Imaging the neurobiological substrate of atypical depression by SPECT

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Abstract. *Purpose:* Neurobiological abnormalities underlying atypical depression have previously been suggested. The purpose of this study was to explore differences at functional brain imaging between depressed patients with and without atypical features and healthy controls.
Methods: Twenty-three out-patients with chronic depressive disorder recruited from a service for patients with audiological symptoms were investigated. Eleven fulfilled the DSM-IV criteria for atypical depression (mood reactivity and at least two of the following: weight gain, hypersomnia, leaden paralysis and interpersonal rejection sensitivity). Twenty-three healthy subjects served as controls. Voxel-based analysis was applied to explore differences in ^{99m}Tc-HMPAO uptake between groups.
Results: Patients in the atypical group had a higher prevalence of bilateral hearing impairment and higher depression and somatic distress ratings at the time of SPECT. Significantly higher tracer uptake was found bilaterally in the atypical group as compared with the non-atypicals in the sensorimotor (Brodmann areas, BA1–3) and premotor cortex in the superior frontal gyri (BA6), in the middle frontal cortex (BA8), in the parietal associative cortex (BA5, BA7) and in the inferior parietal lobule (BA40). Significantly lower tracer distribution was found in the right hemisphere in the non-atypicals compared with the controls in BA6, BA8, BA44, BA45 and BA46 in the frontal cortex, in the orbito-frontal cortex (BA11, BA47), in the postcentral parietal cortex (BA2) and in the multimodal association parietal cortex (BA40).
Conclusion: The differences found between atypical and non-atypical depressed patients suggest different neurobiological substrates in these patient groups. The putative links with the clinical features of atypical depression are discussed. These findings encourage the use of functional neuroimaging in psychiatric disorders.

Keywords: Atypical depression – ^{99m}Tc-HMPAO – rCBF-SPECT – SPM – Unipolar depression

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Introduction

In recent years, functional neuroimaging has gained increasing importance in identifying the neurobiological substrate(s) of psychiatric disorders [1–6]. Investigations using single-photon emission computed tomography (SPECT) have contributed in shedding light on the regional brain involvement linked to depressive symptoms.

The term "atypical depression" was coined in 1969 when Klein and Davis wrote: "So-called 'atypical depressions' consist of patients with depressive mood who reverse the usual consequences of retarded depression and have hypersomnia, hyperphagia, libidinal increase or weight gain, or who have 'primary phobic-anxious trends'" [7]. The DSM-IV criteria for atypical features apply only to non-psychotic and non-melancholic depressive disorders. Mood reactivity is the primary inclusion criterion (the A criterion), and two or more of four other features (the B criteria) must be present: increased appetite or weight gain, hypersomnia, "leaden paralysis" defined as a heavy, leaden feeling in the arms or legs, and long-standing interpersonal rejection sensitivity [8].

Other common features in atypical depression are its association with the female sex, an early age of onset, chronicity, severity, work impairment, neurasthenia, migraine and cognitive impairment [9]. The mandatory criterion of mood reactivity has been questioned, and anxiety has

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been reconsidered as a possible adjunctive criterion [9, 10]. Leaden paralysis and interpersonal rejection sensitivity have been thought to reflect a primacy phenomenon of atypical depression, and increased appetite and hypersomnia to have adaptive homeostatic potential in the disorder [10].

Biochemical features of atypical depression are a reduction in the response to tricyclic antidepressants and an increased response to inhibitors of the outer mitochondrial membrane-bound enzyme monoamine oxidase (MAOIs) [10].

A lifetime rate of 16% has been reported for atypical depression in a cohort of patients with major depression, and a lifetime rate of 0.7% in the general population [11]. It is also more common than the expected prevalence in depressed patients with group level signs of mitochondrial dysfunction [12]. Psychological [13] and brain imaging [14] studies have suggested a right hemisphere involvement in atypical depression.

The purpose of this study was to assess whether differences at functional brain imaging could be detected between atypical and non-atypical depressed patients and healthy controls using ^{99m}Tc-HMPAO SPECT analysed by statistical parametric mapping (SPM).

Materials and methods

Subjects

Twenty-three right-handed patients, 12 males and 11 females (mean age of 47.3±8.8 years), with a chronic type of unipolar depression and a lifetime diagnosis of major depressive disorder were included in the study. The patients were attending a tertiary psychiatric outpatient service affiliated to the psychiatric department of a public general hospital serving clients with any type of audiological symptom and their family members in need of psychiatric care. Eleven of the 23 patients fulfilled the DSM-IV criteria for "atypical features specifier" [10]. Twelve patients did not fulfil the criteria or have any psychotic or melancholic depressive features. Alcohol or drug abuse was not present in any of the patients.

At the start of the study, it was decided to investigate about 12 patients with and 12 patients without features of atypical depression selected from a list of 29 patients without and 51 patients with such features who had been investigated with SPECT during the course of chronic depression. Six males and six females with the least presence of the DSM-IVB criteria features of atypical depression were first selected. The ordering of the list was based on the date of the interview about atypical features. In keeping with the same list construction, the selected atypical patients were the first six males and six females fulfilling the required criteria. One atypical patient was subsequently excluded from the study because it was not possible to spatially normalise her SPECT data at SPM.

The scores of the three "somatic distress" sub-scales of the Karolinska Scales of Personality (KSP), namely Somatic Anxiety, Muscular Tension and Psychasthenia, and the score for Psychic Anxiety [15], were compared (completed by ten atypicals and 12 non-atypicals) for further characterisation of the sub-groups.

Twenty-three right-handed healthy subjects, 12 males and 11 females with a mean age of 48.3±5.9 years, served as controls. These subjects were selected from a large group of individuals who had undergone SPECT with the intention that they would be utilised as a normal healthy control group for SPECT analyses. The controls were without any medication and had no personal history of somatic or psychiatric illness, brain trauma, or alcohol or drug abuse [16]. The Montgomery-Åsberg Depression Rating Scale [17], self-rating version (MADRS-S) and the cognitive screening test Mini-Mental State Examination (MMSE) [18] were performed with normal results.

The study was approved by the local Ethics and Radiation Safety Committees. All subjects gave informed consent.

SPECT

Brain imaging using SPECT was performed using a three-headed gamma camera (TRIAD XLT 20, Trionix Research Laboratory Inc., Twinsburg, OH, USA) equipped with low-energy ultrahigh-resolution (LEUHR) collimators. The projection data relative to each head were acquired for 15 s per projection at 90 equal angles of a complete revolution. The SPECT images were reconstructed by a filtered back projection algorithm using a ramp filter with a cut-off frequency of 0.6 cycles/cm. During pre-processing, the data were smoothed using a first-order 2D Hamming filter with a cut-off frequency of 2.25. Attenuation correction was based on a four-point ellipse [19]. No scatter correction was performed. Data were projected into a 128×128 pixel matrix, resulting in an isotropic voxel size of 2.2 mm^3. In each patient, 1,000 MBq of ^{99m}Tc-*d,l*-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO, Ceretec, Exametazine, Amersham International Plc, Little Chalfont, UK) was injected after 30-min rest in a quiet, dimly lit room.

Voxel-based analysis

SPECT reconstructed transverse images were transformed into the Analyze format by the XMedCon package. Data were analysed with SPM2 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.5.1. All images were spatially normalised by a bilinear interpolation method into a predefined SPECT template based on the MNI reference brain [20] and smoothed with a Gaussian kernel filter of 12 mm (full-width at half-maximum) to account for the inter-subject normal variations and increase the signal-to-noise ratio. The grey matter threshold was set at 0.5 based on simulation data obtained under conditions of focal hypoperfusion [21]. Normalisation of global cerebral blood flow (CBF) to 50 was performed with proportional scaling. The resulting set of values for comparison constituted a statistical parametric map of the statistic SPM$\{t\}$. Then, the SPM$\{t\}$ maps were transformed to the unit of normal distribution (SPM$\{z\}$). Regions were considered significant at a threshold of $p \leq 0.01$ uncorrected for voxel height and $p \leq 0.05$ uncorrected for cluster extent. Only those clusters containing more than 100 voxels were accepted as significant. This was based on the calculation of the partial volume effect resulting from the spatial resolution.

The voxel-based analyses were performed using SPM2 with a "one scan per subject, two-sample *t* test" design model, and significances were found for the following four contrasts: (a) the controls minus all patients, (b) the controls minus the atypicals, (c) the controls minus the non-atypicals, (d) the atypicals minus the non-atypicals, and vice versa. Within each comparison, a *t* value was calculated for each voxel in the brain; then *t* values were transformed into *z* scores and displayed as a statistical parametric map (SPM image) made up of multiple voxels representing the areas of statistically significant differences between the groups, taking into account the volume threshold. SPM2 co-registered the individual SPECT to the 152-brain average of the Montreal Neurological Institute (http://www.bic.mni.mcgill.ca). Because this template does not completely match the Talairach brain, it is necessary to correct the SPM$\{t\}$ coordinates. This was achieved using the subroutine implemented by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html), which gives the correspondence between

Table 1. Demographic and clinical characteristics of the patients

Characteristics at the SPECT examination								Atypical depression criteria (1=yes, 0=no)					Karolinska Scales of Personality (normal score 50±10)			
Gender	Age (yrs)	Years since onset of dysphoria	Tinnitus (1=yes, 0=no)	Bilat. hear. imp.	Work (% capacity)	MADRS-S (a score ≥18 is considered to reflect major depression)	Medication (mg/day)	Mood reactivity	Weight gain	Hypersomnia	Leaden paralysis	Rejection sensitivity	Somatic distress scales			Psychic Anxiety
													Somatic Anxiety	Muscular Tension	Psychasthenia	
Male	38	3	1	1	0	33	None	1	0	0	1	1	99	103	86	80
Male	52	7	1	1	0	36	Fluoxetine (20)	1	1	0	1	1	97	92	94	82
Male	40	15	1	1	0	23	None	1	1	0	1	0	80	98	70	64
Male	33	8	1	1	0	33	Fluoxetine (20)	1	1	0	1	1	89	87	65	66
Male	47	28	1	1	0	33	None	1	1	0	1	1	93	100	95	74
Male	43	8	1	1	0	47	None	1	1	1	1	1	78	98	81	66
Fem	45	19	0 (1)	0	50	NA	Citalopram (40)	1	0	1	1	1	50	64	77	62
Fem	51	38	1	0	0	28	None	1	1	1	1	1	66	73	80	67
Fem	32	22	1	1	0	NA	Citalopram (60)	1	1	1	1	1				
Fem	40	30	1	1	0	31	Citalopram (40)	1	1	1	1	1	63	83	62	73
Fem	57	41	0	1	50	NA	None	1	1	0	1	0	56	56	59	56
Mean or %	43	20	82%	82%	None: 82%	32	45% medicated	100%	82%	45%	100%	82%	77	85	77	69
Male	56	5	1	0	0	NA	None	1	0	0	0	1	71	67	72	67
Male	50	2	0	1	0	22	None	0	0	0	1	0	65	77	84	53
Male	47	30	1	0	75	NA	Citalopram (10)	0	0	1	0	0	47	53	57	55
Male	51	4	1	0	100	8	None	1	0	0	0	0	61	71	64	48
Male	59	2	0 (1)	0	0	30	None	1	0	0	0	0	65	61	57	48
Male	61	8	1	0	0	9	None	1	0	0	0	1	59	67	64	55
Fem	36	8	1	1	50	12	None	1	0	0	0	0	46	60	59	43
Fem	58	38	0	0	0	25	Clomipramine (20)	1	0	0	0	0	63	52	60	70
Fem	50	24	1	0	0	30	None	1	0	0	0	1	73	71	66	61
Fem	51	33	0	1	0	5	None	1	1	0	0	0	45	56	62	50
Fem	57	11	1	0	0	23	None	1	1	0	0	0	60	66	59	55
Fem	35	28	1	0	0	21	None	0	1	0	0	1	73	74	74	58
Mean or %	51	16	67%	25%	none: 75%	19	17% medicated	75%	25%	8%	8%	33%	61	65	65	55

The first 11 patients fulfilled the DSM-IV criteria for atypical depression. The following 12 patients did not fulfil these criteria
For two patients there was onset of tinnitus some time after the SPECT examination
Fem female, *Bilat. hear. imp.* bilateral hearing impairment, *MADRS-S* Montgomery-Åsberg Depression Rating Scale, self-rating version, *NA* not assessed at the time of SPECT

SPM coordinates and Talairach coordinates. Brodmann areas (BAs) were then identified, after importing the corrected coordinates, by the Talairach Deamon Database (http://www.ric.uthscsa.edu/projects/talairachdaemon.html).

Statistical analysis

The significance level was set at $p \leq 0.05$. For the SPM analysis, differences between peak z values were considered. The χ^2 test was used to assess differences of proportions, and the t test to assess mean differences, between the patient groups.

Results

Demographic and clinical data for the patients in both groups are presented in Table 1. No differences were found between the patient groups for years since onset of significant dysphoria ($F(1,21)=0.478$; $p=0.497$), for the proportion of ongoing tinnitus ($\chi^2=1.014$; $p=0.314$), for full work incapacity ($\chi^2=2.294$; $p=0.514$) or for the presence of antidepressant medication at the time of SPECT ($\chi^2=2.25$; $p=0.134$). Bilateral hearing impairment was significantly more common in the atypicals ($\chi^2=7.43$; $p=0.006$). Depression rating scores using the self-rating version of the MADRS [17] were obtained at the time of SPECT in eight atypicals (73%) and in ten non-atypicals (83%). According to this scale, scores higher than 18 are considered abnormal. The mean MADRS-S score was significantly higher in the atypicals ($F(1,16)=13.537$; $p=0.002$; Table 1).

As for the KSP, the mean scores of the four sub-scales were significantly higher in the atypical patients than in the non-atypical patients on all scales: Somatic Anxiety: 77 versus 61 ($F(1,20)=7.582$; $p=0.012$), Muscular Tension: 85 versus 65 ($F(1,20)=15.213$; $p=0.001$), Psychasthenia: 77 versus 65 ($F(1,20)=7.258$; $p=0.014$, and Psychic Anxiety: 69 versus 55 ($F(1,20)=16.110$; $p=0.001$), in the atypicals and the non-atypicals, respectively.

Differences at SPECT between controls and all depressed patients

When controls and all patients were compared, SPM analysis showed significant differences, with decreased tracer uptake in the right premotor cortex in the superior frontal gyri (BA6), in the middle frontal cortex (BA8) and in the prefrontal cortex (BA9) in patients (Fig. 1, Table 2).

Differences at SPECT between controls and atypical depressed patients

No differences in tracer distribution were found between the atypical patients and the controls.

Differences at SPECT between controls and non-atypical depressed patients

Significantly lower tracer uptake was found in non-atypical patients as compared with controls in the frontal cortex (BA6, BA8, BA44, BA45 and BA46), in the orbito-frontal cortex (BA11, BA47), in the postcentral parietal cortex (BA2) and in the multimodal association parietal cortex (BA40). The results are presented in Fig. 2 and Table 3.

Differences at SPECT between atypical and non-atypical depressed patients

SPM showed significantly higher tracer uptake in the atypical group than in the non-atypical group in the sensorimotor (BA1–3) and premotor cortex in the superior frontal gyri (BA6), in the middle frontal cortex (BA8), in the parietal associative cortex (BA5, BA7) and in the inferior parietal lobule (BA40) (Fig. 3, Table 4).

Discussion

The results of the present investigation show significant differences in ^{99m}Tc-HMPAO distribution between patients with and without features of atypical depression.

Unipolar depression is likely to be aetiologically heterogeneous [22], and several "endophenotypes" for major depression have been proposed [23]. Recent studies indicate that the concept of atypical depression may be helpful in the attempt to classify depression into sub-groups [9, 10].

The patients included in this study were recruited from a tertiary psychiatric out-patient service for patients with concomitant audiological symptoms and their family members and are thus not representative of cases of unipolar depression in the general population. Bilateral hearing loss as measured by audiometry testing may be a stable characteristic in middle-aged patients with severe major depression [24], even if, to the best of our knowledge, no study has reported the prevalence of this feature in atypical depression. Of 134 consecutive patients with a chronic type of unipolar depression attending this service, 66% fulfilled the DSM-IV criteria for atypical depression (Gardner, unpublished data), suggesting that atypical features are common in depressed patients with audiological symptoms or with a family history of audiological symptoms, since lower prevalence rates have been reported for other groups, e.g. 29% in depressed out-patients [25]. Other somatic symptoms such as muscle pains, headaches, tinnitus, ocular/visual symptoms and general fatigue are common in major depression [26]. Prevalences of weight gain and hypersomnia similar to those reported in this study were found in patients with (severe) atypical depression in a previous epidemiological study (values in the present study versus those in the study by Sullivan et al. [27]: 82% versus 84% and 45% versus 54%, respectively). The higher depression rating scores in

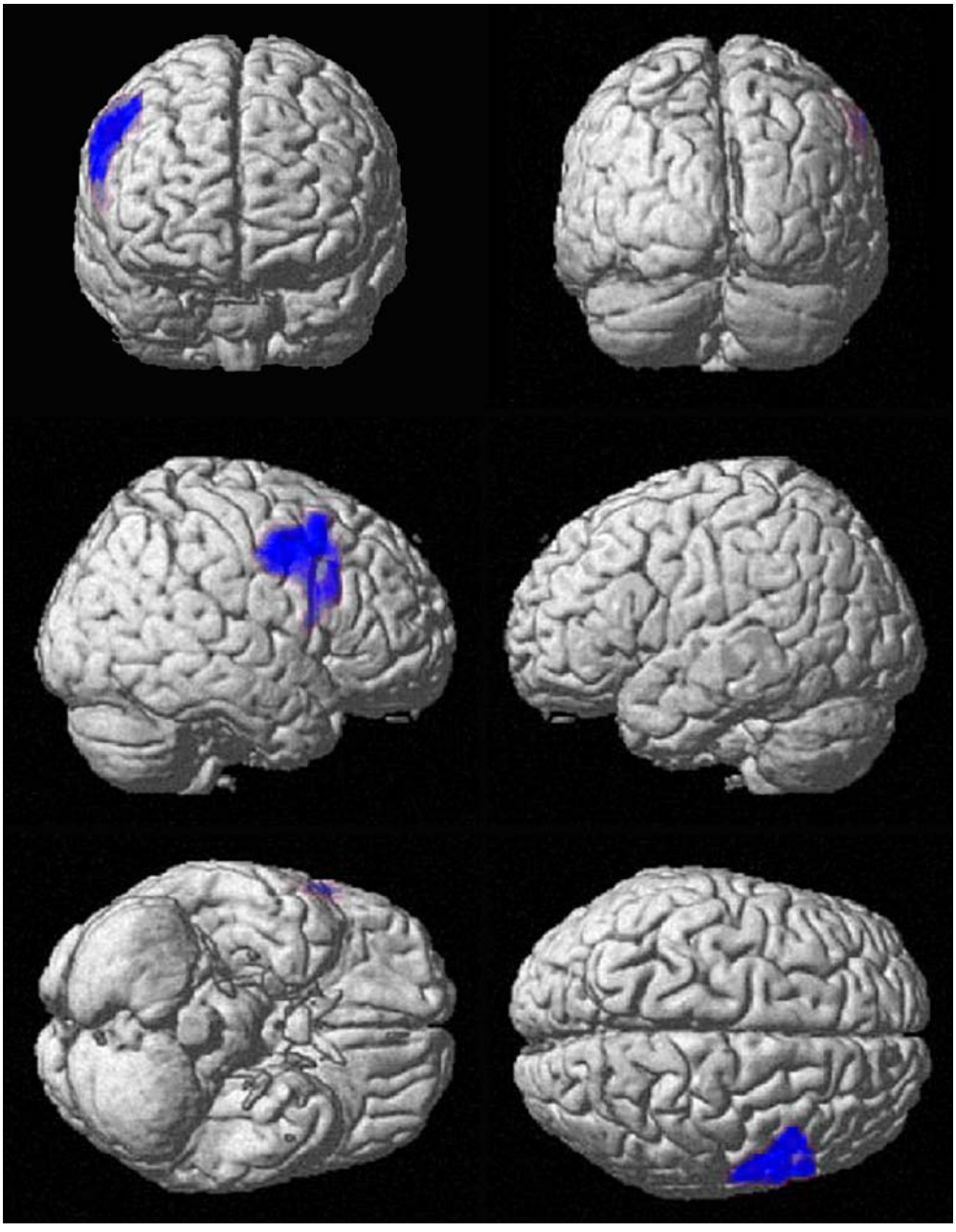

Fig. 1. 3D rendering of voxels reflecting lower tracer distribution in all patients as compared with controls

Table 2. SPM statistical output of the subtraction image resulting from normals minus all patients

Cluster p(cor)	Cluster equivk	Cluster p(unc)	Voxel p(FWE-cor)	Voxel p(FDR-cor)	Voxel T	Voxel equivZ	Voxel p(unc)	Talairach coordinates			
								x	*y*	*z*	
0.359	296	0.046	0.342	1.000	4.05	3.71	0.000	59	2	41	R middle frontal gyrus BA6
			0.672	1.000	3.32	3.12	0.001	50	17	43	R middle frontal gyrus BA8
			1.000	1.000	2.86	2.73	0.003	59	22	24	R inferior frontal gyrus BA9

our atypical patients may reflect the previously reported increased severity of depression in atypical versus non-atypical depressives [9], as well as a tendency towards a more episodic course in the non-atypicals.

The clinical impression that atypical patients are more anxious was supported by the finding of higher anxiety scores in this group of patients as compared with the non-atypicals. Reporting severe pain was common in both groups, and four atypical and six non-atypical patients have had contacts with pain specialists. The origin of the common myalgic and other pain complaints in depression [28] is unknown. A link with the morphological [26, 29] and biochemical [29] muscle cell alterations that have been demonstrated also in unmedicated depressed patients cannot be excluded. Alterations in the ^{99m}Tc-HMPAO distribution in depression may represent the neurobiological correlates of the depressive state and reflect histological abnormalities as well as patho-physiological alterations predisposing the subject to depression [30–32].

Decreased tracer uptake in depressed patients has been reported in previous positron emission tomography and SPECT investigations [1, 33, 34]. In this study the comparisons between non-atypical patients and healthy controls revealed a significant decrease in tracer uptake in large portions of the right frontal lobe and in parts of the right parietal associative cortex. When all patients were compared with controls, the cluster representing significant differences was reduced as compared with the controls minus non-atypical subtraction, covering a smaller region limited to the dorso-lateral right frontal cortex. This damping effect, due to the presence of the atypical patients, was present even though differences in tracer distribution

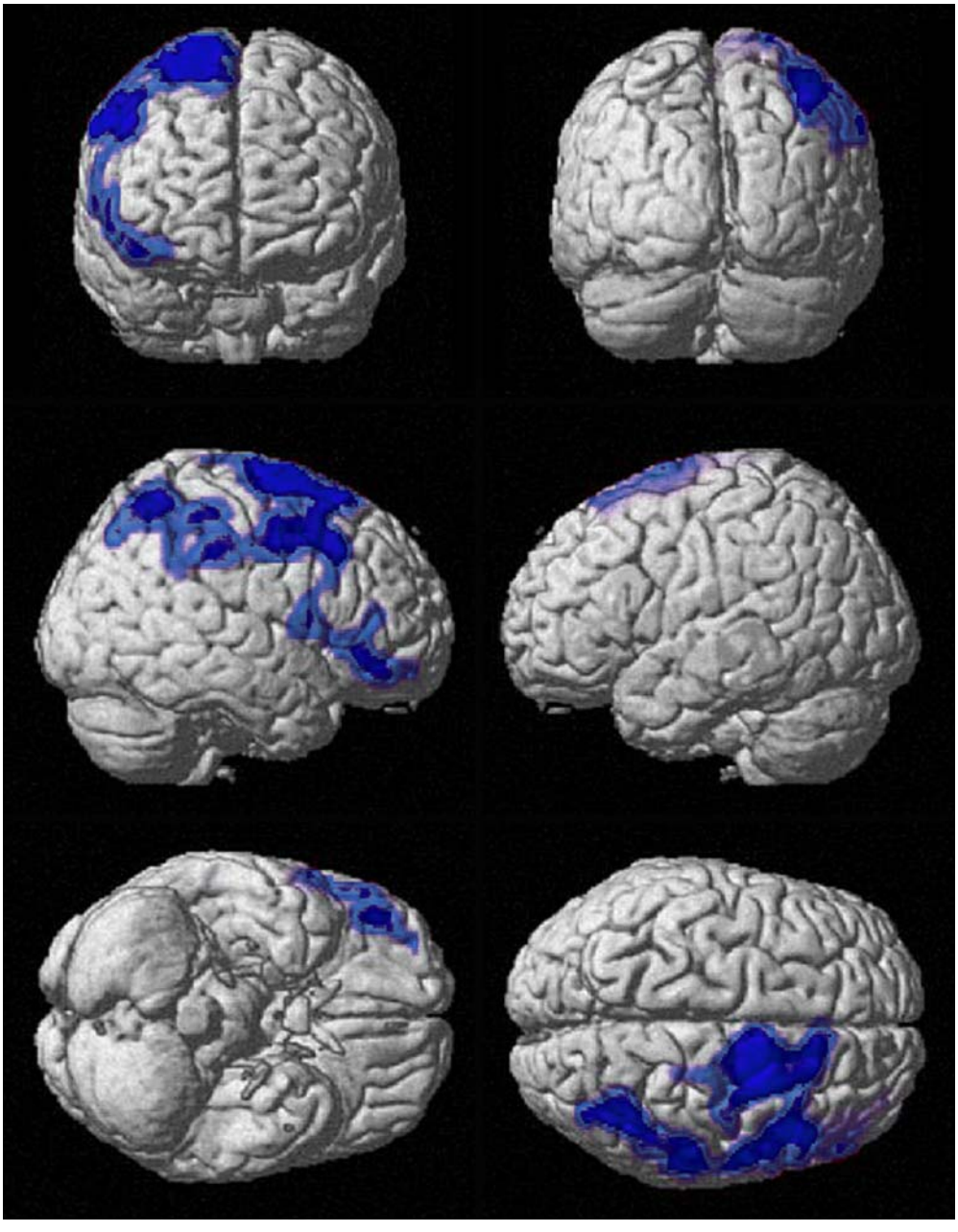

Fig. 2. 3D rendering of voxels reflecting lower tracer distribution in the non-atypical depressed patients as compared with controls

Table 3. SPM statistical output of the subtraction image resulting from normals minus non-atypical depressed patients

Cluster p(cor)	Cluster equivk	Cluster p(unc)	Voxel p(FWE-cor)	Voxel p(FDR-cor)	Voxel T	Voxel equivZ	Voxel p(unc)	Talairach coordinates			
								x	*y*	*z*	
0.000	1714	0.000	0.148	0.188	4.70	4.08	0.000	27	6	66	R superior frontal gyrus BA6 (6)
			0.209	0.188	4.53	3.96	0.000	24	3	69	R superior frontal gyrus BA6 (5)
			0.401	0.188	4.13	3.68	0.000	59	-1	41	R precentral gyrus BA6 (3)
			0.446	0.188	4.05	3.63	0.000	21	23	60	R superior frontal gyrus BA6 (5)
			0.503	0.188	3.95	3.55	0.000	50	22	38	R middle frontal gyrus BA8 (1)
			0.66	0.2	3.54	3.23	0.001	39	-53	55	R inferior parietal lobule BA40 (3)
			0.671	0.2	3.47	3.18	0.001	48	14	49	R middle frontal gyrus BA6 (3)
			0.676	0.2	3.43	3.15	0.001	59	-24	37	R postcentral gyrus BA2 (1)
			0.677	0.2	3.43	3.15	0.001	45	37	-12	R middle frontal gyrus BA11 (3)
			0.693	0.217	3.12	2.90	0.002	53	-29	51	R postcentral gyrus BA40 (3)
			1.00	0.24	2.92	2.73	0.003	59	12	5	R precentral gyrus BA44 (3)
			1.00	0.254	2.82	2.65	0.004	53	-45	35	R supramarginal gyrus BA40 (5)
			1.00	0.263	2.74	2.58	0.005	56	32	-2	R inferior frontal gyrus BA47 (1)
			1.00	0.271	2.69	2.54	0.006	53	38	9	R inferior frontal gyrus BA46 (3)
			1.00	0.271	2.68	2.53	0.006	33	55	-13	R superior frontal gyrus BA11 (1)
			1.00	0.28	2.56	2.43	0.008	59	19	21	R inferior frontal gyrus BA45 (1)

between atypical patients and controls did not reach statistical significance in any region of the brain. The decrease in the right lateral dorso-frontal cortex found in all patients versus the controls might replicate the neurobiological traits of depression widely described in the literature.

A preferential involvement of the right hemisphere has been demonstrated in the processing of emotions [35, 36], particularly negative ones [37]. Liotti and Mayberg have indicated the right dorso-lateral prefrontal cortex to be the key brain structure in emotion and cognition interactions in negative mood states [38]. This region was also described as the crucial convergence zone, being the substrate of sustained attention to the external environment and the main target of limbic-cortical influences during changes in mood state across health and disease. Our finding of lower tracer uptake in the right hemisphere in the non-atypical patients as compared with the controls might also reflect a lower ability of these patients to process emotional stimuli owing to loss of cellular constituents or impaired tissue function. The opposite might hold true for the atypical patients, in whom mood reactivity denotes an emotional over-sensitivity counteracting, when grouped with non-atypicals, the decrease in tracer distribution found in the latter group.

Upon comparison of the atypical and the non-atypical depressed patients, higher uptake was found in the atypicals in the supplementary motor area involved in movement functions (BA6), the posterior frontal associative cortex (BA8), the somatosensory cortex (BA1–3), the parietal association cortex in the superior parietal lobule (BA5 and 7), and the multimodal association cortex (BA40). Such a diffuse increase in bilateral fronto-parietal tracer uptake could have been due to the combined effect on tracer distribution of several distinct features discriminating the atypical from the non-atypical group.

Mood reactivity, the inclusion criterion for atypical depression and thus present in all our atypical patients, is likely to result in higher uptake of the tracer owing to the presence of traits of hysteroid dysphoria and irritability in

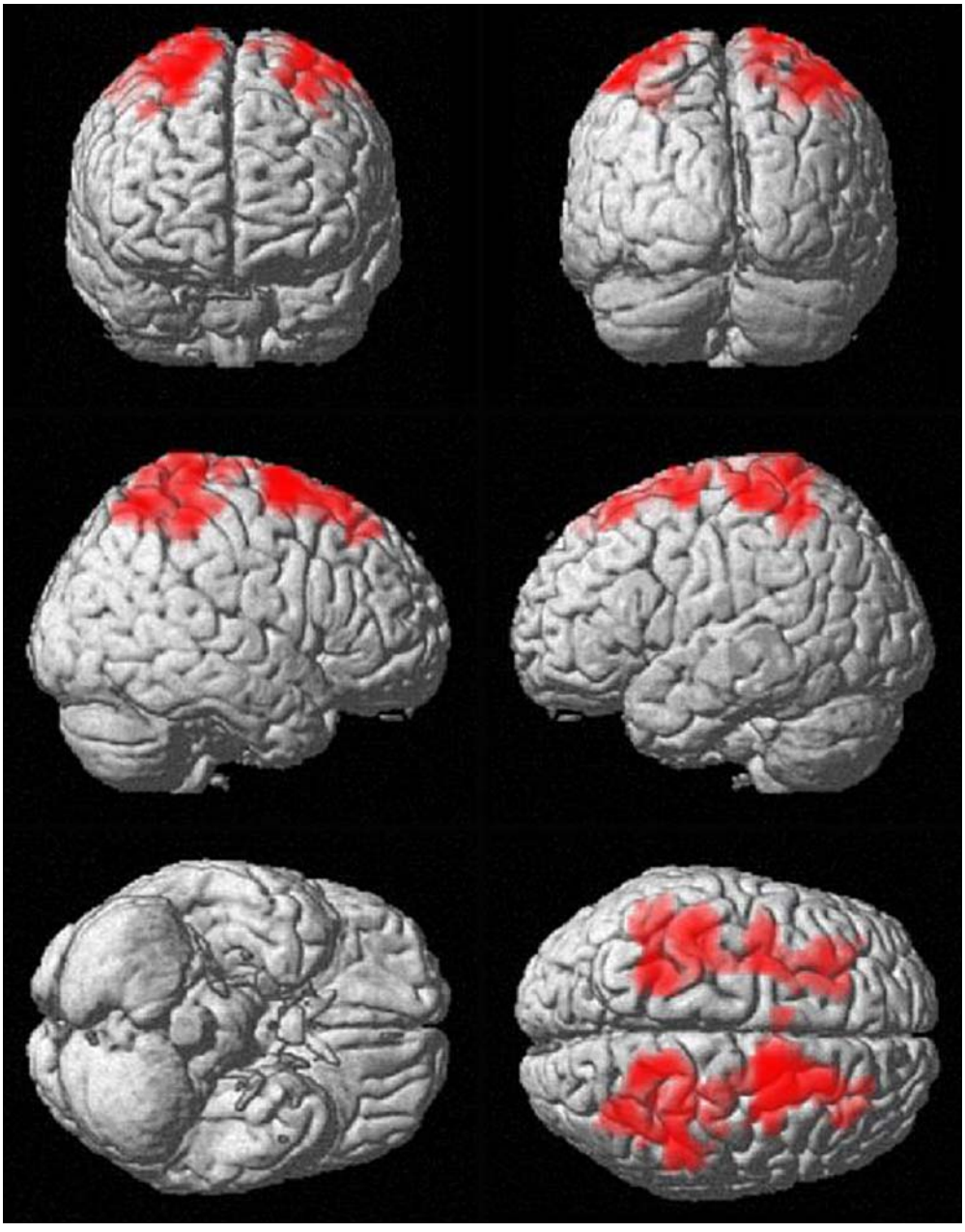

Fig. 3. 3D rendering of voxels reflecting higher tracer distribution in the atypical as compared with the non-atypical depressed patients

these patients [39]. Furthermore, an important role for anxiety has been suggested in atypical depression [10] and it has been reported to be directly proportional to the CBF [40].

"Leaden paralysis" was present in all our patients with atypical depression. This might reflect the involvement in atypical depression of brain regions known to be the neurobiological substrates for motor and sensory-motor functions, such as BA6 in the frontal cortex and BA1–3, BA5 and BA7 in the parietal cortex [41]. Higher tracer uptake was found in these BAs in our patient sample. In keeping with our findings, previous studies have reported higher tracer uptake in the medial and upper frontal regions in patients with chronic fatigue syndrome when compared witho depressed patients [42, 43].

In the only functional brain imaging study of atypical depression we are aware of, Fountoulakis et al. [14] performed region of interest analyses and found that, compared with controls, patients with atypical depression had higher uptake of ^{99m}Tc-HMPAO at SPECT in the right frontal lobe, and lower tracer distribution in the bilateral parietal lobes, the left occipital lobe and the right thalamus. Compared with undifferentiated (not atypical or melancholic) depressed patients, atypicals had higher tracer distribution in the right frontal and bilateral temporal lobes, the right thalamus, the left globus pallidus and the bilateral caudate, and lower tracer distribution in the right occipital lobe. Consistent with this, we found a trend towards higher uptake in the atypicals compared with the non-atypicals.

On the other hand, even though in our study no differences were found between the atypical patients and

Table 4. SPM statistical output of the subtraction image resulting from atypical minus non-atypical depressed patients

Cluster p(cor)	Cluster equivk	Cluster p(unc)	Voxel p(FWE-cor)	Voxel p(FDR-cor)	Voxel T	Voxel equivZ	Voxel p(unc)	Talairach coordinates			
								x	*y*	*z*	
0.000	2322	0.000	0.213	0.216	5.03	4.03	0.000	15	4	72	R superior frontal gyrus BA6 (11)
			0.44	0.216	4.46	3.70	0.000	−27	29	57	L superior frontal gyrus BA8 (11)
			0.487	0.216	4.36	3.64	0.000	−36	3	63	L middle frontal gyrus BA6 (5)
			0.602	0.216	4.06	3.45	0.000	−45	−26	62	L postcentral gyrus BA1 (3)
			0.682	0.216	3.64	3.17	0.001	33	−29	71	R postcentral gyrus BA3 (9)
			0.684	0.216	3.62	3.15	0.001	21	26	59	R superior frontal gyrus BA6 (5)
			0.685	0.216	3.61	3.15	0.001	27	−41	49	R sub-gyral BA40 (9)
			0.687	0.216	3.57	3.12	0.001	50	−32	57	R inferior parietal lobule BA40 (1)
			0.693	0.216	3.35	2.97	0.002	27	40	48	R middle frontal gyrus BA8 (3)
			0.693	0.216	3.33	2.95	0.002	15	−38	63	R postcentral gyrus BA3 (3)
			0.694	0.216	3.33	2.95	0.002	−30	−41	49	L inferior parietal lobule BA40 (9)
			0.694	0.216	3.30	2.93	0.002	−45	−47	58	L inferior parietal lobule BA40 (3)
			0.694	0.216	3.27	2.91	0.002	−9	9	71	L superior frontal gyrus BA6 (9)
			0.694	0.216	3.27	2.91	0.002	36	−58	58	R superior parietal lobule BA7 (3)
			0.694	0.216	3.25	2.90	0.002	42	−35	49	R inferior parietal lobule BA40 (5)
			0.694	0.216	3.25	2.89	0.002	−24	−43	71	L postcentral gyrus BA5 (9)
			1.00	0.216	3.12	2.80	0.003	42	−17	67	R precentral gyrus BA6 (11)
			1.00	0.216	3.08	2.76	0.003	18	−49	74	No GM found
			1.00	0.216	2.95	2.67	0.004	−59	−44	49	L inferior parietal lobule BA40 (5)
			1.00	0.216	2.94	2.66	0.004	45	−47	60	R inferior parietal lobule BA40 (7)

GM grey matter

the healthy controls, the presence of a sub-threshold difference in tracer distribution between atypicals and controls was suggested by the effect on the statistical outcome of the group of atypicals once they were merged with the non-atypicals and compared with controls. Such a statistical impact might be due to the spread of subliminal changes in the hemispheres that do not significantly cluster in specific regions when comparing the tracer distributions of atypicals and controls.

The discrepancy with the findings of Fountoulakis et al. may have even been due to methodological issues. In this respect, Bonne et al. recently demonstrated that, owing to methodological differences, results cannot be directly compared when ROI analysis and SPM are used in different studies [44]. Summarising inconsistent results that have been reported for brain imaging in depression, Videbech concluded that skewed age and gender distributions, and different symptom profiles, may explain the differences in results across studies [45].

Conclusion

We found lower right hemisphere tracer uptake in the whole group of patients, and particularly in the non-atypicals, as compared with the controls. Higher tracer uptake was found in the atypical as compared with the non-atypical depressed patients in an extended network involving brain regions linked to motor and sensorimotor functions and to the association cortices. The latter findings encourage further studies on the possible involvement of extensive parts of the bilateral fronto-parietal cortex as neurobiological substrates for various symptoms in atypical depression.

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