Clinical staging is a tool found useful in general medicine. It defines the extent of progression of disease at a particular point in time and where a person lies along the continuum of the illness course. For example, stages of certain cancers are distinguished by assessing the extent of local invasion of tumor, lymphatic involvement, and metastatic spread. Thus, early and milder clinical phenomena are differentiated from later stages that have evidence of illness extension, progression, and/or chronicity.

From a practical perspective, clinical staging enables selection of treatments relevant to stage, such that interventions for earlier stages will be less invasive and more benign than those delivered later in the course. Again, the cancer analogy is useful: minor surgery and local radiotherapy may be appropriate for early-stage breast cancer, while in later stages this would be insufficient and more radical treatment such as mastectomy and chemotherapy may be indicated.

We have previously proposed that this model can be applied to psychiatry, at least heuristically (2,3), and hypothesized that severe mental disorders, such as schizophrenia and severe mood disorders, develop from initial nonspecific symptoms and syndromes and from a background of specific and nonspecific risk factors (e.g., genes, early environment). From the initial nonspecific clinical picture, worsening of symptoms and acquisition of new symptoms occur, together with progressive neurobiological abnormalities and related neurobehavioural deficits, until clear-cut recognizable mental disorders appear. Thus, the natural history of mental illnesses, such as psychotic and mood disorders, is theorized to consist of transition from being asymptomatic and non-help seeking, through undifferentiated general symptoms (e.g., mild anxiety), then worsening of existing symptoms and acquisition of new ones (e.g., psychotic-like experiences, substance use problems), potentially associated with behavioral and functional decline. Further progression of illness may still occur, with development of chronic symptoms, frequent relapses, and ongoing impairment, although the key point is that progression is not inevitable.

One of the points of a neuroscience approach to psychopathology research is to develop a classification system based on underlying causal processes to replace the current, purely descriptive taxonomies. While a number of nonpsychiatric conditions, such as ischemic heart disease, are diagnosed and classified based on pathophysiology rather than symptoms, this was not always the case. For example, in the 19th century, there was a detailed taxonomy of fevers based on their time course (e.g., diurnal fevers, nocturnal fevers, frequent fevers, episodic fevers, etc.). As the underlying etiopathology of disease became understood, these reified categories simply disappeared (4) and fevers became rightly seen as epiphenomena.

Linking neuroscience and psychopathology research may achieve this in psychiatry, so that symptoms are seen as manifestations of different underlying disorders.

An Initial Staging Model

Developing a staging model across all severe mental disorders is a complex effort. Here, we present a buttressing of the staging model for psychosis and severe mood disorders presented by McGorry et al. (2), using pathophysiologically based criteria. This necessarily focuses on psychotic illnesses, where we have conducted the majority of our work, but is intended to apply just as readily to severe mood disorders. Research into the early phase of psychotic disorders, particularly the ultra-high risk phase (stage Ib of our proposed model), began with Yung and McGorry (5,6) and has now extended across multiple sites. The criteria for stage Ib are based on a combination of trait and state risk factors for psychosis. These include attenuated positive psychotic symptoms, brief self-limited psychotic symptoms, and family history of psychotic disorder in combination with marked functional decline. Several longitudinal follow-up studies have assessed the predictive validity of the criteria (7–10), with rates of ultra-high-risk patients developing first-episode psychosis (stage II of our model) within 1 year between 10% and 50% (11). In the initial heuristic model, chronic schizophrenia would fall under stage IV—it is currently unknown what percentage of stage Ib patients eventually develop this stage of illness. For the purposes of this article, only these three stages will be discussed. The boundaries of the stages (shown in Table 1) are somewhat arbitrary but represent our best estimate of potential discontinuities across psychotic disorders.
Table 1. Outline of Clinical Staging Model

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Definition</th>
<th>Example Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Increased risk of psychotic or severe mood disorder. No symptoms currently.</td>
<td>First-degree teenage relatives of probands. Individuals referred to youth mental health service by primary care physicians or school counselors.</td>
</tr>
<tr>
<td>Ia</td>
<td>Mild or nonspecific symptoms, including neurocognitive deficits, subthreshold psychotic-like experiences associated with only mild functional decline, mood or anxiety symptoms that are distressing and/or have resulting in help-seeking with or without comorbid substance abuse. Mild functional change or decline.</td>
<td>Individuals who meet CAARMS criteria.</td>
</tr>
<tr>
<td>Ib</td>
<td>Ultra high risk: Moderate but subthreshold symptoms, with/without mild to moderate neurocognitive changes, comorbid substance abuse, and with functional decline.</td>
<td>Individuals who meet psychosis criteria as defined by the CAARMS.</td>
</tr>
<tr>
<td>II</td>
<td>Full threshold disorder with moderate-severe symptoms, neurocognitive deficits, and functional decline.</td>
<td>Individuals with a recurrence of stage II psychosis.</td>
</tr>
<tr>
<td>III</td>
<td>Incomplete remission or recurrence/relapse.</td>
<td>Patients with established schizophrenia with functional impairment.</td>
</tr>
<tr>
<td>IV</td>
<td>Severe, persistent, and unremitting illness as judged on symptoms and disability criteria.</td>
<td></td>
</tr>
</tbody>
</table>

In this context, we assess three key predictions of our proposed staging model. First, pathologic measures should be more abnormal in more severe stages. Second, measures showing such differences should show progressive change as patients move between the stages. Finally, treatment should be more effective in earlier stages and more benign treatments will be equally effective. After presenting the evidence for these predictions, we consider the limitations of this approach and potential confounding factors that prevent strong inferences being drawn, followed by a suggested roadmap for further study.

Pathological Measures Should Be More Abnormal in More Severe Stages

The vast majority of neuroimaging data in psychotic disorders is volumetric in nature and examines gray matter specifically. However, direct comparisons of stage IV with stage II are relatively rare. A recent anatomical likelihood estimation analysis (12) showed that gray matter decreases were far more widespread in stage IV than in stage II, predominantly in the frontal cortex. Our own work extended this to stage Ib. The brain region most commonly shown to be abnormal in schizophrenia, the lateral ventricles (13), is less affected in stage II (14) and completely unaffected in stage Ib (15). Similar results can be shown for the hippocampus (16–18), the superior temporal gyri (19,20), lateral ventricles (13), is less affected in stage II (14) and completely unaffected in stage Ib (15). Similar results can be shown for the hippocampus (16–18), the superior temporal gyri (19,20), and insula cortices (21,22), with clear evidence for an increase in volumetric abnormality across stages.

Studies of white matter structures are less prevalent but show the same pattern. The first such study (23) used a voxel-based morphometric (VBM) approach to look for white matter volume differences between control subjects, stage Ib and stage II participants. While there was significantly lower white matter volume in the right superior temporal lobe of stage Ib patients compared with control subjects, stage II patients had widespread differences. Our own work examining the thickness of the corpus callosum, a key white matter region connecting the cerebral hemispheres, also demonstrated the tendency for abnormalities to be greater in later stages of psychotic disorders. In stage IV, we observed callosal thinning in the anterior and posterior genu, as well as the isthmus, while in stage II, this was limited to the anterior genu (24). Individuals in stage Ib did not show significant thinning at all (M. Walterfang, Ph.D., personal communication; June 25, 2010).

An alternative approach to the study of white matter is to use diffusion imaging techniques. These allow a more detailed investigation of white matter integrity than standard methods and are sensitive to changes in myelination, fiber diameter, and packing density (25). Few studies directly compared stages Ib, II, and IV, but what evidence there is suggests reduced myelination or fiber density in stage IV compared with stage II (26), while stages Ib and II do not differ from each other (27).

There is no robust evidence for a difference in brain spectroscopy measures between stage II and stage IV (28), although some authors have argued for specific differences in glutamate and gluta- mine concentrations in the anterior cingulate and thalamus (29,30). There are only three published spectroscopy studies in stage Ib, of which only two perform a direct comparison with stage II. The earliest study found elevated levels of creatine in the left prefrontal region in stage Ib compared with stage II and control subjects (31), whereas the more recent study found comparable reductions of the neuronal marker N-acetylaspartate in left frontal and cingulate regions for both clinical groups (32). While interpretation in the light of staging is virtually impossible, additional study is important given that spectroscopy can measure specific neurotransmitters of interest to the development of psychosis, such as glutamate and gamma-aminobutyric acid (33).

To our knowledge, only one functional imaging article compared across stages Ib, II, and IV (34). Using a visual oddball task, Morey et al. (34) showed that, compared with control subjects, patients in all three stages had significantly reduced target-related activation in the prefrontal cortex. Quantitative assessment showed that this reduction in activation was linearly related to illness stage, such that the greatest effect was seen in stages II and IV. Similar linear relationships have been found in studies of stages Ib and II. During both an n-back and a verbal fluency task, stage II patients showed less activation across a number of brain regions (left inferior frontal gyrus, left anterior insula, anterior cingulate, bilateral inferior parietal lobule, bilateral precuneus) compared with stage Ib, who showed less activation than control participants (35). This was also reflected in the coupling between prefrontal and superior temporal regions (36) for the n-back and is similar to the pattern of findings seen in a delayed match-to-sample task (37) and an object-location paired-associate memory task (38). All of these studies have small samples, and for the latter four, it is unclear how the participants overlap, but these findings do clearly support the hypothesized pattern of impairments.
Notwithstanding the evidence presented above, there are cases where differences between stages I and II are not found or where the pattern of increasing pathology with increasing stage does not occur (for example, in amygdala volumes [17], VBM measures of the left superior temporal gyrus and insula [39], or striatal uptake of F-DOPA [40]). Clearly, not all brain networks or imaging modalities are affected in the same way by stage of illness, and indeed there are likely to be some markers that predict progression from one stage to another (41) (although these markers may be highly complex, including both areas of gray matter increase and decrease [42]). When it is recognized that the biomarkers we are seeking are likely to include vulnerability markers (present from stage 0 to stage IV and invariant), markers of progression (which might be the same for all stage transitions or differ greatly), and markers of specific stages, the task will clearly require detailed analysis of large data sets.

**Patients Who Progress Between the Stages Should Show Change in These Same Pathologic Measures**

To date, the only longitudinal imaging data across the stage Ib-stage II transition are volumetric, and all suggest progressive brain changes across the stage boundary, as predicted by the staging model. The earliest report was a small VBM study (43), which showed significant reductions in gray matter within medial temporal and orbitofrontal regions on the left, as well as the anterior cingulate bilaterally. These changes were not seen in patients who remained within stage Ib or improved clinically. These findings have since been supported by a study in separate samples at another research center (44)—changes in frontal, temporal, and parietal gray matter were seen in those who transitioned to stage II, while no changes were seen in patients who remained stage Ib. A third sample, ascertained through a genetic risk model, also replicated these results (45).

While being landmark studies, neither was without limitations, the primary one being that the changes seen in those who transitioned to stage II were not significantly different from changes in those who were stable stage Ib. Other problems included relatively thick image slices, small sample size, and concerns about registration and the VBM approach per se (46). To address some of these issues, we combined two approaches—cortical pattern matching (47) and a longitudinal cortical surface motion technique (48,49). This allowed us to examine changes over time at the submillimeter level and provided better image registration across individuals. We also expanded our sample and used images with thinner slices. In this analysis (50), we were again able to show significant reductions in patients who progressed from stage Ib to stage II. Importantly, we were able to show that these reductions were significantly greater than the changes seen in those who remained stage Ib (or remitted).

One feature of the Sun et al. (50) study that did not match our earlier study was the region of significant change, which was limited to the right prefrontal cortex. However, the regions reported by Pantelis et al. (43) (orbitofrontal cortex, anterior cingulate, and medial temporal lobe) could not be examined by the surface-based approach. Furthermore, other cortical regions of interest in psychotic disorders, such as the insula and the superior temporal gyrus, could also not be examined because the methodology could not accurately assess cortical surface motion in these deep sulci. We have recently used manual tracing methods to assess these two regions (22,51), in both cases finding significantly more rapid reductions in patients progressing from stage Ib to stage II than were seen in those remaining stage Ib (—5%/year vs. —6%/year for the insula; —4.5%/year vs. —2%/year for the superior temporal gyrus).

These changes are not limited to gray matter. In a similar approach to our initial study (43), we have shown that white matter also changes across the stage Ib-stage II boundary (52). Specifically, over the transition to stage II, there were significant reductions in the volume of the left fronto-occipital fasciculus. In contrast, those who stayed within stage Ib showed a significant increase in a region subjacent to the right inferior parietal lobule.

Overall, there is good evidence for progression of volumetric abnormalities between stage Ib and stage II. Indeed, there is evidence for pathological discontinuity between stage Ib and II, which provides some validity for the categorical staging approach rather than conceptualizing progression of illness as occurring on a continuum. However, it should be noted that the majority of this evidence comes from a single sample and needs extension into other imaging modalities.

**Treatment Should Be More Effective in the Earlier Stages, As Well As More Benign**

One assumption of clinical staging models is that patients in the early stages of illness have a better response to treatment and a better prognosis than those in later stages. Because of this, the risk-benefit ratio is altered in the early stages, meaning that treatments should be more benign. In addition, because the symptoms seen in the early stages are more nonspecific, the treatments should have broad applicability.

One potential treatment is high-dose essential fatty acid (EFA) supplementation (53). Although the mechanism of action is still unclear, EFAs may have neuroprotective properties (54) and are known to be required for normal brain development (55). In psychotic disorders such as schizophrenia, administration of a neuroprotective agent aims to prevent or minimize synaptic or neuronal damage at a stage of illness where relevant neuronal circuits are intact or only functionally impaired. Therefore, we would predict that EFAs had greatest impact in the earlier stages of the disorder. An additional point in their favor is their tolerability, making them an ideal choice of treatment for early-stage disorder.

The first supplementation studies were in chronic schizophrenia patients with tardive dyskinesia and showed moderate improvement in psychopathology (56). At least one subsequent trial was also positive (57). Two trials in stage IV schizophrenia bear closer scrutiny. In the first trial (58), patients were randomized to either eicosapentaenoic acid (EPA), docosahexaenoic acid, or placebo. All three groups showed clinical improvement, which was greatest in the EPA group. However, the sample was small and the study was statistically limited. The second larger study was also a randomized placebo-controlled trial, involving only EPA (59). The trial showed no between-group differences for any measure of psychopathology or for cognitive functioning in patients with chronic schizophrenia and residual symptoms. Overall, it seems unlikely that EFA supplementation will prove an effective treatment in stage IV (60).

There are only two trials of EFAs in stage II psychosis, both using EPA. In the first trial, 30 new or relapsed patients (i.e., not a homogenous stage II sample) who were currently unmedicated were recruited and prescribed EPA or placebo in a double-blind, randomized manner (58). After 12 weeks, one third of patients in the EPA arm required no antipsychotic medication at all, compared with all of the patients taking placebo. Those in the EPA group also showed greater improvement in symptoms. However, there were serious statistical problems with the analysis and some unusual treatment approaches (three participants in the placebo arm were put on clozapine during the trial, although this is not normally a first-line medication [61]).
A larger, more methodologically rigorous study in previously untreated first-episode psychosis patients (i.e., a clearly stage II sample) was recently reported (62). Berger et al. (62) conducted a 12-week, randomized, double-blind, placebo-controlled trial of EPA augmentation in 80 patients, looking primarily for improved symptom change and shorter time to first response. Neither outcome measure was significantly different between the treatment groups. While there was some evidence of reduced antipsychotic use (roughly 20% less in the EPA group), this did not reach significance.

The efficacy of EFAs has now also been tested in a stage Ib population (63). In this randomized, double-blind, placebo-controlled trial, the primary outcome measure was the prevention of transition to stage II psychosis, rather than symptomatic improvement. Eighty-one participants were recruited, given either a mixture of EPA and docosahexaenoic acid or placebo for 12 weeks, and then followed for a further 40 weeks, with only a 6% dropout rate. At the end of the study, 5% of the EFA group had made a transition to stage II, compared with 27.5% of the placebo group, a highly significant difference. The EFA group also had significantly lower symptom scores and improved functioning at 12 weeks, 6 months, and 12 months as compared with the placebo group.

Although not conclusive, these studies do support the prediction of the staging model that treatment can be more effective in earlier stages—indeed, EFAs appear to only be effective before stage II. Interestingly, similar findings have been reported for cognitive-behavioral therapy (CBT). A recent meta-analysis indicated that CBT was not effective in stage IV schizophrenia (64), and there is unconvincing evidence for its effectiveness in stage II (65,66).

However, as with EFAs, when delivered in stage Ib, CBT appears to significantly reduce both the likelihood of progressing to stage II psychosis (67) and the level of positive symptoms (68).

Limitations

We are aware that the evidence for clinical staging presented above is not without alternative explanations, either in part or entirely. These include the impact of neuroleptic medication (which is rarely prescribed in stage Ib but almost always present in stage II), comorbid substance use, age (and therefore developmental trajectory), diagnosis (which is generally more homogenous in later stages), and our current definitions for the transition boundaries, which may be too narrowly drawn (69). A more detailed evaluation of the impact of these factors can be found in Supplement 1.

Does Staging Have to Mean Progression?

Does a classification of stage Ib psychotic disorder imply an inexorable progression to stage II and beyond? Clearly not, given that the transition rate is under 50% in all studies (11). The meaning of stages in the presented context is that the disorder described tends to progress or may progress, rather than inevitably progresses. One reason for nontransition may be that the vulnerability the person displayed was not, in the end, fully expressed for some reason. That is, although he or she was phenotypically indistinguishable from someone who did progress to the next stage, these two people had different underlying disorders or differing severity of the same disorder. If this were the case, then they would be expected to have different underlying trait markers or risk indicators. For example, they might have different genes, neurobiology, early environmental and family influences, or different methods of coping with stress.

Alternatively a person might not make the transition from one stage to the next because he or she was prevented from doing so by some intervention or other protective (resilience) factors. For example, EFAs or CBT may prevent someone with psychotic-like experiences and functional decline (stage Ib) from developing a first episode of psychosis (stage II). Thus, those people who would have progressed from one stage to the next, but did not, should share trait markers with those who do make the transition (for example, have the same gene markers, brain structure, etc.).

It is unclear to what extent people move backward between stages, i.e., if a person in stage II responds to treatment and the symptoms are no longer above threshold, whether that person is regarded as being stage II in remission or has returned to stage I. For the latter to be so, must the neurobiological changes mentioned above also have reversed? One longitudinal study of ventricular volume in stage II suggests such a reversal (70). Some patients showed a progressive ventricular enlargement, whereas others showed marked reduction in ventricular size (more than one standard deviation). The authors suggested that this might reflect improvements in nutrition or hydration following treatment, which emphasizes how little we know about the underlying neurobiology of any of the imaging changes seen in schizophrenia (71).

Neurobiological Inferences

In this article, we have suggested that there is evidence for an increase in pathology with clinical stage in psychotic disorders, which leads to the question of what mechanism might account for this. The development of the staging model did not rely on any specific pathophysiological model of schizophrenia, not least because it was always intended to be nonspecific with respect to diagnosis (2). Instead, it would be better to embed neurobiological hypotheses about the clinical stages of severe mental illness in the developmental phase in which they arise, adolescence (72). Feinberg (73) was the first to posit a relationship between schizophrenia and synaptic pruning in adolescence, and this has been supported by evidence that age-appropriate gray matter reductions are accelerated in both childhood- and adult-onset schizophrenia (74,75). This suggests that brain systems that develop through adolescence will be most relevant to the clinical staging model. Networks that subserve reasoning, social cognition, cognitive control (particularly of emotions), motivation, and reward processing, all of which involve prefrontal cortical areas, are likely to be specifically affected. Additional pathology may arise as a result of the physiological response to mental illness, which can include altered activity of the hypothalamic-pituitary-adrenal axis (76). Both suggested mechanisms offer ways to intervene, either through supporting the normal developmental processes of adolescence or dealing with the heightened stress response after transition to stage II.

A Road Map for Future Research

There are two main research paths required for the further testing of the clinical staging model. First, we need to reduce our reliance on symptomatology for the definition of the stages and look for specific biological markers. This will require multimodal imaging studies, perhaps focusing on the brain networks that develop through adolescence. For example, studying the development of long-range neural connections, which mature later than short-range connections (77), might aid the development of altered frontotemporal connectivity as a stage specifier (36). This effort should proceed in concert with a rethinking of transition away from positive symptoms alone to include poor functioning or similar (69). This will allow exploration of whether pathology develops from local abnormality before spreading.

The second approach is to examine the pluripotential nature of stage I. While the increased risk of progression to stage II psychotic illness is well established for young people who meet criteria for

www.sobp.org/journal
stage Ib (7), it is not known whether they are also at risk for progression to stage II of any other disorder. It is also unclear whether diagnosis is even relevant to staging, given the heterogeneous nature of the current definitions of schizophrenia and major depression. Dimensions such as cognitive and psychosocial functioning and positive, negative, disorganized, and depressive symptoms may be more relevant as outcomes than categorical diagnoses per se. Studying this will require the recruitment of a large population of help-seeking young people, presenting with psychological distress but without clearly being stage II for any disorder. Comprehensive baseline assessment, coupled with rigorous longitudinal follow-up, will allow a better understanding of what outcomes are possible from stage I and what markers predict progression or remission of symptoms and disability and acquisition of new symptoms and disability.

**Summary**

The key predictions of a clinical staging model have significant support from existing literature in psychotic disorders, but many questions remain. A great deal of work remains to be done before the biomarkers of individual stages are understood.

The research described here has been supported by two National Health and Medical Research Council (NHMRC) Program Grants (ID numbers 350241 and 566529). The NHMRC had no role in the preparation, review, or approval of the manuscript. Professor Wood was supported by a Clinical Career Development Award (ID 628711) from the NHMRC. Professors Yung and Pantelis are the recipients of NHMRC Senior and Senior Principal Research Fellowships, respectively.

Professor Wood has no biomedical financial interests or potential conflicts of interest. Professor Yung has received honoraria and travel grants from Eli Lilly, Bristol-Myer Squibb, Astrazeneca, and Janssen-Cilag. Professor Pantelis has received research funding from Janssen-Cilag, Eli-Lilly, Hospira (Mayne), and Astrazeneca and honoraria and travel grants from Janssen-Cilag, Eli-Lilly, Hospira (Mayne), Astrazeneca, Pfzer, Schering Plough, and Lundbeck. Professor McGorry currently receives research support from a National Health and Medical Research Council of Australia Program Grant (number 566529) and the Colonial foundation. He has also received unrestricted research funding from Astrazeneca, Eli Lilly, Janssen-Cilag, Pfizer, and Novartis, as well as honoraria for educational and consultancy roles with Astra Zeneeca, Eli Lilly, Janssen-Cilag, Pfizer, and Bristol-Myer Squibb.

Supplementary material cited in this article is available online.

11. S.J. Wood et al.


Supplemental Information

Limitations

Medication

One potential explanation for the difference in neurobiological measures between the stages is medication, since Stage Ib patients are less likely to be treated with neuroleptics, while Stages II and above almost always are. Therefore it is possible that findings such as gray matter loss and reduced hippocampal volume are due to medication effects (i.e., the possible toxic effect of early introduction of neuroleptic medication) and not (or not solely) neurobiological processes associated with progression of psychosis. There is evidence that long-term neuroleptic treatment of primates has a widespread effect on brain volume (1, 2). However, evidence from human studies is not convincing, largely because of the difficulty in conducting placebo controlled trials of the impact of neuroleptics on imaging measures. It is clear that treatment with typical medications produces basal ganglia hypertrophy (3), which is reversible when patients are switched to an atypical neuroleptic (4). Furthermore, such medications can affect brain regions, such as the frontal cortex, that are frequently reported to be abnormal in people with the illness (5). However, it is also the case that significant volumetric reductions are found across the brain in patients who are neuroleptic-naïve (6), that progressive brain changes can occur in the absence of medication (7), and that treatment with antipsychotic medication does not necessarily induce brain changes (8). In addition, the only study to specifically examine whether changes across the Stage Ib-Stage II transition are the same in medicated and unmedicated patients found no significant differences (although it was probably underpowered for this analysis (9)). Therefore, while there may be some dynamic effects of treatment on brain structure, it seems unlikely that this explains all of the differences between Stage Ib and Stage II onwards. Nonetheless, more controlled studies are needed to accurately determine the impact of medication.
Comorbid Substance Use

Rates for current substance use in schizophrenia have been reported to be as high as 65% (10), and although rates may be lower in Stages Ib and II (11), this represents a real problem for determining the extent to which neuroimaging differences are a result of clinical stage. Chronic heavy cannabis use, for example, has been shown to result in smaller volumes of both the hippocampus and amygdala (12). Furthermore, Stage II psychosis patients who use cannabis show significantly more brain volume loss over time than those who do not (13). While cannabis-related cortical thinning in Stage II has been localized to the left dorsolateral prefrontal cortex, anterior cingulate and occipital lobe, additional reductions are seen across the brain in both users and non-users (14). Importantly, cortical thickness differences between users and non-users are not seen at baseline, suggesting that brain changes across the Stage Ib-Stage II boundary may not be related to cannabis, even if subsequent changes are. Similarly, patients with schizophrenia have significantly smaller brain volumes than controls, even after controlling for alcohol consumption (15). Clearly, more research is necessary to confirm these findings and extend them to earlier stages, but it appears unlikely that different rates of comorbid substance use alone can explain the findings presented above.

Age

One obvious confound of clinical staging is that people in Stage Ib tend to be younger than those in Stage II, who in turn are likely to be younger than those in Stage IV. For example, in our study of hippocampal and amygdala volume the mean ages for these three stages were 20.1, 21.5 and 34.9 years (16). Clearly the near fifteen-year age difference between those in Stage IV and the other two groups is likely to make a major difference to brain features (17).
Diagnosis

Another important potential confounding factor is the differing degrees of diagnostic specificity between the stages. Stage IV is essentially all schizophrenia (although there are cases of schizoaffective disorder in some studies), but Stage II (as we have defined it) is only about 50% schizophrenia with some psychotic mood disorders, etc. Furthermore, Stage Ib is very heterogeneous, with a high degree of mood disorder (18, 19). While mood disorders are included in our staging model (20), participants in the studies reported here were not staged on that basis, but only on the severity of psychotic symptoms. It is possible that this explains some of the inconsistencies in neuroimaging data. Diagnostic heterogeneity may also be relevant for response to treatment with essential fatty acids. For example, treatment with eicosapentaenoic acid (EPA) in Stage II was associated with more rapid response to antipsychotic medication, which was more marked for those with a non-affective psychosis. Further exploration of the role of diagnosis in this regard is clearly required.

Transition Boundaries

To date the only transition boundary to be operationally defined is between Stage Ib and Stage II, and is obviously arbitrary – a dividing line drawn within continuous phenomena (the intensity, frequency and duration of psychotic experiences) – although not random. Throughout this paper we have used the definition developed by Yung and colleagues as presented in the Comprehensive Assessment of Mental States (CAARMS), which was based on clinical estimates of when antipsychotic medication might first be required (21). These criteria require that the person experience at least one fully (positive) psychotic symptom several times a week for over one week. The arbitrary nature of this “Stage II threshold” can be seen if one examines in detail the CAARMS definitions for Stage Ib or Stage II status. Essentially, a change of one point – from a score of 5 to a score of 6 on, for example, the
Unusual Thought Content scale – accompanied by a one point increase in frequency in these phenomena, sustained for one week, is sufficient to redefine an individual from Stage Ib to Stage II.

Nonetheless, this threshold does have some validity, since patients on either side of it have measurably different brains, and crossing the threshold is associated with progression of neurobiological abnormalities. Further development of the staging model will require both the extension of the boundary criteria into biological measures, and a continued appraisal of the validity of the focus on positive symptoms. Already we have some inkling that such a focus may be misplaced, since some Stage Ib patients appear to make ‘trivial transitions’ to Stage II (22). Furthermore, there is evidence that some neurobiological measures, such as poor white matter integrity, can predict deterioration of social and role functioning in Stage Ib over 15 months (23). One possibility is to incorporate negative symptoms into the stage definitions, building on the work of Huber and others, although exactly how this should be done remains unclear (24).

References
