Clinical staging in severe mental disorder: evidence from neurocognition and neuroimaging

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Summary
A new approach to understanding severe mental illnesses such as schizophrenia and affective disorders is to adopt a clinical staging model. Such a model defines the extent of the illness such that earlier and milder phenomena are distinguished from later, more impairing features. Part of the appeal of such a model is that it should have cross-diagnostic applications, but to date there has been no attempt to examine imaging or neurocognitive evidence for staging in this way. We review these two domains of study with particular focus on major depression and bipolar affective disorder. Although there is some support for the staging model in affective disorders, conclusions are limited by the large variability in the clinical samples studied, especially with regard to the presence of psychotic symptoms. We suggest that future research needs to take a transdiagnostic and longitudinal approach.

Declaration of interest
None.

Clinical staging is a practical tool that has demonstrated utility in general medicine. It defines the extent of progression of disease at a particular point in time, and where a person’s condition currently lies along a continuum of the course of illness. For example, stages of certain cancers are distinguished by the extent of local invasion of tumour, lymphatic involvement and metastatic spread. Thus, early and milder clinical phenomena are differentiated from later stages that have evidence of illness extension, progression and chronicity. From a practical perspective, clinical staging enables the clinician to select treatments relevant to the stage, with less invasive interventions being more effective in earlier stages than when delivered later in the illness course. Again, the cancer analogy is useful here: minor surgery and local radiotherapy may be appropriate for early stages of breast cancer, whereas in later stages this would not be sufficient and more radical treatment such as mastectomy and chemotherapy might be indicated.

It has been proposed that the concept of a staging model can be applied to psychiatry. In particular we put forward the hypothesis that severe mental disorders, such as schizophrenia, bipolar affective disorder and severe depression, develop from initial non-specific symptoms and syndromes (i.e. a pluripotential state) and from a background of specific and non-specific risk factors such as genes or early environment. From the initial non-specific clinical picture, worsening of symptoms and acquisition of new symptoms occur, together with progressive neurobiological changes and related neurobehavioural deficits, until clearly recognisable mental disorder appears. Further progression of symptoms and neurobiological abnormalities may occur after ‘threshold’ diagnosis. Thus, the natural history of major mental illness is postulated to consist of transition from being asymptomatic and not seeking help, through a stage of undifferentiated general symptoms such as mild anxiety, depressive and somatic symptoms, followed by the worsening of existing symptoms and acquisition of new ones (e.g. psychotic-like experiences, substance use) which may be associated with behavioural and functional decline. Further progression of illness may still occur, with development of chronic symptoms, relapses and ongoing impairment. Although the staging approach has much intellectual appeal, it is still a heuristic concept with extensive research work required to develop stage markers. Previously we have examined the evidence for clinical staging in schizophrenia, with a particular focus on neuroimaging and treatment data. Here we extend this investigation to neurocognitive findings and to affective disorders.

Neurocognition
Neurocognitive impairments are a feature of severe mental illness, but it is unclear whether these impairments support a clinical staging model. In schizophrenia, cognitive impairment is large and documented across a range of cognitive domains, most notably verbal learning and memory, performance and full-scale IQ scores, sustained attention and cognitive flexibility. Similarly, moderate impairments in a number of domains are documented in bipolar affective disorder, the largest occurring in verbal learning and memory and in executive function; these are evident during euthymia and amplified when symptoms are experienced. Individuals with major depressive disorder also show neurocognitive impairment, although the affected domains are unclear; impairments have most consistently been demonstrated in verbal learning and memory, attention and executive function, although to a lesser extent than in schizophrenia and bipolar disorder.

If neurocognition is to be a reliable indicator of clinical stage, then variability in performance should indicate illness severity, chronicity and progression. In schizophrenia the relationship between chronicity and impairment is not straightforward. The magnitude of neurocognitive impairment in the first psychotic episode is equivalent to that of samples with established illness, suggesting that there is no further decline in neurocognitive ability after the onset of frank psychotic symptoms. This is supported by a lack of longitudinal evidence of progressive deterioration over illness course. A subgroup of these individuals who develop ‘deficit’ schizophrenia, characterised by a chronic illness course, prominent negative symptoms, poor functional outcome and significantly reduced cognitive performance, might show progressive impairment. However, it seems more likely that deficits are longstanding rather than associated with transition between clinical stages; cognitive deficit early in the illness course...
is predictive of poor functional outcome and negative symptoms many years later.\textsuperscript{18,19} In contrast, data from samples of people with bipolar disorder show evidence of a relationship between multiple episodes (both manic and depressive) and poorer neurocognitive performance, particularly for verbal learning and memory and for executive function.\textsuperscript{4,5} In these individuals longer illness duration is also associated with greater impairment, although not as robustly as number of affective episodes.\textsuperscript{7,8} Similarly, meta-analytic evidence from individuals with major depression suggests that symptom severity is significantly associated with neurocognitive impairment in episodic memory, executive function and processing speed, but these associations explain less than 10\% of the variance in performance.\textsuperscript{20} Other cross-sectional evidence for a relationship between other indices of severity (duration of illness, number of episodes and length of episodes) and cognitive deficits is variable and conclusions are difficult to draw.\textsuperscript{12}

Evidence regarding the longitudinal course of neurocognitive impairment in affective disorders is limited by the lack of longitudinal studies.\textsuperscript{11,12} The longest follow-up of individuals with bipolar disorder showed that cognitive impairment persisted but did not deteriorate over a 3-year period.\textsuperscript{21} Longitudinal studies of neurocognition in major depression are rarely longer than 6 months,\textsuperscript{12} making it impossible to ascertain how impairment progresses over the illness. Our understanding of the course of neurocognitive impairment in affective disorders is further complicated by the fact that state-related reductions in cognitive performance may persist over the short term, leading to the misclassification of such impairment as trait-related.\textsuperscript{5,11}

Another problem in interpreting the neurocognitive performance of individuals with affective disorders is the effect of confounding factors, which are often not controlled for in analyses.\textsuperscript{11,21} These include the impact of medication, illness subtype, age, comorbid disorders and substance use, all of which may influence cognitive performance at the time of testing. In particular, a history of psychosis is rarely reported or controlled for, yet almost all of the published research has shown that current or past psychotic symptoms are associated with greater and more broad cognitive impairments in bipolar disorder and major depression.\textsuperscript{23–27} Individuals with affective disorders without psychotic features have been shown to perform at a level equivalent to healthy controls or show only minimal impairment.\textsuperscript{28–30} The profile of individuals with non-psychotic depression is more consistent with frontostriatal dysfunction (i.e. reduced performance was most evident in attention and executive function), as opposed to the frontotemporal dysfunction associated with schizophrenia.\textsuperscript{27} In line with this, meta-analytic evidence demonstrates that the largest decrements in samples with affective psychosis are in psychomotor speed, sustained attention, verbal learning and memory and semantic fluency, similar to those observed in schizophrenia.\textsuperscript{2,3} Altogether, this suggests that psychotic rather than affective pathology is driving impairments; teasing out the effects of psychosis and other confounds is vital to our understanding of the pattern of neurocognitive impairment in affective disorder in regard to clinical staging.

The utility of neurocognition in clinical staging is enhanced if alterations in cognitive performance are evident early in the illness. Research has shown that individuals who later develop schizophrenia demonstrate poor academic performance and intellectual ability in childhood and adolescence.\textsuperscript{32–37} Furthermore, it is now accepted that individuals at ultra-high risk of psychosis also perform worse than healthy controls across a range of neurocognitive domains. Within this group, those who make the transition to frank psychosis show greater impairment than those who do not develop psychosis, primarily in the verbal domain. The most often cited reductions include lower general vocabulary or verbal IQ score,\textsuperscript{38–41} verbal learning and memory,\textsuperscript{38,39,42–44} verbal fluency\textsuperscript{43,45} and slower processing speed.\textsuperscript{38,40,46} It remains unclear whether a decrement in cognition occurs from the prodromal stage to the first-episode stage of illness. Some cross-sectional studies have demonstrated that the magnitude of impairment in the ultra-high risk group who later develop psychosis is comparable to first-episode populations, at least in overall ability,\textsuperscript{38,44} verbal IQ score\textsuperscript{41} and verbal memory.\textsuperscript{38,41} Only a few studies have followed ultra-high risk samples over the period of transition to psychosis, and these found little or no progressive impairment in neurocognitive ability.\textsuperscript{47–49} (Further information available from the authors.)

Potential early neurocognitive impairment in bipolar disorder is less well understood. There is evidence of lowered performance in unaffected relatives of patients, particularly in verbal learning and memory and some executive functions,\textsuperscript{7,50} suggesting that cognitive reductions may be trait-related. However, findings to date show neurocognition to be an unreliable indicator of future bipolar disorder. Some studies have identified intellectual and language delays and lowered visual spatial reasoning and set-shifting in young people who later developed the illness,\textsuperscript{31–53} but others found no reduction relative to healthy controls.\textsuperscript{32,33,37,54} Once again, conclusions from these studies are limited by confounding psychotic symptoms; most studies did not differentiate the outcomes of bipolar disorder with and without psychosis.

High-risk clinics do not exist for bipolar disorder in the same way that they do for schizophrenia, making it difficult to characterise neurocognitive ability immediately prior to illness onset. Only one study has assessed cognitive performance in the prodromal period of bipolar disorder by investigating the onset of this disorder in patients at ultra-high risk of psychosis.\textsuperscript{55} The authors found no difference in premorbid IQ, current IQ or global ability between individuals who developed bipolar disorder and those who did not develop either bipolar disorder or schizophrenia. It is similarly unclear which impairments might be present immediately after the onset of bipolar disorder, especially since a first episode of mania could have been preceded by a period of depression. Albus et al found that individuals with a first episode of mania without psychosis demonstrated cognitive performance that was equivalent to healthy controls.\textsuperscript{28} Two other studies of first-episode mania have shown impairment in verbal fluency, perceptual–motor ability, set-shifting and psychomotor speed/attention;\textsuperscript{56,57} however, neither study reported the prevalence of psychotic symptoms in the samples.

The evidence also suggests that early neurocognition is not useful as an indicator of later major depression. Studies of offspring of women with depression have identified a specific reduction in verbal ability\textsuperscript{58} or no decrement at all,\textsuperscript{98,60} relative to healthy controls. Interestingly, in offspring of women with depression there was an association between current depressive symptoms and performance on some indices of executive function and processing speed,\textsuperscript{69} suggesting that reductions in these domains might be related to current symptoms or occur as part of the disease process rather than being markers of vulnerability. On the other hand, evidence from a large population study demonstrated that children who later developed major depression showed poorer performance on tasks of psychomotor speed and attention at age 13 years but no reduction in other domains,\textsuperscript{53} nor deviations in motor or language development.\textsuperscript{62} Considering the evidence to date it is unclear whether cognition is impaired before the diagnosis of depressive disorder.

It is important to note that not all individuals with these severe mental illnesses show cognitive impairment. A quarter to a third of individuals with schizophrenia demonstrate ‘normal’
neurocognitive performance within the average range.\textsuperscript{30,61} Furthermore, it has been estimated that only 28% of people with major depression,\textsuperscript{30,62} and 38–41% of those with bipolar disorder,\textsuperscript{62,63} have neurocognitive impairment. It is possible that people with psychotic and affective disorders who present with neurocognitive impairments represent a different underlying disease process. Support for the concept of different disease processes comes from demographic and clinical differences between those with impaired and intact neurocognitive performance in schizophrenia and bipolar disorder.\textsuperscript{61,63} Clinical staging offers the potential to overcome artificial diagnostic boundaries by incorporating cognitive performance into stage definitions, although its usefulness is dependent on how well it can be used to predict illness progression and treatment response.

In summary, although there is some evidence that neurocognitive impairment might fit within a clinical staging framework, there are too many confounds at present for it to be incorporated into the model. Critically, these conclusions are limited by the large variability of clinical populations with affective disorders, particularly where data from individuals with and without psychotic symptoms are combined. Further, the lack of longitudinal data examining progression over time in affective disorders and comparing individuals with early-\textsuperscript{v} late-stage disorder reduces our ability to draw strong inferences.

### Neuroimaging

In addition to neurocognitive functioning, a model of clinical staging should differentiate the neurobiological correlates of the disorder’s distinct stages. Neurobiological changes associated with mental disorders do not necessarily develop in parallel with behavioural symptoms or correlate with behaviour,\textsuperscript{14} highlighting the importance of investigating both. We recently reviewed the imaging literature for psychotic disorders and showed how whereas some neurobiological changes are already present before imaging literature for psychotic disorders and showed that the importance of investigating both. We recently reviewed the imaging literature for psychotic disorders and showed that whereas some neurobiological changes are already present before the illness onset, others arise as it progresses and tend to be more pronounced with severity of illness.\textsuperscript{7,65} Similar differential patterns of biomarkers have been suggested for early \textsuperscript{v} late stages of major depression and bipolar disorder,\textsuperscript{66–69} suggesting it might also be possible to find neuroimaging markers of specific illness stages in affective disorders.

Enhanced vulnerability to psychosis is associated with grey-matter volume reductions in prefrontal, limbic and temporoparietal regions of the brain,\textsuperscript{70} whereas those who later develop first-episode psychosis have more specific reductions in the inferior frontal, superior temporal and parietal regions.\textsuperscript{70,71} Not surprisingly, therefore, individuals with schizophrenia commonly present with reductions in grey matter in the frontotemporal regions.\textsuperscript{72,73} Consistent with the predictions of clinical staging, these changes become more extensive through first-episode and chronic illness.\textsuperscript{74–77} A similar staging pattern has been observed for cortical thickness,\textsuperscript{78} and for structural abnormalities affecting white matter.\textsuperscript{79}

Progressive brain changes and increased pathological signs related to severity of illness have also been observed in affective disorders. In major depression reduced thickness of the posterior cingulate cortex has been observed in people with non-remitted disorder compared with those in remission, and decreased perfusion in frontal regions and the anterior cingulate cortex has been shown in the non-remission group compared with healthy controls.\textsuperscript{80} There are cautious suggestions that reductions in cerebral and cerebellar grey matter volume,\textsuperscript{81} as well as basal ganglia volume,\textsuperscript{82} are related to severity of illness. Furthermore, basal ganglia volume reductions have been linked to illness duration and the number of prior depressive episodes.\textsuperscript{83} With increased duration of illness, individuals with major depression have shown reduced glutamate and increased choline concentrations in ventromedial prefrontal regions,\textsuperscript{84} and (more inconsistently) a reduction in hippocampal volume.\textsuperscript{85–88} In bipolar disorder the number of episodes of illness has been related to enlargement of the lateral ventricles,\textsuperscript{89,90} and decreased cerebellar vermal volume.\textsuperscript{91} Compared with healthy individuals, grey matter density of the hippocampus, fusiform gyrus and cerebellum of individuals with bipolar disorder has been shown to reduce at an accelerated rate.\textsuperscript{92}

Many structural abnormalities such as ventricular enlargement have been repeatedly associated with both schizophrenia and affective disorders, albeit with greater enlargements in schizophrenia.\textsuperscript{8,88,93,94} Such non-specific changes perhaps reflect the presence of psychotic symptoms in the affective disorder group,\textsuperscript{8} and/or similarities relating to clinical stage. Diagnostic differences do exist, however. Smaller hippocampal and amygdala volumes have been observed in individuals with schizophrenia compared with bipolar disorder.\textsuperscript{95} Further distinctions on the basis of grey matter deficits have been made,\textsuperscript{96} and functional differences in medial frontal and visual cortex, as well as differential disruptions in white matter tracts associated with the occipital and frontal lobes,\textsuperscript{97} have been shown. Whereas volumetric reductions in brain tissue, in particular temporal lobe grey matter, are more consistently found in schizophrenia than in bipolar disorder, white matter hyperintensities are more common in affective disorders.\textsuperscript{8} Individuals with bipolar disorder additionally show enlargement of basal ganglia and amygdala, whereas those with major depressive disorder are characterised by volume reduction in these regions as well as in the hippocampus.\textsuperscript{88,98,95} Affective disorders are furthermore distinguished by increased corpus callosum cross-sectional area in major depression compared with bipolar disorder.\textsuperscript{98} These neurobiological differences may provide useful diagnostic markers in relation to the different stages of the individual disorders.

The reports of white matter pathology indicate that severe mental illness may not simply be a result of structural lesions to the brain,\textsuperscript{5} but rather of abnormal connectivity between regions.\textsuperscript{100} As early as 1998 Friston suggested that schizophrenia was caused by dysfunctional interaction in the dynamics of associated brain regions rather than by dysfunctional specialisation within a region.\textsuperscript{101} Certainly in psychotic disorders, stage of illness affects structural and functional networks differently.\textsuperscript{5} Consistent across stages of illness are findings of reduced (or in some cases increased) connectivity in frontal lobe and frontotemporal interactions, but as illness progresses these patterns become more widespread across the brain and are observed with higher frequencies.\textsuperscript{100} Progression between stages could represent weakened strength of connections or even a total loss of connections in a network with a consequential imbalance between local and global connections. Indeed, connection patterns could show alterations, resulting in a loss of function such as working memory impairment,\textsuperscript{102} or phenomena such as positive symptoms.\textsuperscript{103} Evidence for dysconnectivity in grey and white matter across all stages of this disorder, and even before onset of illness, is building.\textsuperscript{64,104–106} Suggestive of dysconnectivity in affective disorders are also rapidly emerging.\textsuperscript{5,107–109} With distinct patterns for schizophrenia and bipolar disorder being identified.\textsuperscript{110} Factors such as genetics, insults during brain development and neurotransmitter imbalance are thought to influence the process of dysconnectivity.\textsuperscript{111}

For neurobiological changes to consolidate their position in a model of clinical staging, changes caused by the illness need to be distinguished from epiphenomena. Factors such as life stress and
substance use have been related to progression in severity of illness, and individual differences in disconnectivity have been shown to relate to individual differences in symptom presentation.  

Antidepressant medication has been found to decrease resting-state functional connectivity, and the effects of medication on brain structure, volume and functioning also require further investigation. In addition, the influence of adolescent development, gender, and comorbidity should be considered. Accounting for these factors provides important challenges for the immediate future.

Current models of clinical staging do not make explicit whether an individual can move down a stage, i.e. whether a remission of symptoms is equivalent to moving from stage 2 to stage 1. However, certain functions can (at least partially) be related to individual differences in symptom severity to some extent, which should be reflected in the staging model.

Neurobiological evidence for staging in severe mental illness is still limited. Different methods adopted by the various studies make it difficult to compare findings and stress the need for future research to adopt a transdiagnostic perspective. Studies investigating disorders with overlapping features will not only be able to highlight shared neurobiological features but may provide evidence for distinct neurobiological markers important for treatment and prognosis. As adolescence is the critical period for onset of severe mental illness, studies should focus on brain networks that develop during this period. Furthermore, multimodal longitudinal studies will be crucial in monitoring transition between stages and associated neurobiological changes.

Future research

Clinical staging is a promising model for improving our understanding of the way in which severe mental illnesses develop and helping clinicians choose the most appropriate treatment. Both neurocognition and neuroimaging evidence provide tentative support for the application of a staging model to schizophrenia and affective disorders. The paradox here is that we are using the current diagnostic categories to investigate the validity of a model that explicitly attempts to negate the current categorical system. Future work needs to take a transdiagnostic and longitudinal view, covering both neurocognition and neuroimaging in order to overcome current issues.

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