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Fourthly, throughout the programme, we monitor the causal mechanism targeted in a module, as well as the three overarching goals of the intervention. This enables us to track and demonstrate change with patients. Scores are also used in the regular, frequent supervision, particularly to rapidly identify cases requiring greater discussion.

Fifthly, the style that has evolved from this systematic step-by-step approach is akin to interval training: bursts of activity and intensity followed by periods of reflection and integration. Of course, within this approach, the absolute pace of the intervention remains tailored to the individual's needs and preference. Time is predominately dedicated to the implementation of strategies in day-to-day life. Substantial additional contact (e.g., telephone calls) between weekly sessions is expected. This is *not* "low intensity" working.

Finally, the clarity of the model, and strong evidence-base for each element, enables the therapeutic style to be encouraging and optimistic, often holding hope when the patient struggles (e.g., many patients with persistent delusions, right at the start, are not expecting improvement). Transparency, offering direct answers to questions, and providing expert opinion (that is accurate), in tandem with the monitoring of progress and collaborative style, helps substantiate that optimism for patients. All written materials are shared between therapist and patient. There is no separate therapist manual. The therapy booklets provide the framework and key messages of the intervention, but are not prescriptive. Creativity by both the therapist and patient is often fostered, ensuring personal meaning and successful embedding of strategies for change.

We are currently testing the full Feeling Safe Programme in a randomized controlled trial[8]. There are, of course, caveats. The approach does not benefit all patients: our target at this stage is recovery in half of patients with persistent delusions. If this is achieved, there will then be a problem of accessibility. We have developed the programme in a highly manualized form to aid later dissemination, but technological solutions may also prove important. For example, we have found that immersive virtual reality can help patients learn safety[9]. Mobile apps and web-based programs also offer alternative delivery methods[10].

New treatments for persecutory delusions obviously require empirical testing in rigorous trials. Different forms of treatment should not be regarded as a single class, given the varied mechanistic targets, delivery methods, and outcomes pursued. We believe that the concept of specificity, inherent in our approach, should be retained when evaluating treatment developments. In this way, promising routes to improved outcomes for patients with persistent delusions will not be obscured.

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Does neuroimaging have a role in predicting outcomes in psychosis?

A key difficulty in the management of psychotic disorders is that clinical outcomes are difficult to predict on the basis of the patient's clinical features. As a result, patients with psychosis are generally treated in a similar way, even though there may be marked differences in their course of illness or response to medication. However, recent research using neuroimaging suggests that, within a sample of patients with psychosis, the pattern of abnormalities may vary in relation to different clinical outcomes. This raises the possibility that neuroimaging could be used to stratify patients according to clinical outcome; subgroups of patients could then be offered different forms of treatment.

Data from a number of structural magnetic resonance imaging (MRI) studies suggest that patients with relatively poor outcomes have, compared to those with good outcomes, more marked reductions in total and regional grey matter volume, and greater ventricular enlargement[1]. However, other studies have not found a relationship between alterations in brain structure and clinical outcomes[2]. This inconsistency may reflect the use of patient samples that were small, and heterogeneous for age, stage of illness, and pharmacological treatment, all of which can affect neuroimaging findings. Moreover, clinical outcomes have often been determined retrospectively, on the basis of clinical records.

Recent neurochemical imaging studies have suggested that the response to antipsychotic medication in patients with psychosis is related to both subcortical dopamine function, as measured using positron emission tomography, and regional brain glutamate levels, as assessed using magnetic resonance spectroscopy. A good therapeutic response has been associated with elevated dopamine function and relatively normal glutamate levels, whereas a poor response has been linked to normal dopamine function and elevated glutamate levels[3]. Independent work has also linked the response to antipsychotic medication to differences in cortical gyrification[4], and to diffusion tensor imaging measures of white matter integrity[5]. However,

again, these studies involved relatively small samples, and the patients were scanned after they had been treated with antipsychotic medication: it is thus unclear whether the neuroimaging findings predated treatment or were secondary to it.

Most studies to date have related clinical outcomes to a single cross-sectional neuroimaging measure. Serial neuroimaging measurements provide data on how the brain changes over time within the same patient, and recent studies involving longitudinal scanning of patients suggest that measuring the progression of findings facilitates the prediction of outcome[6]. For example, longitudinal data from patients with first episode psychosis and from those with childhood-onset schizophrenia suggest that reductions in hippocampal volume over the first few years of illness are associated with poorer functioning at follow-up[7].

All of the studies mentioned above reported differences between *groups* of patients. However, in order for neuroimaging to be useful in a clinical setting, it must be able to facilitate outcome prediction using data from an *individual* patient. Multivariate statistical approaches such as machine learning provide a means of addressing this issue. For example, application of machine learning analyses to MRI data from patients with first episode psychosis showed that baseline neuroimaging data could predict a non-remitting course of illness over the subsequent six years with an accuracy of 72%[8].

Ongoing studies in this field are seeking to address the methodological issues that may have limited earlier work. Sample sizes can be increased through the involvement of multiple research sites. Although multi-centre studies are logistically challenging, and there are significant confounding factors associated with acquiring data on a variety of different scanners, these disadvantages are probably outweighed by the increased statistical power that results from having much larger samples. Similarly, serial neuroimaging studies are more difficult to carry out than those involving a single scan, but may provide more predictive power. Ongoing studies have also sought to enroll samples that are homogeneous with respect to stage of illness and previous treatment, and that are treated in a standardized way subsequent to scanning. A good example of this is OPTiMiSE (Optimization of Treatment and Management of Schizophrenia in Europe), a large multicenter study funded by the European Commission[1]. This involves a neuroimaging assessment of a large multi-centre sample of medication-naïve or minimally treated first episode patients, all of whom are then treated with amisulpride following a standardized protocol. Their clinical outcomes are evaluated prospectively.

Future studies may also benefit from using more than one modality of neuroimaging; there is some evidence that this may improve prediction of outcomes[9], although other data do not support this[10]. Similarly, integrating neuroimaging data with non-imaging measures that have independently been linked with altered outcomes in psychosis, such as polygenic risk score, substance use, inflammatory markers and central nervous system autoantibodies, may enhance predictive power. However, although this may be a reasonable expectation, it has yet to be tested.

Even if a neuroimaging measure is established as a robust statistical predictor of clinical outcomes, this does not necessarily mean that it can be translated into mainstream clinical practice. Financial and practical considerations will apply, such as the cost of scanning and the availability of the scanner. The development of tools that can be used in a clinical setting is likely to require neuroimaging measures that can be acquired without the need for highly specialized training or equipment. Some ongoing studies are explicitly focused on the development of such tools for psychosis (see, for instance, www.psyscan.eu).

Given that psychotic disorders are pathophysiologically heterogeneous, it is reasonable to expect that neuroimaging techniques which can identify pathophysiological differences within patient samples may be useful in predicting clinical outcomes. However, at present, it is unclear which particular neuroimaging measures will be the most useful, and whether combining these with non-imaging biomarkers will enhance their ability to facilitate prediction of outcomes in psychosis.

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The role of expectations in mental disorders and their treatment

Expectations are defined as cognitions which are future-directed and focused on the incidence or non-incidence of a specific event or experience[1]. In the treatment of mental disorders, examining and modifying patients' expectations is discussed as a central mechanism of change[2,3]. This focus on expectations does not disregard any past experiences, but considers them only of relevance if they determine predictions about future events.