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Editorial

Towards clinically useful neuroimaging in psychiatric practice†

Deborah Cooper, Natalie Limet, Ian McClung and Stephen M. Lawrie

Summary
When psychiatrists see a patient, they consider a diagnosis, estimate a prognosis and treat accordingly, but very few of these decisions are informed by objective tests. Recent advances in neuroimaging data analysis have shown that brain scans can make powerful diagnostic and prognostic predictions in patients with psychosis and depression.

Declaration of interest
None.

Deborah Cooper (on the right of the photo) is a core trainee, and Natalie Limet and Ian McClung are senior trainees in old age psychiatry, in south east Scotland. Stephen M. Lawrie (not pictured) is Head of Psychiatry in Edinburgh University, Director of the Scottish Mental Health Research Network and Director of the MRF/MRC Clinical Research Fellowship programme for mental health ('PsySTAR').

Brain imaging in general psychiatry as it is now

Most of the major psychiatric disorders are associated with statistically significant differences on various neuroimaging measures, when comparing groups of patients and controls. These 'abnormalities' are, however, quantitative not qualitative: one cannot eyeball a brain scan to determine whether it belongs to someone with psychosis or depression. Neuroimaging, like most investigations in psychiatry, is therefore generally reserved for atypical cases with neurological or other features suggestive of physical disease. This is a rational practice, as lesion detection rates are low; although a rigorous analysis of the cost-effectiveness of neuroimaging demonstrated that routine structural brain imaging in people with psychotic symptoms could be cost-effective in samples with organic brain disease in more than 1% of patients.[1]

Lessons from dementia investigation

Practice is different in old age psychiatry, particularly in the evaluation of dementia. Patients with memory difficulties routinely get brain scans and many other tests, as recommended in clinical guidelines, to confirm the diagnosis or exclude other possibilities. Dopamine transporter scans can confirm a diagnosis of dementia with Lewy bodies, and atrophy can sometimes be seen on (serial) structural brain scans, but management-altering lesions are similarly rare as in 'functional' psychosis. Moreover, the usual neuroradiological assessment of 'dementia' is a subjective judgement of whether or not any loss of brain substance is in keeping with the patient's age.

Over-investigation is rife in medicine and costly, with sometimes hazardous exposures as well as substantial risks of finding irrelevant anomalies. We need research identifying the clinical features in psychosis or dementia that justify neuroimaging investigation. Although those studies are awaited, others have demonstrated additional clinical potential of imaging in psychiatry.

Imaging breakthroughs in psychosis

In recent years, several research groups have shown that schizophrenia can be detected years in advance of the full-blown syndrome, even with relatively simple, single variable ('univariate') analysis of structural[2] or functional[3] magnetic resonance imaging (MRI) or positron emission tomography (PET)[4] scans.[5] Functional MRI can distinguish between individuals with schizophrenia and bipolar disorder;[5,6] whereas PET has particular promise for predicting patients' antipsychotic treatment response.[5,7] Moreover, these imaging assessments generally have more positive predictive power (around 70–80%) than clinical, cognitive and other biological assessments.[5] What has not been done to any extent is to see whether combinations of multiple variables – in 'multivariate' analyses – would further increase diagnostic or prognostic accuracy, as one would expect.

Applying that principle to neuroimaging data, using more information than is available in one measure should improve predictive power. Very recently, 'pattern classification' approaches have been developed to use the information from the tens or hundreds of thousands of volume elements ('voxels') that comprise brain scans and find what combinations of these optimally discriminate between groups. In 'machine learning', an artificial intelligence system can learn from this experience to assign group membership to new data based on prior examples. The classification procedure consists of two phases: training (or learning) and testing (or applying). During the training phase, the computer finds a mathematical function that optimally separates the examples into their classes. Once this is learned it can be used to predict the group membership of test individuals, in a case-by-case fashion. This approach has been repeatedly shown to discriminate between various disorder groups and controls with ~90% accuracy. So, however, can psychiatrists! More usefully, multivoxel pattern analysis approaches of structural MRI scans have been shown to be able to predict psychosis in individuals at high risk,[8] or to predict outcome in first-episode cases,[9] with about 80–90% overall accuracy.

A diagnostic and treatment response biomarker for depression?

Machine-learning approaches have also offered very promising results in depression. A pioneering study[10] achieved 86% accuracy in correctly identifying patients with major depressive disorder, compared with controls, based on functional MRI patterns of

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activity to sad facial processing. An equally innovative study[11] developed this work, in the context of a randomised clinical trial, to correctly identify 70% of the patients who did not respond to antidepressant treatment and 89% of those who did.

In this month's *Journal*, Almeida *et al*[12] provide evidence that this approach can differentiate patients with depression on a background of either bipolar disorder or recurrent unipolar depression. Given the possible risks of antidepressants in bipolar disorder, this is an important clinical distinction. Thirty-six females in a depressive episode (18 with bipolar I disorder, 18 with recurrent unipolar depression) and 18 healthy females, had statistically significant differences in blood flow at rest, measured with arterial spin labelling (ASL), in subdivisions of anterior cingulate cortex (ACC). The focus on ACC subdivisions is well motivated given their role in mood disorders and in predicting response to treatment in previous studies. Almeida *et al* evaluated the performance of their machine to discriminate between groups using a variant of the leave-one-out cross-validation test. Here, data from all but one individual in each group is used to train the classifier, and then group membership is allocated using the brain scan of the remaining individual. This process is repeated for every combination of scans, and permutation testing used to derive a *P*-value (as the number of successful classifications out of all classification attempts). In the current study, subgenual ACC blood flow classified females with unipolar *v.* bipolar depression with 81% accuracy. Whole-brain blood flow and grey matter volume were much less successful in discriminating groups.

Inevitably, there are limitations to this study. The groups are relatively small and all female, limiting generalisability. Curiously, the univariate analyses show significant blood flow differences between females with unipolar and bipolar depression in rostral/perigenual ACC (Brodmann area BA32/24), whereas the pattern recognition analysis shows maximal discrimination in subgenual ACC (BA25). Critically, as in most such studies thus far, an independent data-set to test the classifier was not available. This is understandable given the time and money required to generate these data, but leaves the diagnostic potential as not proven.

Problems to be overcome before clinical application

Many technical and clinical issues remain. The ASL technique used by Almeida *et al* and PET scans have the potential to be quantitative tools, but are usually analysed in relative terms. Functional MRI is inherently a relative (and indirect) measure of neuronal activity. Structural MRI has the appeal of relatively easy quantification and low cost (currently around £150 for a 15-minute scan), as well as the wide availability that comes from using a standard MRI scanner without complicated imaging protocols. These considerations are important. The studies required to change clinical practice will need to be large, with truly independent data test sets, as well as generalisable to and potentially applicable in routine clinical settings. This will require scans from multiple sites. As with many technologies in medicine, there is little standardisation of how neuroimaging data are acquired, making it difficult (but not impossible) to combine data. Further, it is desirable that clinical centres can access reference data beyond those collected locally, to increase control for the impact of factors such as age, gender, genetic risk and substance misuse on brain scans, when testing the likelihood that an individual belongs to a disease or response group.

Most importantly, all the studies cited here have produced predictions for individuals but have done so after preprocessing their scans as part of a group. This is standard practice is research, to allow one to generalise from a particular data-set, but would be time-consuming and possibly not viable in practice. Novel ways of quantitatively analysing scans from individual patients have however recently been developed for structural MRI and other neuroimaging approaches and may help surmount these difficulties.[13]

The multivariate data we currently obtain from history-taking and mental state examination are haphazardly elicited and unreliably interpreted.[5] In a field as complex as psychiatry, formalised clinical decision rules or risk-prediction algorithms are more not less desirable, but there are as yet precious few examples in the literature, let alone in use. Testing the clinical impact of neuroimaging should preferably involve comparison with such systems. In an ideal world, candidate neuroimaging measures of putative clinical utility would be assessed in a clinical trial setting, including assessment of cost-effectiveness, but this would be a much more rigorous evaluation than usual in the rest of medicine.

The greatest test for neuroimaging measures in psychiatry may be whether they can validate or refine diagnostic and prognostic distinctions, for example by stratifying patients by treatment response. Distinguishing between those in a first episode of psychosis who will go on to have schizophrenia *v.* bipolar disorder could influence treatment, but not all such patients will cooperate with imaging assessments and one could simply hedge one's bets by prescribing antipsychotics. Identifying those likely to benefit from clozapine or lithium, without needless or potentially hazardous exposure to such treatment, could however be very useful.

Conclusions

Several recent studies have shown proof of concept that neuroimaging could facilitate early diagnosis, subgroup patients according to treatment response, and measure outcome in depression, psychosis and dementia. Brain scanning may soon be able usefully to predict whose symptoms will settle spontaneously, who will only need acute treatment, or who would likely benefit from maintenance therapy. All practising psychiatrists should prepare themselves for the likelihood that neuroimaging will provide objective markers that could revolutionise clinical practice.

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poems by doctors

Insomnia

Helen Chiu

Once again he has to stand guard and watch,
His heart sinks as the crimson torch
Of a glorious sunset,
Heralds the falling night, and the dreaded hours in bed.

Silently he waits for the soft caress
And the tender touch of sleep and rest.
Yet their gentle fingers elude his hand
And he never crosses the borderland,
To that velvety twilight zone,
Land of magic, world of its own.

Without sleep or dreams is the night,
Doomed is he to this eternal plight.
Rising to face a new day once more,
Tired and unrefreshed as the thousand days before.
(. . .)

Helen F. K. Chiu, Department of Psychiatry, The Chinese University of Hong Kong. This is an extract; the full poem is available from the author.

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