Cerebral perfusion after a 2-year remission in major depression

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Abstract

Although patients suffering from major depression respond to antidepressant treatment within several weeks, full reinstatement of premorbid capabilities requires much longer. Nevertheless, most research in major depression seeking the pathophysiological correlates of remission has focused upon the acute post-treatment period. Brain imaging research offers no exception. We have recently shown that cerebral perfusion in depressed patients responding to 6-wk antidepressant medication increases in parieto/cerebellar regions and becomes similar to that of healthy control subjects. We now present technetium-99m hexamethylpropylene amine oxime single-photon emission computed tomography (99mTc-HMPAO SPECT) data collected from 11 of these patients 2 years in remission. Images were analysed using Statistical Parametric Mapping. After 2 years, perfusion normalization found immediately after treatment was maintained, with further increases in frontal and decreases in parieto/cerebellar regions. These findings suggest that perfusion increases in parieto/cerebellar regions may be involved in acute response to treatment whereas increases in frontal regions may be related to its consolidation.

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Introduction

Patients suffering from major depression typically respond to treatment with antidepressant medication or electroconvulsive therapy (ECT) within several weeks. However, it is long established that full reinstatement of premorbid capabilities, if at all, requires much longer (Judd et al., 2000). Most of the research in major depression performed to date, including brain imaging research, has focused upon cross-sectional comparisons between depressed and healthy subjects, or pre-post treatment comparisons in depressed patients who respond to treatment (response generally defined as an improvement of 50% in a rating scale for depression). Therefore, only little data in the neuroimaging literature are available regarding putative changes in brain structure or function in the phase of ‘rehabilitation’, i.e. the time period between the initial ‘response’ to treatment and resumption of full health.

Cross-sectional studies typically show increased metabolism and/or perfusion in depressed patients in ventral frontal and prefrontal regions and decreased metabolism and/or perfusion in more rostral regions within the cingulate gyrus and dorsolateral prefrontal cortex (DLPFC). In other regions postulated to play a role in the pathophysiology of depression, such as limbic/paralimbic regions and basal ganglia, findings have been inconsistent (Drevets et al., 2002; Mayberg, 2003). Although this diversity in findings may reflect various factors, it should be pointed out that technetium-99m hexamethylpropylene amine oxime (99mTc-HMPAO) single-photon emission computed tomography (SPECT) findings in patients with major depression are much more homogenous, showing decreased perfusion in DLPFC, rostral and ventral anterior cingulate cortex, amygdala and basal ganglia (Smith and Cavanagh, 2005).

Data regarding longer term findings in depression are scanty. A significant reduction in cerebral blood flow (CBF), measured by the xenon-133 (133Xe) rCBF
technique, was observed in remitted depressed patients 0–3 months after ECT (Silfverskiold et al., 1986), with return to baseline 4–12 months after the end of treatment (Silfverskiold and Risberg, 1989). In contrast, another study using the same technique reported a significant increase in the left frontal region after 6 months of antidepressant (amitriptyline and amineptine) treatment (Passero et al., 1995). SPECT evaluation of rCBF using $^{99m}$Tc exametazime before and 9–28 months after treatment for major depression revealed significant bilateral increases in the basal ganglia and inferior anterior cingulate cortex. Increases were also found in the thalamus and posterior cingulate cortex on the right (Goodwin et al., 1993). An HMPAO SPECT study reports normalization of left anterior frontal deficits 1 yr after pretreatment evaluation in 35 remitted depressed patients. Patients were treated with citalopram, nortriptyline or ECT (Navarro et al., 2002). O$^{15}$ H$_2$O PET imaging of depressed patients who responded to 6 wk of serotonin selective reuptake inhibitor (SSRI) treatment (Mayberg et al., 2000), and of a different group of remitted depressed patients after 18 months of SSRI treatment, shows a similar perfusion pattern at both time-points with hypoperfusion in Brodmann area (BA) 25 (subgenual cortex) and hyperperfusion in the rostral anterior (BA 24) and posterior (BA 31) cingulate gyri (Liotti et al., 2002; Mayberg, 2003). A FDG PET study reported significant decreases in metabolism after maintaining remission for 3 months compared to a baseline-depressed scan in left prefrontal, anterior temporal and anterior cingulate cortex, bilateral thalamus, bilateral putamen and cerebellum (Holthoff et al., 2004).

In the present study we used $^{99m}$Tc-HMPAO SPECT to evaluate rCBF in depressed patients who were treated with medication and maintained remission for 2 yr (long-term follow-up). SPECT scans at long-term follow-up were compared with pretreatment scans and scans acquired immediately after treatment as a part of an earlier study (Kohn et al., 2007). Thus we were able to assess rCBF in the same group of patients before, shortly after and long after attaining remission.

**Methods**

**Subjects**

Participants in this long-term study were drawn from a larger group of patients suffering from major depressive disorder (MDD), according to DSM-IV criteria, who underwent HMPAO SPECT before and immediately after an acute course of treatment with antidepressant medication or ECT (Kohn et al., 2007). For inclusion into the current study patients had to meet criteria for full remission [21-item Hamilton Rating Scale for Depression (HAMD; Ecdeu, 1976) score of $\leq$7] after the acute phase of treatment, maintain remission and continue medication throughout the 2-yr duration of the study. ECT-treated patients were not included in this phase of the study because their rCBF perfusion pattern after acute treatment significantly differed from that of medication responders (Kohn et al., 2007; data available on file).

Seventeen antidepressant-treated patients [nine treated with SSRIs, eight treated with tri- or tetracyclic antidepressants (TCAs)] from the parent study met remission criteria (HAMD scores of 5.3 $\pm$ 2.1 and 5.1 $\pm$ 2 respectively) after acute treatment. Of these, four relapsed, one was lost to follow-up and one maintained remission but discontinued medication. Thus, 11 medicated patients [six female, age (values are ±s.d.) 49 $\pm$ 16 yr, HAMD score 4.1 $\pm$ 2.2] with MDD in remission were eligible for participation in the current study. Patients’ HAMD scores before treatment were 27.1 $\pm$ 5. For five depressed patients the current episode was the first depressive episode and for six a recurrence (range 2–5 previous episodes).

Five patients were treated with paroxetine (25 $\pm$ 10 mg/d), one with fluoxetine (20 mg/d) and five with clomipramine (140 $\pm$ 29 mg/d). Patients were evaluated ($^{99m}$Tc-HMPAO SPECT scan, psychiatric interview, HAMD questionnaire) before treatment, after 6 wk medication and 25 $\pm$ 2 months after the first, pretreatment assessment. Patient scans were compared with those of a matched control group comprising 25 healthy subjects (13 female, age 49 $\pm$ 15 yr). Inclusion and exclusion criteria and sociodemographic characteristics for patient and control groups are described in detail elsewhere (Kohn et al., 2007). The research protocol was approved by Hadassah–Hebrew University Medical Center Helsinki Committee. All participants signed the appropriate informed consent forms.

**SPECT imaging**

All SPECT scans were performed between 09:00 and 10:00 hours. Images were acquired with a double-headed gamma camera (Helix, Elscint, Israel) with two rectangular 540 × 400 mm field-of-view (FOV) detectors, equipped with low-energy, ultra-flared fan-beam collimators. Twenty mCi (740 MBq) of $^{99m}$Tc-HMPAO were injected into each subject 20 min after placement of an in-dwelling i.v. catheter, while resting supine in a quiet, darkened room with eyes open and ears unplugged. Patients were placed in the SPECT gantry...
with head immobilized in a head holder and positioned in the centre of the FOV. Sixty projections were obtained over 360°, with 25 s acquisition time per projection. Spatial resolution of the system is 11 mm full width at half maximum (FWHM), and 1000 Kcounts per head. Immediately after the end of the acquisition, corrections for centre of rotation, isotope decay, sensitivity and scanning velocity were implemented. Processing included spatial normalization, back-projection, filtering, transaxial reconstruction and attenuation correction (Chang method). Reconstruction of the transaxial datasets was performed with 1-pixel-thick (3.655 mm) slices using ramp-filtered back-projection.

Data analysis

Images were realigned to the Montreal Neurological Institute (MNI) brain atlas, resampled to pixel size 2 × 2 × 2 mm and smoothed with an isotropic Gaussian kernel with a FWHM of 10 mm. Each image was normalized to the mean total activity within the brain. Pixels below 80% of the global mean were removed. Data were analysed using Statistical Parametric Mapping (SPM2; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/), implemented on a Matlab platform. Initial voxel threshold was set at \( p < 0.05 \) and minimum cluster extent was 50 voxels; only clusters with a significance level, corrected for multiple comparisons, of \( p < 0.01 \) are reported. Wherever findings were significant according to these criteria, MNI coordinates of the most significant voxel are reported (see Table 1), and since extensive clusters were found, coordinates of additional separate maxima within the clusters were also reported. Unpaired \( t \) tests were used for comparisons between patient and control groups, and paired \( t \) tests were used to compare pre-, immediate and long-term post-treatment scans within depressed patients group.

Results

Results of all comparison of rCBF between depressed patients after a 2-yr remission and their rCBF before and immediately after acute treatment; as well as comparison with healthy controls are listed in Table 1. No differences in rCBF were observed between medication- treated depressed patients after 2 yr in remission and healthy controls. rCBF of remitted depressed patients at this time was significantly higher than their rCBF before the beginning of treatment (when depressed), in bilateral orbitofrontal cortices and left dorsolateral frontal cortex, as shown in Figure 1. This increase in frontal lobe perfusion was

### Table 1. A comparison of regional cerebral blood flow (CBF) between depressed patients after a 2-yr remission (\( n = 11 \)) and the same patients before and immediately after acute treatment (healthy controls, \( n = 25 \))

<table>
<thead>
<tr>
<th>Comparison</th>
<th>( p )</th>
<th>Voxel of maximal difference</th>
<th>Cluster size (voxels)</th>
<th>Regions of higher CBF (one or more clusters)</th>
<th>Main structures in regions of higher CBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients time 1 vs. patients time 3</td>
<td>n.s.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients time 3 vs. patients time 1*</td>
<td>0.004</td>
<td>–50, 50, –4</td>
<td>7734</td>
<td>Bilateral orbitofrontal, left dorsolateral frontal</td>
<td>Rectal gyrus (L), rectal gyrus (R), orbital gyrus (L), inferior frontal gyrus (L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–50, 28, 20</td>
<td></td>
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<td></td>
<td>–36, 4, –22</td>
<td></td>
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<tr>
<td>Patients time 2 vs. patients time 3</td>
<td>&lt;0.001</td>
<td>–16, –62, 70</td>
<td>10823</td>
<td>Bilateral parietal lobes and cerebellum</td>
<td>Posterior cingulate (L), postcentral gyrus (L), medial cerebellum (L), medial cerebellum (R)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–24, –44, 60</td>
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<td></td>
<td></td>
<td>–14, –36, 66</td>
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<tr>
<td>Patients time 3 vs. patients time 2</td>
<td>n.s.</td>
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<tr>
<td>Controls vs. patients time 3</td>
<td>n.s.</td>
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<tr>
<td>Patients time 3 vs. controls</td>
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</tbody>
</table>

Time 1, before treatment; Time 2, immediately after treatment; Time 3, 2-year follow-up. Controls (\( n = 25 \)); Patients (\( n = 11 \)); n.s., non- significant (\( p > 0.01 \)). Voxel of maximal difference = units in MNI coordinates. Main structures in regions of higher CBF defined as those in which >30% of the structure is included within a significant cluster of voxels; L, left; R, right.

* This comparison is presented in Figure 1.
also noted when the 2-yr follow-up scans were compared with scans done immediately after treatment, but did not reach statistical significance. The regions of increased rCBF on long-term follow-up were more anterior than the regions in which rCBF increased immediately following treatment. In contrast with the increase in right parietal CBF immediately after treatment found in the previous study (Kohn et al., 2007), CBF in remitted patients decreased in the left parietal cortex and in bilateral cerebellar regions when scans in long-term remission and immediately after treatment were compared.

Discussion

We present cerebral perfusion correlates of long-term remission in medication-treated patients. Our previous findings suggest that perfusion deficits in medication-treated depressed patients are reversible and largely normalize upon acute response to treatment (Kohn et al., 2007). In the present study we demonstrate that normalization of CBF is consolidated in medication-treated patients in remission for 2 yr.

Consistent with previous HMPAO SPECT reports (Smith and Cavanagh, 2005), we previously found (Kohn et al., 2007) that rCBF in depressed patients before treatment was lower than in healthy controls over much of the frontal lobes, insular cortex, and subcortical nuclei. Response to medication was associated with a widespread increase in cerebral perfusion, most prominent in mid/posterior cortical regions and cerebellum but also discernible in frontal regions. The increase in perfusion was related to the change in clinical status rather than to the effect of medication per se. We now show that rCBF in remitted, medication-treated patients became even more similar to that of controls 2 yr after successful treatment. This is in agreement with the few available long-term studies of depressed patients in remission (Goodwin et al., 1993; Navarro et al., 2002, 2004a). A unique advantage of this study compared to others, is that we evaluated the same patients soon after treatment as well as after long-term follow up. Thus, we were able to show that while normalization of CBF in depression is largely achieved soon after successful medication treatment and maintained after long-lasting remission, more subtle changes in rCBF continue to take place after the depressive crisis subsides. These changes may correspond to the protracted rehabilitation process often required in many depressed patients who remain considerably symptomatic after acute treatment although meeting standard treatment-response criteria (Judd et al., 2000).

Long-term CBF changes are located in two major regions: an increase in the anterior frontal lobe and a decrease in the posterior cingulate gyrus and cerebellum. Normalization of frontal lobe perfusion in parallel with response to antidepressive treatment has been the most consistent finding in previous functional imaging treatment studies of depression. The increase in frontal perfusion is compatible with previous findings of Navarro et al. (2004b) showing that reduced left fronto-cerebellar perfusion ratio is associated with positive response to antidepressant medication. The long-term increase in anterior frontal lobe rCBF could represent consolidation and extension of the partial immediate post-treatment normalization of perfusion deficits in this region.

Decreases in perfusion were observed in regions that in our previous study exhibited an increase in CBF after acute treatment: posterior cingulate, parietal and cerebellar regions. The posterior cingulate is highly connected to common frontal, subgenual cingulate, limbic, and brainstem regions considered
necessary for inducing clinical response in depression. Its ability to up-regulate activity may reflect the brain’s compensatory capacity critical for bringing about short-term response to medication and improvement in clinical state. In fact, it has been suggested that the increase in posterior cingulate perfusion may be a general marker of treatment responsivity, identifiable during the initial phase of treatment (Mayberg, 2003). Accordingly, we suggest that perfusion increases in the posterior cingulate in the acute treatment phase (Kohn et al., 2007) are related to the initial response to medication, and that perfusion in this region normalizes once it completes its adaptive role. Cerebellar modulation of neural circuits linking prefrontal, posterior parietal, superior temporal and limbic cortices has also been described (Schmahmann, 2000, 2004). Although not traditionally considered a major contributor to the neurocircuitry of mood regulation, cerebellar dysfunction is known to influence cognition and affect (Rapport et al., 2000; Schmahmann, 2004). Interestingly, reduction in cerebellar glucose metabolism after 6 months of remission has recently been reported (Holthoff et al., 2004). Thus, increased perfusion and function in both cerebellum and posterior cingulate may facilitate treatment response during the acute phase of treatment, with a gradual return to baseline levels once an initial rapid response to treatment has been achieved.

The distinction between trait- (or non-reversible) and state-related perfusion deficits in depression is complex. Partial or full normalization of reduced CBF in depressed patients who respond to medication is consistent with lower CBF being a state marker for depression, and is supported by other studies with similar results (Bonne et al., 1996; Mayberg, 2003). Evidence for trait changes of CBF in depression is less abundant. Liotti et al. (2002) have found similar and unique (compared to controls) CBF changes in response to mood induction experiments both in acutely depressed and remitted patients. Depression is also associated with persistent structural brain changes, such as frontal cortex and hippocampal volume reduction (Sheline, 2003; Videbech and Ravnikilde, 2004). However, given that magnitude of decrease is ~5%, conceivably without reduction in cerebral blood flow or metabolism unit volume, it may not be captured by SPECT imaging. Data from post-treatment and long-term follow-up studies combining functional and structural imaging are needed to further elucidate these issues.

The present study has certain limitations. The inclusion of only medication-treated patients in remission for the long-term comparison lowered the size of our cohort and limited the power of our study, potentially inducing type II error. However, the differences we found appear widespread and robust. Furthermore, additional safeguards were used to prevent random error, such as setting statistical thresholds for significance at levels lower than usually employed. It should be noted that in all results reported in this study, as in most other studies cited, variations reported in regional cerebral perfusion are relative to global brain activity, and absolute differences in perfusion are not measured. It should also be noted that while resolution and sensitivity of the SPECT perfusion technique are not as high as those of PET, for example, a great deal of high-quality research has been done using HMPAO SPECT. It may be argued that at least partly, the long-term perfusion changes observed in our remitted cohort reflect continued medication treatment. A definite answer to this possibility would require a comparison with untreated depressed patients in remission. Since cessation of medication after response to treatment would clearly be unethical, such research is currently unfeasible. Studies of administration of antidepressants to healthy control subjects show that medication may (Bonne et al., 1999) or may not (Geday et al., 2005) affect cerebral perfusion. While the study showing an effect for medication was an O\(^{15}\) H\(_2\)O PET study that examined subjects on the same day of antidepressant administration, the negative study, performed several years ago by our group using \(^{99}\)mTc-HMPAO SPECT, examined antidepressant effect upon cerebral perfusion after 6 wk of treatment and may therefore be somewhat more similar to the current long-term study. In addition, and in a similar time-frame to that of our fluoxetine paper, in the current study cerebral perfusion did not change in medicated depressed patients who did not respond to treatment (Kohn et al., 2007).

Another limitation of our study is the absence of a repeated long-term (e.g. 2-year) scan of healthy control subjects. Although the presence of such comparison would have been useful, since our analysis is based upon perfusion ratios, we do not expect a major change in any given brain region in healthy subjects within a period of 2 yr. Thus, a longitudinal \(^{99}\)mTc-HMPAO SPECT study in dementia found no change in cerebral perfusion in a group of healthy control subjects studied after a 2-yr time-interval (Brown et al., 1996). Finally, previous long term post-treatment depression studies (Goodwin et al., 1993; Navarro et al., 2002, 2004a, b) have also not included repeated scanning of healthy controls.

To summarize, in this pilot study we found that cerebral perfusion in remitted depressed patients...
normalizes after a 2-yr period of clinical stabilization and rehabilitation. However, the initial rapid increase observed in our study of short-term effects (Kohn et al., 2007), followed by the currently demonstrated gradual decrease in perfusion in posterior cingulate, parietal and cerebellar regions, relative to the continuous and gradual increase in perfusion in frontal regions suggests that the former regions may be particularly involved with the first phase of clinical improvement whereas the latter may be more implicated with the achievement of full remission and preservation of wellbeing. Further long-term prospective research utilizing larger patient groups is indicated for several reasons. First, to replicate our findings and advance our understanding of brain mechanisms involved in mediating acute and longer term remission from depression. Second, to examine whether such mechanisms differ between patients treated with ECT and pharmacotherapy. Third, and on a more clinically oriented note, prospective functional imaging studies may enable detection of CBF patterns associated with response or resistance to treatment (acute phase) and relapse or maintenance of remission (longer time-frame).

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Statement of Interest

Professor Lerer is Editor-in-Chief of the International Journal of Neuropsychopharmacology.

References


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