Functional imaging, affective disorder and dementia

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Perfusion imaging has had modest success thus far in mood disorder. The most consistent findings in both primary major depression and in secondary depression have been reductions in inferior frontal cortex, adjacent cingulate cortex, temporal cortex and basal nuclei. They are compatible with a primary network for the integration of emotional experience in inferior frontal cortex, striatum and amygdala which is partially supported by the findings from relevant lesions and activation studies in normal controls. There are additional findings implicating dorso-lateral prefrontal and adjacent medial/limbic cortex in some patient groups. In elderly men particularly, reductions in prefrontal cortex appear to correlate with cognitive impairment.

In dementia, perfusion imaging with single photon emission tomography (SPET) is becoming established as an important clinical tool ancillary to neuropsychological testing. Quantitation and statistical definitions of regional abnormality will be worthwhile innovations as camera systems become more technically advanced.

Perfusion imaging

Contemporary neuroscience has increasingly progressed by identifying where, as well as what, events occur in the brain in association with particular behaviours. This emphasis on functional anatomy is the particular strength of the methods for imaging which have been employed in recent years for the investigation of brain function in normal subjects and increasingly in patients with psychiatric disorder. Those methods based on brain perfusion only will be considered in detail. They require the detection of the distribution of appropriate isotopes, using either positron emission tomography (PET) or single photon emission tomography (SPET or SPECT), or so-called functional magnetic resonance imaging (fMRI). The current cost of PET means that it is unlikely ever to be widely available for clinical use, in contrast to SPET.
and fMRI. The technical background to these methodologies can be found in appropriate review articles\textsuperscript{1-3}, although understanding the physics is less important than understanding the physiology. The energy supply for neurones comes primarily from glucose which must be delivered to the brain continuously by its blood supply. Uptake of non-metabolisable 2-deoxyglucose (2-DG) gives a measure of this process\textsuperscript{4} and a method based on $^{18}$F-2-DG is available for PET studies in man. In practice, this fully quantitative measure of metabolism must be made over 30 min or more, which is inconveniently long and requires relatively high radiation exposure. However, regional brain perfusion or blood flow is also intimately yoked to local neuronal activity and thereby to local neuronal metabolism. Detecting regional perfusion allows the sampling of brain activity over a much shorter time interval than is possible with 2-DG. In addition, the signal associated with local dynamic changes in brain perfusion may actually exceed the demand for substrate and so amplify the relationship between neuronal activity and local blood supply\textsuperscript{5}. Detection of brain perfusion forms the basis of $^{15}$O-labelled water methods for PET and the $^{99m}$Tc-exametazime method for SPET. There is good reason to think that the measures from either method are closely correlated, although the SPET method cannot be made fully quantitative\textsuperscript{6}. The relative uncoupling between supply of, and demand for, substrate is believed to form the basis for the T2* signal detected in the currently most widely adopted fMRI methodology\textsuperscript{3}. Indeed, the term blood oxygen level dependent (BOLD) imaging has sometimes been used as a synonym for fMRI. More ways in which MRI may be adapted for measuring brain physiology are given elsewhere in this issue. fMRI has yet to make a significant contribution to our understanding of the functional anatomy of the affective disorders and dementias.

A few small problems

The disadvantages of all techniques for perfusion imaging lie in the uncertain relationships between perfusion, metabolism and neuronal activity. The activity of terminals is likely to dominate the metabolic response because large ionic fluxes will require more energetic compensation for small structures than for large ones. However, an 'increase' may, of course, represent activity in excitatory or inhibitory terminals. In relatively large and complex structures it is seldom likely to be possible to say what circuits are actually active and it seems quite possible that opposite effects of activation and de-activation may prevent a net signal. Even if the underlying change in neuronal metabolism has an unambiguous meaning, the coupling between it and local vascular
response may have a different gain in different brain areas or during different transient processes; it is also unlikely to be strictly linear. This means that parametric studies that depend upon the magnitude of the signal must be subject to a variety of unknown biases. Finally, the vascular response imposes a rate limiting filter that will distort the potentially rapid underlying changes in neuronal activity.

The objections to perfusion imaging should not obscure its current practical importance in offering a unique means to identify the tomographic locations of dynamic changes in human brain function. It is a unifying method which brings together evidence from traditionally separate disciplines for the development of brain based cognitive neuroscience. It also has the potential for serving as a functional index of drug action in psychopharmacology; the actions of specific agonists or antagonists may allow inferences about the balance of regional neurotransmitter function in man (see Grasby et al., this issue). Finally, perfusion imaging offers the potential for looking at the differential effects of psychological activation in different morbid states.

Statistical analysis of the enormous number of measurements made in imaging studies has generated two main methods. In the simplest, regions of interest are drawn from an atlas or the aligned structural scans of the same patients and by combining data from large numbers of picture elements or pixels, the number of comparisons is reduced to a reasonable size. By contrast, a pixel-by-pixel approach allows functional regions of interest to be defined post hoc (see also Friston, this issue). This is valuable when there are no compelling a priori hypotheses to identify a particular region or regions of interest especially when focal effects are likely (e.g. in activation studies). Pixel-by-pixel analysis for comparisons of groups of subjects requires individual brain shapes to be transformed into standard co-ordinates and the higher spatial frequency signals of the images must be heavily filtered; it otherwise makes maximal use of all the available data. Region of interest analysis is most appropriate when the hypothesis to be tested assumes a defined anatomy and the effects being sought are relatively diffuse. So far the primary interest of perfusion imaging for psychiatric conditions has been in the investigation of baseline function where either approach appears potentially informative.

**Major depression**

**Differences between depressed patients and controls or other patient groups**

In a majority of studies, reductions of function in anterior brain structures have been described in depressed patients compared with
Table 1  A summary of the main published perfusion imaging studies in major depression

<table>
<thead>
<tr>
<th>Method</th>
<th>CON/MD</th>
<th>Mean age</th>
<th>Drug-free</th>
<th>Localisation</th>
<th>Effect size</th>
<th>Correlation</th>
<th>Laterality</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>195Xenon</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathew et al 1980</td>
<td>13/13</td>
<td>30</td>
<td>2 weeks</td>
<td>Global</td>
<td>-0.5</td>
<td>Neg</td>
<td>None</td>
<td>NK</td>
</tr>
<tr>
<td>Warren et al 1984</td>
<td>18/18</td>
<td>65</td>
<td>?</td>
<td>Global</td>
<td>-1.9</td>
<td>None</td>
<td>None</td>
<td>NK</td>
</tr>
<tr>
<td>Uytdenhof et al 1983</td>
<td>20/6</td>
<td>51</td>
<td>2 weeks</td>
<td>Frontal</td>
<td>+1.0</td>
<td>NK</td>
<td>L &gt; R</td>
<td>NK</td>
</tr>
<tr>
<td>Gur et al 1984</td>
<td>25/14</td>
<td>30</td>
<td>No</td>
<td>Global</td>
<td>-0.2</td>
<td>None</td>
<td>None</td>
<td>NK</td>
</tr>
<tr>
<td>Silverskiold 1989</td>
<td>31/31</td>
<td>56</td>
<td>No</td>
<td>Global</td>
<td>-0.16</td>
<td>Pos (Depr/rel)</td>
<td>None</td>
<td>NK</td>
</tr>
<tr>
<td>Schule et al 1989</td>
<td></td>
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<td></td>
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<tr>
<td>Baxter et al 1989</td>
<td>12/14</td>
<td>34</td>
<td>2 weeks</td>
<td>Anterolat frontal</td>
<td>-ve</td>
<td>Neg</td>
<td>None</td>
<td>NK</td>
</tr>
<tr>
<td>Hurwitz et al 1990</td>
<td>6/6</td>
<td>26</td>
<td>1 week</td>
<td>Inf &amp; sup frontal, temporal, parietal</td>
<td>-ve</td>
<td>NK</td>
<td>R &gt; L</td>
<td>NK</td>
</tr>
<tr>
<td>Martinot et al 1990</td>
<td>10/10</td>
<td>49</td>
<td>No</td>
<td>Inf &amp; sup frontal</td>
<td>-ve</td>
<td>?Pos (suicidal ideation)</td>
<td>L &gt; R</td>
<td>NK</td>
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<tr>
<td>Post et al 1987</td>
<td>18/13</td>
<td>?</td>
<td>13 days</td>
<td>Temporal</td>
<td>+ve</td>
<td>None</td>
<td>R &gt; L</td>
<td>NK</td>
</tr>
<tr>
<td>112O PET</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bench et al 1992</td>
<td>23/33</td>
<td>57</td>
<td>No</td>
<td>Ant cing. Sup frontal, parietal</td>
<td>-ve</td>
<td>Neg (Depr/rel)</td>
<td>L &gt; R</td>
<td>NK</td>
</tr>
<tr>
<td>Dreves et al 1992</td>
<td>33/13</td>
<td>36</td>
<td>3 weeks</td>
<td>Sup frontal</td>
<td>+ve</td>
<td>Neg</td>
<td>L &gt; R</td>
<td>NK</td>
</tr>
</tbody>
</table>

A summary of the main published perfusion imaging studies in major depression. Numbers are of controls and unipolar patients are given as CON/MD, mean age refers to the patient group, effect sizes are given for studies giving global flow values (-ve implies reductions in major depression), and the sign of the main effect where results do not lend themselves to a comparable single statistic. Correlation is with severity (Hamilton score) unless specified; negative implies reduced perfusion correlating with symptom severity. Laterality is given where the effect appears to be greatest on one side, and gender where the effect is greatest in either sex (NK means data not analysed to be informative in this respect).
controls. Table 1 summarises the findings using different scanning techniques and illustrates the important variations between them. Age is a particularly critical variable and reduced global flow is most likely in older subjects. Lateralisied effects, while often discussed, are very inconsistent. Tomographic methods have usually localised the greatest hypoperfusion in frontal, temporal and parietal areas. In frontal regions, inferior or orbital cortex tends to be more consistently implicated than dorso-lateral pre-frontal cortex. The largest and most spatially extensive frontal reductions may be most likely in older patients and particularly in males. In PET and SPET studies, such reductions in function could be an expression of associated structural change in older subjects, although there has been a paucity of investigations that directly relate structural to functional images. In any case, CT or MRI would be inadequate to identify loss of terminals in vivo. There have been no attempts to relate in vivo imaging findings to post mortem findings in affective disorder and relatively few attempts even to follow-up patients and identify the associations between perfusion decrements and the prognosis, response to treatment or the subsequent risk of dementia.

The cross-sectional findings are compatible with the view that major depression is usually associated with extensive depression of function in predominantly anterior brain structures and the pathways that interconnect them. Cross-sectional observation does not establish whether such effects relate to temporary features of the depressed state, are permanent and enduring or represent some interaction between the two.

**Cross-sectional correlations between perfusion and symptoms**

If the differences between patients and controls were simply due to the neurophysiological activity underlying the depressed state, one would expect correlations between aspects of that state and the perfusion image. The states we call major depression are many and various. As well as depressed mood, patients may describe prominent anxiety, intrusive thoughts, motor agitation or retardation, impaired capacity for any form of effortful activity, impairment of concentration and memory, disturbance of appetite, sleep and sexual function, even delusions and hallucinations. Accordingly, the scales most commonly employed to measure depressive symptoms capture either overall severity, an approach best embodied by the Hamilton Scale, or the type of symptoms present.

**Correlations with the Hamilton Scale**

Many of the studies reporting differences between patients and controls have also reported the association between regional perfusion in the
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depressed group and the severity of depression. Most of such studies have shown negative associations, i.e. a high Hamilton score tends to be associated with reduced uptake usually in those areas showing reductions compared with control series (Table 1). Such findings provide preliminary support for the idea that differences from control groups represent, in part if not in whole, state changes, with the obvious prediction that reversal of the symptoms should see a normalisation of brain perfusion. However, by no means all the published studies have actually shown the expected negative correlation (Table 1). Furthermore, the association appears to be most clear-cut in those subjects showing the most extensive frontal reductions. This is paradoxical because it is just those subjects, often elderly, in whom a contribution from enduring organic reductions in function might be expected. The corroborating finding of a reversal of the reduced function on treatment and recovery is described below.

**Association between specific symptoms and regional brain perfusion**

The syndrome of major depression is associated with impairment of neuropsychological function, particularly in the mnemonic and psychomotor domains. Measured neuropsychological decrements appeared to be good candidates for identifying the underlying regional involvement of brain areas in affective disorder and have been the subject of several studies in recent years. The first such study in younger patients with major depression\(^9\)\(^{-10}\) showed relative sparing of fluency, block design and other conventional tests of dorso-lateral pre-frontal function and clear cut impairment of cognitive function in the mnemonic and psychomotor domains: the severity of depression was related to the impairment and there was a corresponding pattern of reduced perfusion with SPET implicating inferior frontal cortex and temporo-parietal cortex. The actual correlations between cognitive impairment and brain perfusion were confined to a relatively small number of areas in posterior cingulate cortex and basal nuclei\(^9\). The correlations were positive, implying increased activity as a critical correlate of impaired function and, perhaps, a failure to de-activate posterior cingulate cortex which is known to have an important role in complex attentional mechanisms\(^11\). A comparable correlation with increased perfusion in posterior cingulate cortex\(^12\) was for a factor described as ‘anxiety’, but which also loaded weight loss, anergia, insomnia and agitation. These two studies were among the largest to employ tomographic imaging and although they clearly recruited slightly different patient populations, such a focal common finding may be worth highlighting. It raises the possibility that
the level of activity in posterior cingulate cortex is a core determinant of
the depressive state and the wide network of reciprocal connections to
frontal areas may underlie a variety of the associated symptoms.

Factor analysis can always be used arbitrarily to reduce many
measured clinical variables to a few dimensions, although it is unlikely
to yield consistent results in different populations. It reached its fullest
expression in the five publications that have resulted from the single
cross-sectional $^{15}$O-PET study of the MRC Cyclotron Unit on major
depression$^{12-16}$. The relationship between brain perfusion and the
unrotated first principal component of the data set, which would have
reflected severity, was not described. The factors loading cognitive
impairment and retardation mapped to mesial frontal and adjacent
cortex. This largely paralleled the finding with SPET for older male
patients with marked frontal decrements which correlated with
psychomotor slowing$^{17}$. It seems quite possible that structural change
may have contributed to these findings at the macroscopic$^{18}$ or
microscopic levels. Functional imaging generates questions for other
disciplines better equipped directly to address the functional integrity of
frontal projections in the elderly$^{19}$.

**Correlations with depressive sub-type**

The best validated division of symptoms within the existing literature
relates to the difference between endogenous or melancholic symptoms
and the neurotic pattern, traditionally seen as reactive to life events. It
was claimed that patients could be dichotomised into groups showing
primarily endogenous and primarily neurotic patterns of illness using the
Newcastle Scale$^{20}$, although more recently it has been argued that the
scale represents a dimension$^{21}$. Despite its arbitrary nature, interest is
now justified by the association between Newcastle Scale scores and
ratings on the CORE system, a sign rather than a symptom-based
typology for depression which may embody the critical association
between melancholic or endogenous illnesses and motor disorder$^{22}$.

Austin et al$^{20}$ showed increased uptake in dorso-lateral pre-frontal
cortex in association with high Newcastle Scores. This finding may imply
a tendency for younger, more endogenous patients to show uptake which
may even exceed control values, as in a highly selected group with strong
family history$^{23}$. What is unsure is whether ongoing mental state
characteristics are different in such patients. It is possible, for example,
that increased frontal activity reflects increased activation in association
with frequent negative thoughts or ruminations. Reductions may be more
likely in patients with impoverished mental states.
Limitations of the correlational approach

It is a strong expectation that the pattern of brain perfusion should reflect the pattern of activity in an ongoing mental state. In schizophrenia, the intrinsic variability of the mental state has been invoked as a reason for preferring activation studies to those conducted at baseline but depressive illness is much more clearly a stable albeit temporary state. Thus far, all imaging studies have tended to be, to a greater or lesser extent, confirmatory of the general hypothesis that depressive symptoms and the existence of a depressive illness is associated with particular patterns of abnormal activity in the brain; they have not served to take us very much further forward and to do so will require more imaginative experimental designs that address more critical models of the illnesses.

It will be possible specifically to investigate the core functions in depression, such as motivation and reward mechanisms, effortful capacity or mnemonic function. The functional anatomy of such constructs should lie within those areas frequently shown to be abnormal in depressive illness. The further apparently logical step is to carry the appropriate activation tasks into depressed patients. The particular difficulty is then how to treat discrepant performance between patient and control groups when designing comparison studies. Encoding operations, as distinct from active or efferent processes may be easier to study, but this risks ignoring critical components of the depressed state. One may define the problem to be identification of abnormal processing in patients versus controls when external performance is appropriately matched. This usually requires pacing of normal performance to match it with the abnormal performance of patients. A different pattern of activation for patients versus controls would be a novel reflection of the brain activity that underlies the depressed state. If we knew that the particular operation represented a core abnormality in depressive illness which predicted both symptoms, response to treatment, modulation by neurotransmitter challenge and outcome, then we might have a very strong argument for saying that it is the critical network involved in affective disorder.

If a task is so fundamental to a disorder that subjects are almost unable to perform it, then we might expect, simply, no activation. Some early activation studies in dementia effectively used activations the subjects could not do, with this potentially uninteresting result. Failure to activate a particular network becomes interesting if it can be shown that the same areas can be activated normally by dissociated tasks (i.e. tasks the patients can perform). This generates an alternative argument that the failure to activate a brain network for a critical task defines the abnormality that underlies the illness more precisely than a test of the sort.
defined in the previous paragraph. Indeed, the process of matching performance in patients and controls may run the risk of identifying spurious differences between the groups. This is effectively the argument used to defend the use of the Wisconsin Card Sort Test as a challenge for schizophrenia.

**Activation studies**

The choice of activation study will obviously follow from our hypotheses of what forms the core of mood disorder. Explicit inclusion of mood related experience or judgement appears to have face validity. There have already been several studies of mood induction employing standard procedures. Pardo et al. described increases in inferior orbito-frontal cortex comparing a sad state with baseline. George et al. described more widespread activation of bilateral cingulate, medial prefrontal and medial temporal cortex, basal ganglia and thalamus in a better controlled design. Interestingly, happiness produced widespread frontal, temporal and parietal reductions in perfusion compared with the sad state. The sign of the perfusion effects is thus the opposite of that expected from the clinical finding of reductions in perfusion in limbic, frontal and basal nuclei. It raises the paradoxical but interesting possibility that the patterns of reduced perfusion seen in clinical depression are dominated by mechanisms usually involved in mood enhancement.

More complex studies of emotional recognition and memory will be of great interest. A preliminary study to identify the brain regions involved in detecting emotional cues from faces has again implicated orbito-frontal and cingulate activation in volunteers. A bilateral lesion of the amygdala disrupts the recognition of facial emotion rather specifically. The representation of emotion as an attribute of others and as a personal experience could share common pathways and imaging will allow a direct approach to the problem. The way in which both relate to autonomic function has been given impetus by the findings of a disrupted autonomic response to social stimuli in sociopathic patients with orbito-frontal lesions. The prototype for such patients may have been Phineas Gage whose precise injury has been the subject of recent reconstruction. Understanding the social experience of patients in neurophysiological terms appears incredibly audacious but who is to say that our understanding of affective disorder may not depend ultimately upon it.

**Serial changes on recovery**

The most striking difference between depressive illness and other functional psychoses like schizophrenia and, indeed, Alzheimer’s disease,
Table 2  Studies employing functional scanning after clinical recovery

<table>
<thead>
<tr>
<th>Method</th>
<th>N</th>
<th>Test-retest condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{133}$Xenon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silvenskild 1989</td>
<td>18</td>
<td>Recovered after ECT (‡+drug)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Reschies et al 1989</td>
<td>20</td>
<td>Recovered (‡+drug)</td>
<td>Sup. frontal †</td>
</tr>
<tr>
<td>Nobler et al 1994</td>
<td>50</td>
<td>Recovered after ECT (27 responders)</td>
<td>Frontal †, assoc with good response (1 week after ECT)</td>
</tr>
<tr>
<td>$^{39}$mTc-exametazime</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ebert et al 1991</td>
<td>10</td>
<td>Recovered+Sleep Dep.</td>
<td>Ant. Cing., inf. frontal † (responders)</td>
</tr>
<tr>
<td>Volk et al 1992</td>
<td>20</td>
<td>Recovered+Sleep Dep.</td>
<td>Tempero-parietal † (responders)</td>
</tr>
<tr>
<td>Goodwin et al 1993</td>
<td>28</td>
<td>Recovered (16 drug free or matched)</td>
<td>Ant. Cing. (left), basal ganglia †</td>
</tr>
<tr>
<td>$^{18}$F-DG PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baxter et al 1985</td>
<td>5</td>
<td>Recovered ± drug Rx</td>
<td>Fl. Caudate † (N.S.)</td>
</tr>
<tr>
<td>Martinot et al 1990</td>
<td>10</td>
<td>Recovered+TCA</td>
<td>Sup. frontal †</td>
</tr>
<tr>
<td>Hurwitz et al 1990</td>
<td>6</td>
<td>Recovered+TCA (IMI)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Wu et al 1992</td>
<td>4</td>
<td>Recovered+Sleep Dep.</td>
<td>Ant. Cing. (responders)</td>
</tr>
<tr>
<td>$^{15}$O$_2$ PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drewes et al 1992</td>
<td>4</td>
<td>Recovered+TCA (IMI)</td>
<td>L. Sup. frontal †, Fl. Caudate † (N.S.)</td>
</tr>
<tr>
<td>Bench et al 1995</td>
<td>25</td>
<td>Recovered (15 drug free or matched)</td>
<td>Ant. Cing. (sup) †, L DLPFC †</td>
</tr>
</tbody>
</table>

Abbreviations: ECT, electroconvulsive therapy; N.S., not significant; Rx, treatment; TCA, tricyclic antidepressant; IMI, imipramine; Ant. Cing., anterior cingulate; DLPFC, dorso-lateral pre-frontal cortex

is that recovery of function is, at least in principle, complete and can be facilitated by specific psychopharmacological interventions. One of the simplest ways around the empirical difficulties with correlational studies is to examine the changes that take place when patients recover from illness. Within-subject partitioning of variance should then give a powerful indication of where in the brain change occurs most strikingly with treatment. Unfortunately, the number of patients entered in such studies has been small, not all recover or can be studied drug free and the findings are by no means consistent (Table 2); most implicate basal ganglia and mesial frontal cortex. We published the first and largest of the series using three dimensional tomography and region of interest analysis. In those patients who recovered best and could be matched drug free before and after a course of treatment, changes were localised to inferior anterior cingulate cortex and basal ganglia. Localisation of changes in basal ganglia and medial frontal cortex may implicate dopaminergic projections. A number of studies have also described normalisation of regional perfusion in dorso-lateral prefrontal cortex on recovery from depression and changes in basal ganglia (Table 2).

Bench et al also found changes in mesial frontal/cingulate cortex, but in a more superior location corresponding to the area showing the greatest reductions when the patients were most depressed. The analysis of test/retest data using pixel-by-pixel approaches must run a risk of detecting effects primarily due to regression to the mean. Other evidence
of short term changes in cingulate cortex has come from sleep
deprivation, where, for responders, two groups\textsuperscript{34,35} have described
relative hyperperfusion in anterior cingulate cortex in the depressed
state with normalisation in the recovered state. The short-term effects of
electroconvulsive therapy were also in this area and correlated with
Hamilton scores\textsuperscript{36}. The reductions in brain perfusion seen with ECT
persist after completion of treatment and are greatest in the responders\textsuperscript{37};
the dissociation of ECT effect upon perfusion from the direction of effect
expected with recovery is interesting.

**Secondary depression**

There have been a number of studies in which the pattern of brain
perfusion associated with depressive symptoms have been described in
patients with a primary organic diagnosis. In Parkinson’s disease, a
maximal decrement has been localised to superior medial frontal cortex
comparable with the previous work of the same group in primary
unipolar depression\textsuperscript{38}. However, echoing the more common pattern in
major depression (Table 1), other studies have found depressive
symptoms to be associated more with inferior frontal cortex, and
associated limbic areas (in Parkinson’s disease\textsuperscript{39}, Huntington’s dis-
ease\textsuperscript{40}). The finding of this pattern of disturbance in patients with basal
ganglia disease lends strength to the idea that the inter-connections
between inferior frontal cortex and basal ganglia are involved in the
expression of depressive symptoms. By contrast, in Alzheimer-type
dementia, more depressed patients showed increased decrements in
parietal and temporal cortex\textsuperscript{41}. While there is clearly the potential for
teasing out different aspects of mood disorder and cognitive impairment
on the basis of dissociation between either individuals or groups of
patients, so far the findings have done little more than confirm what has
been seen already in primary affective disorder.

**Studies in the dementias**

**Difference between demented patients and controls or other patient
groups**

As has already been emphasised, perfusion imaging primarily gives an
indication of anatomical localisation of abnormal functions. While this
has been of some interest in diagnosing and sub-dividing the dementias,
the real advances in diagnosis are likely to be molecular. There remains,
nevertheless, an interest in the relationship between clinical symptoms and brain localisation, identification of early dementia and the measurement of change over time. Perfusion imaging should always be complementary to, rather than a substitute for careful neuropsychological investigations since there is little evidence that perfusion imaging is itself the more sensitive method.

There has been a consensus that Alzheimer-type dementia tends to show posterior decrements in perfusion which can probably be correlated with reductions in the density of neuronal terminals in association cortex. Those studies that have made this finding have been cross-sectional and have usually entered patients with moderate to severe dementia. The observation is of clinical relevance, and has prompted quite widespread application of SPET to diagnosis. However, clinical evaluation of perfusion SPET has usually remained subjective and rested on interpretation of images rather than measurement. There seems little reason not to quantify SPET images and express abnormalities in statistical terms, but this is only emerging slowly. The sensitivity and specificity of SPET imaging needs to be defined in a quantitative way for a particular clinical contrast. Perhaps the most important of such contrasts is that between depressed patients and patients with dementia, since cognitive impairment is a consistent and striking feature of depression in the elderly and may genuinely be confounded with dementia when it reaches levels that attract the term pseudodementia. Patients with well-preserved posterior temporal perfusion and frontal deficits are more likely to be depressed than have Alzheimer dementia. The limits to this finding have been quantitatively illustrated for 99mTc-exametazime SPET and 133Xe and in a more limited study with 18F-DG PET. More difficulty will arise if cases with early dementia rather than cases with established and often severe Alzheimer's disease are entered into cross-sectional comparisons with depressed patients. It is anecdotally true that there are occasions when a SPET scan is extremely useful either in showing an absolutely typical posterior temporal parietal perfusion deficit in a patient where there is, for one reason or another, real doubt about the diagnosis; this is supported by estimates of the sensitivity and specificity for SPET with qualitative rating. More rarely, frontal lobe dementias may be confused with affective states and will usually show obvious perfusion deficits. In practice, however, the clinical uncertainty frequently results from a poor appreciation of the value of formal neuropsychological testing. Where patients present early with isolated memory problems, the role of functional imaging is even less established and may require more quantitative high resolution images of the medial temporal cortex and hippocampus. Finally, the old problem of distinguishing Alzheimer-type from multi-infarct dementia has been addressed at the level of clinical comparison. The findings suggest a
variety of differences between the syndromes, but lack the necessary clinicopathological validations. The largest study which will allow such validation is the OPTIMA project which has already suggested that there may be a role for repeated testing or combining the SPET findings with structural scans in the diagnosis of Alzheimer-type dementia. The role of structural imaging in the investigation of Alzheimer's disease is reviewed by Smith and Jobst in this issue.

Cross-sectional correlation between perfusion and symptoms

Most studies have shown an association between the degree of dementia and the extent of perfusion decrements in a range of brain areas. Left parietal perfusion seems to be particularly predictive of global cognitive impairment in probable Alzheimer's disease. By contrast, in Korsakoff's psychosis, it is frontal perfusion which appears to be correlated with cognitive difficulties. In Huntington's disease, again despite primary sub-cortical pathology, cortical decrements are again correlated with clinical features. As would be expected, frontal decrements are also associated with frontal presentations in some dementia syndromes.

In the foregoing examples the neuropsychological measures averaged a very broad spread of the impairments or symptoms associated with the diagnoses of interest. Any correlation with affected brain regions in a cross-sectional series will have been heavily influenced by global severity. Potentially of more interest, is the identification of restricted cognitive deficits, for example in semantic memory, which might, in principle, be localisable by using perfusion imaging with careful statistical comparison of single brains against normal control series using pixel-by-pixel analysis.

Progression of disease and functional imaging

While serial decline is implied by the cross-sectional correlations between cognitive impairment and brain perfusion, the trajectory of decline in individual cases might prove to be a more sensitive measure than any cross-sectional comparison could hope to be. This certainly appears to be the case with structural measures of the medial temporal lobe (see Smith and Jobst, this issue), but the full integration of quantitative functional data into such studies is awaited. By the same token, either structural imaging or perfusion imaging could act as a surrogate marker for the effectiveness of treatments, were such to become available. For the moment, information on treatments is confined to acute effects of
cholinesterase inhibitors in probable Alzheimer’s dementia in which there are apparent increases in brain perfusion\textsuperscript{66}. Interestingly, the primary action of cholinergic stimulation is to increase frontal perfusion. This may reflect the limited capacity of more directly damaged brain areas to respond to drug treatment and it may correspond to a role for frontal cortex in making the most of preserved perceptual, cognitive and executive abilities. SPET studies have also shown reversal of perfusion deficits following surgical interventions for hydrocephalus\textsuperscript{67,68} and medical intervention for temporal arteritis\textsuperscript{69}.

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**References**

15 Dolan RJ, Bench CJ, Liddle PF et al. Dorsolateral prefrontal cortex dysfunction in the major psychoses; symptom or disease specificity? J Neurol Neurosurg Psychiatry 1993; 56: 1290-4
20 Carney MPW, Roth M, Garside RF. The diagnosis of depressive syndromes and the prediction of ECT response. Br J Psychiatry 1965; 111: 659-74
24 Berman KF, Doran AR, Pickar D, Weinberger DR. Is the mechanism of prefrontal hypofunction in depression the same as in schizophrenia? Regional cerebral blood flow during cognitive activation. Br J Psychiatry 1993; 162: 183-92
29 Damasio AR, Tranel D, Damasio H. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav Brain Res 1990; 41: 81-94
31 Goodwin GM, Austin MP, Dougall N et al. State changes in brain activity shown by the uptake of 99mTc-exametazime with single photon emission tomography in major depression before and after treatment. J Affect Dis 1993; 29: 243-53
36 Noble MS, Sackeim HA, Prohovnik I et al. Regional cerebral blood flow in mood disorders. III. Treatment and clinical response. Arch Gen Psychiatry 1994; 51: 884-97


67 Waldemar G, Schmidt JF, Delecluse F et al. High resolution SPECT with (99mTc)-d1-HMPAO in normal pressure hydrocephalus before and after shunt operation. *Neurol Neurosurg Psychiatry* 1993; 56: 655–64


70 Silfverskild P, Risberg J. Regional cerebral blood flow in depression and mania. *Arch Gen Psychiatry* 1989; 46: 253–59


80 Gur RE, Skolnick BE, Gur RC et al. Brain function in psychiatric disorders. II. Regional cerebral blood flow in medicated unipolar depressives. *Arch Gen Psychiatry* 1984; 41: 695–9

81 Sackeim HA, Prohovnik I, Moeller JR et al. Regional cerebral blood flow in mood disorders. I. Comparison of major depressives and normal controls at rest. *Arch Gen Psychiatry* 1990; 47: 60–70


83 Lesser IM, Mena I, Boone KB, Miller BL, Mehringer CM. Reduction of cerebral blood flow in older depressed patients. *Arch Gen Psychiatry* 1994; 51: 677–86


91 Baxter Jr LR, Schwartz JM, Phelps ME et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 1989; 46: 243–50
