczka, A., Miewald, J.M., Meltzer, C.C., Price, J.C., Sembrat, R.C., Wood, A., Thase, M.E., 2001. Effects of bupropion SR on anterior paralimbic function during waking and REM sleep in depression: preliminary findings using. Psychiatry Research 106, 95–111.

Oda, K., Okubo, Y., Ishida, R., Murata, Y., Ohta, K., Matsuda, T., Matsushima, E., Ichimiya, T., Suhara, T., Shibuya, H., Nishikawa, T., 2003. Regional cerebral blood flow in depressed patients with white matter magnetic resonance hyperintensity. Biological Psychiatry 53, 150–156.

Okada, G., Okamoto, Y., Morinobu, S., Yamawaki, S., Yokota, N., 2003. Attenuated left prefrontal activation during a verbal fluency task in patients with depression. Neuropsychobiology 47, 21–26.

Oquendo, M.A., Placidi, G.P., Malone, K.M., Campbell, C., Keilp, J., Brodsky, B., Kegeles, L.S., Cooper, T.B., Parsey, R.V., van

Heertum, R.L., Mann, J.J., 2003. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. Archives of General Psychiatry 60, 14–22.

Padberg, F., Zwanzger, P., Thoma, H., Kathmann, N., Haag, C., Greenberg, B.D., Hampel, H., Möller, H.J., 1999. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. Psychiatry Research 88, 163–171.

Pascual-Leone, A., Rubio, B., Pallardo, F., Catala, M.D., 1996. Rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348, 233–237.

Rajkowska, G., Goldman-Rakic, P.S., 1995a. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. Cerebral Cortex 5, 307–322.

Rajkowska, G., Goldman-Rakic, P.S., 1995b. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. Cerebral Cortex 5, 323–337.

Shajahan, P.M., Glabus, M.F., Steele, J.D., Doris, A.B., Anderson, K., Jenkins, J.A., Gooding, P.A., Ebmeier, K.P., 2002. Left dorsolateral repetitive transcranial magnetic stimulation affects cortical excitability and functional connectivity, but does not impair cognition in major depression. Progress in Neuropsychopharmacology and Biological Psychiatry 26, 945–954.

Siegle, G.J., Steinhauer, S.R., Thase, M.E., Stenger, V.A., Carter, C.S., 2002. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biological Psychiatry 51, 693–707.

Smith, G.S., Reynolds 3rd, C.F., Pollock, B., Derbyshire, S., Nofzinger, E., Dew, M.A., Houck, P.R., Milko, D., Meltzer, C.C., Kupfer, D.J., 1999. Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. American Journal of Psychiatry 156, 683–689.

Smith, G.S., Kramer, E., Hermann, C.R., Goldberg, S., Ma, Y., Dhawan, V., Barnes, A., Chaly, T., Belakhleff, A., Laghrissi-Thode, F., Greenwald, B., Eidelberg, D., Pollock, B.G., 2002. Acute and chronic effects of citalopram on cerebral glucose metabolism in geriatric depression. American Journal of Geriatric Psychiatry 10, 715–723.

Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain. Thieme Medical Publishers, Stuttgart, Germany.

Teneback, C.C., Nahas, Z., Speer, A.M., Molloy, M., Stallings, L.E., et al., 1999. Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. The Journal of Neuropsychiatry and Clinical Neuroscience 11, 426–435.

Turkeltaub, P.E., Eden, G.F., Jones, K.M., Zeffiro, T.A., 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 16, 765–780.

Videbech, P., 2000. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. Acta Psychiatrica Scandinavica 101, 11–20.

Videbech, P., Ravnkilde, B., Pedersen, T.H., Hartvig, H., Egander, A., Clemmensen, K., Rasmussen, N.A., Andersen, F., Gjedde, A., Rosenberg, R., 2002. The Danish PET/depression project: clinical symptoms and cerebral blood flow. A regions-of-interest analysis. Acta Psychiatrica Scandinavica 106, 35–44.

Volk, S.A., Kaendler, S.H., Hertel, A., Maul, F.D., Manoocheri, R., Weber, R., Georgi, K., Pflug, B., Hor, G., 1997. Can response to partial sleep deprivation in depressed patients be predicted by regional changes of cerebral blood flow? Psychiatry Research: Neuroimaging 75, 67–74.

Wu, J., Buchsbaum, M.S., Gillin, J.C., Tang, C., Cadwell, S., Wiegand, M., Najafi, A., Klein, E., Hazen, K., Bunney Jr., W.E., Fallon, J.H., Keator, D., 1999. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. American Journal of Psychiatry 156, 1149–1158.

Yatham, L.N., Liddle, P.F., Dennie, J., Shiah, I.S., Adam, M.J., Lane, C.J., Lam, R.W., Ruth, T.J., 1999. Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment: a positron emission tomography study with fluorine-18-labeled setoperone. Archives of General Psychiatry 56, 705–711.