

Special article

Clinical staging in severe mental disorder:
evidence from neurocognition and neuroimagingAshleigh Lin,[†] Renate L. E. P. Reniers[†] and Stephen J. Wood**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.^{1,2} 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.¹ 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.¹ 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.² 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.³ 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;^{4–7} these are evident during euthymia and amplified when symptoms are experienced.^{8,9} 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,^{10–12} 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 episode¹³ is equivalent to that of samples with established illness,³ 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.¹⁴ A subgroup of these individuals who develop 'deficit' schizophrenia,¹⁵ characterised by a chronic illness course, prominent negative symptoms, poor functional outcome and significantly reduced cognitive performance,^{16,17} 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

[†]These authors contributed equally to the work.

is predictive of poor functional outcome and negative symptoms many years later.^{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.^{4,5} In these individuals longer illness duration is also associated with greater impairment, although not as robustly as number of affective episodes.^{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.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.¹²

Evidence regarding the longitudinal course of neurocognitive impairment in affective disorders is limited by the lack of longitudinal studies.^{11,21} The longest follow-up of individuals with bipolar disorder showed that cognitive impairment persisted but did not deteriorate over a 3-year period.²² Longitudinal studies of neurocognition in major depression are rarely longer than 6 months,¹¹ 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.^{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.^{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.^{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.^{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.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.^{3,31} 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.^{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,^{38–41} verbal learning and memory,^{38,39,42–44} verbal fluency^{39,43,45} and slower processing speed.^{39,40,46} 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,^{38,44} verbal IQ score⁴¹ and verbal memory.^{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.^{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,^{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,^{51–53} but others found no reduction relative to healthy controls.^{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.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.²⁸ Two other studies of first-episode mania have shown impairment in verbal fluency, perceptual-motor ability, set-shifting and psychomotor speed/attention;^{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 ability⁵⁸ or no decrement at all,^{59,60} 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,⁶⁰ 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,³³ nor deviations in motor or language development.³² 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.^{30,61} Furthermore, it has been estimated that only 28% of people with major depression,^{30,62} and 38–41% of those with bipolar disorder,^{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.^{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- *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,⁶⁴ highlighting 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.^{2,65} Similar differential patterns of biomarkers have been suggested for early *v.* late stages of major depression and bipolar disorder,^{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 temporo-parietal regions of the brain,⁷⁰ whereas those who later develop first-episode psychosis have more specific reductions in the inferior frontal, superior temporal and parietal regions.^{70,71} Not surprisingly, therefore, individuals with schizophrenia commonly present with reductions in grey matter in the frontotemporal regions.^{72,73} Consistent with the predictions of clinical staging, these changes become more extensive through first-episode and chronic illness.^{74–77} A similar staging pattern has been observed for cortical thickness,⁷⁸ and for structural abnormalities affecting white matter.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.⁸⁰ There are cautious suggestions that reductions in cerebral and cerebellar grey matter volume,⁸¹ as well as basal ganglia volume,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.⁸³ With increased duration of illness, individuals with major depression have shown reduced glutamate and increased choline concentrations in ventromedial prefrontal regions,⁸⁴ and (more inconsistently) a reduction in hippocampal volume.^{85–88} In bipolar disorder the number of episodes of illness has been related to enlargement of the lateral ventricles,^{89,90} and decreased cerebellar vermal volume.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.⁹²

Many structural abnormalities such as ventricular enlargement have been repeatedly associated with both schizophrenia and affective disorders, albeit with greater enlargements in schizophrenia.^{5,8,88,93,94} Such non-specific changes perhaps reflect the presence of psychotic symptoms in the affective disorder group,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.⁹⁵ Further distinctions on the basis of grey matter deficits have been made,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,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.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.^{88,98,99} Affective disorders are furthermore distinguished by increased corpus callosum cross-sectional area in major depression compared with bipolar disorder.⁸⁸ 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,⁵ but rather of abnormal connectivity between regions.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.¹⁰¹ Certainly in psychotic disorders, stage of illness affects structural and functional networks differently.² 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.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,¹⁰² or phenomena such as positive symptoms.¹⁰³ Evidence for dysconnectivity in grey and white matter across all stages of this disorder, and even before onset of illness, is building.^{64,100,104–106} Suggestions of dysconnectivity in affective disorders are also rapidly emerging,^{5,107–109} with distinct patterns for schizophrenia and bipolar disorder being identified.¹¹⁰ Factors such as genetics, insults during brain development and neurotransmitter imbalance are thought to influence the process of dysconnectivity.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,^{2,112–114} and individual differences in dysconnectivity have been shown to relate to individual differences in symptom presentation.¹¹¹ Antidepressant medication has been found to decrease resting-state functional connectivity,¹¹⁵ and the effects of medication on brain structure, volume and functioning also require further investigation.^{2,70,100,113,116,117} In addition, the influence of adolescent development,^{2,90,100,113,118,119} gender,¹⁰⁰ and comorbidity,^{2,86,120,121} 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 recovered.^{122,123} Furthermore, brain volume abnormalities seem to be potentially reversible (in first-episode psychosis),¹²⁴ or at least to lessen with continued development in childhood-onset schizophrenia.¹²⁵ This suggests regression in severity of illness 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, multi-modal longitudinal studies will be crucial in monitoring transition between stages and associated neurobiological changes.²

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.

Ashleigh Lin, PhD, **Renate L. E. P. Reniers**, PhD, School of Psychology, University of Birmingham, UK; **Stephen J. Wood**, PhD, School of Psychology, University of Birmingham, UK, Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Australia

Correspondence: Professor Stephen Wood, School of Psychology, University of Birmingham, Edgbaston B15 2TT, UK. Email: s.j.wood@bham.ac.uk

References

- McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry* 2006; **40**: 616–22.
- Wood SJ, Yung AR, McGorry PD, Pantelis C. Neuroimaging and treatment evidence for clinical staging in psychotic disorders: from the at-risk mental state to chronic schizophrenia. *Biol Psychiatry* 2011; **70**: 619–25.
- Heinrichs RW, Zakzanis KK. Neurocognitive deficits in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 1998; **12**: 426–45.
- Quraishi S, Frangou S. Neuropsychology of bipolar disorder: a review. *J Affect Disord* 2002; **72**: 209–26.
- Savitz J, Solms M, Ramesar R. Neuropsychological dysfunction in bipolar affective disorder: a critical opinion. *Bipolar Disord* 2005; **7**: 216–35.
- Robinson O, Sahakian B. Recurrence in major depressive disorder: a neurocognitive perspective. *Psychol Med* 2008; **38**: 315–8.
- Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord* 2009; **113**: 1–20.
- Bearden CE, Hoffman KM, Cannon TD. The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. *Bipolar Disord* 2001; **3**: 106–50.
- Kurtz MM, Gerraty RT. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology* 2009; **23**: 551–62.
- Zakzanis KK, Leach L, Kaplan E. On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry Neuropsychol Behav Neurol* 1998; **11**: 111–9.
- Douglas KM, Porter RJ. Longitudinal assessment of neuropsychological function in major depression. *Aust N Z J Psychiatry* 2009; **43**: 1105–17.
- McClintock SM, Husain MM, Greer TL, Cullum CM. Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. *Neuropsychology* 2010; **24**: 9–34.
- Meshulam-Gately RI, Giuliano AJ, Goff D, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology* 2009; **23**: 315–36.
- Szöke A, Trandafir A, Dupont M-E, Méary A, Schürhoff F, Leboyer M. Longitudinal studies of cognition in schizophrenia: meta-analysis. *Br J Psychiatry* 2008; **192**: 248–57.
- Carpenter WT, Heinrichs DW, Wagman AMI. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* 1988; **145**: 578–83.
- Fenton WS, McGlashan TH. Antecedents, symptom progression, and long-term outcome of deficit syndrome schizophrenia. *Am J Psychiatry* 1994; **151**: 351–6.
- Cohen AS, Saperstein AM, Gold JM, Kirkpatrick B, Carpenter WT, Buchanan RW. Neuropsychology of the deficit syndrome: new data and meta-analysis of findings to date. *Schizophr Bull* 2007; **33**: 1201–12.
- Milev P, Ho BC, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry* 2005; **162**: 495–506.
- Lin A, Wood SJ, Nelson B, Brewer WJ, Spiliotacopoulos D, Bruxner A, et al. Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. *Schizophr Res* 2011; **132**: 1–7.
- McDermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. *J Affect Disord* 2009; **119**: 1–8.
- Lewandowski K, Cohen B, Ongur D. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychol Med* 2011; **41**: 225–41.
- Balanza-Martinez V, Tabares-Seisdedos R, Selva-Vera G, Martinez-Aran A, Torrent C, Salazar-Fraile J, et al. Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. *Psychother Psychosom* 2005; **74**: 113–9.
- Martinez-Aran A, Vieta E, Reinares M, Colom F, Torrent C, Sanchez-Moreno J, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry* 2004; **161**: 262–70.
- Torrent C, Martínez-Aran A, Daban C, Sánchez-Moreno J, Comes M, Goikolea JM, et al. Cognitive impairment in bipolar II disorder. *Br J Psychiatry* 2006; **189**: 254–9.
- Glahn DC, Bearden CE, Barguil M, Barrett J, Reichenberg A, Bowden CL, et al. The neurocognitive signature of psychotic bipolar disorder. *Biol Psychiatry* 2007; **62**: 910–6.
- Fleming SK, Blasey C, Schatzberg AF. Neuropsychological correlates of psychotic features in major depressive disorders: a review and meta-analysis. *J Psychiatr Res* 2004; **38**: 27–35.
- Hill SK, Keshavan MS, Thase ME, Sweeney JA. Neuropsychological dysfunction in antipsychotic-naïve first-episode unipolar psychotic depression. *Am J Psychiatry* 2004; **161**: 996–1003.
- Albus M, Hubmann W, Wahlheim C, Sobizack N, Franz U, Mohr F. Contrasts in neuropsychological test profile between patients with first episode schizophrenia and first episode affective disorders. *Acta Psychiatr Scand* 1996; **94**: 87–93.
- Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Færden A, et al. Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders

- depends on history of psychosis rather than diagnostic group. *Schizophr Bull* 2011; **37**: 73–83.
- 30 Rund BR, Sundet K, Asbjørnsen A, Egeland J, Landro NI, Lund A, et al. Neuropsychological test profiles in schizophrenia and non-psychotic depression. *Acta Psychiatr Scand* 2006; **113**: 350–9.
 - 31 Bora E, Yucel M, Pantelis C. Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *Br J Psychiatry* 2009; **195**: 475–82.
 - 32 Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry* 2002; **59**: 449–56.
 - 33 Cannon M, Moffitt TE, Caspi A, Murray RM, Harrington H, Poulton R. Neuropsychological performance at the age of 13 years and adult schizophreniform disorder. Prospective birth cohort study. *Br J Psychiatry* 2006; **189**: 463–4.
 - 34 David AS, Malmberg A, Brandt L, Allebeck P, Lewis G. IQ and risk for schizophrenia: a population-based cohort study. *Psychol Med* 1997; **27**: 1311–23.
 - 35 Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *Am J Psychiatry* 1999; **156**: 1328–35.
 - 36 MacCabe JH, Lambe MP, Cnattingius S, Torrang A, Bjork C, Sham PC, et al. Scholastic achievement at age 16 and risk of schizophrenia and other psychoses: a national cohort study. *Psychol Med* 2008; **38**: 1133–40.
 - 37 Reichenberg A, Weiser M, Rabinowitz J, Caspi A, Schmeidler J, Mark M, et al. A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *Am J Psychiatry* 2002; **159**: 2027–35.
 - 38 Eastvold AD, Heaton RK, Cadenhead KS. Neurocognitive deficits in the (putative) prodrome and first episode of psychosis. *Schizophr Res* 2007; **93**: 266–77.
 - 39 Pukrop R, Ruhrmann S, Schultze-Lutter F, Bechdolf A, Brockhaus-Dumke A, Klosterkötter J. Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. *Schizophr Res* 2007; **92**: 116–25.
 - 40 Seidman LJ, Giuliano AJ, Meyer EC, Addington J, Cadenhead KS, Cannon TD, et al. Neuropsychology of the prodrome to psychosis in the NAPLS Consortium: relationship to family history and conversion to psychosis. *Arch Gen Psychiatry* 2010; **67**: 578–88.
 - 41 Woodberry KA, Seidman LJ, Giuliano AJ, Verdi MB, Cook WL, McFarlane WR. Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. *Schizophr Res* 2010; **123**: 188–98.
 - 42 Brewer W, Francey S, Wood S, Jackson H, Pantelis C, Phillips L, et al. Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *Am J Psychiatry* 2005; **162**: 71–8.
 - 43 Kim HS, Shin NY, Jang JH, Kim E, Shim G, Park HY, et al. Social cognition and neurocognition as predictors of conversion to psychosis in individuals at ultra high risk. *Schizophr Res* 2011; **130**: 170–5.
 - 44 Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, et al. Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biol Psychiatry* 2006; **59**: 863–71.
 - 45 Becker HE, Nieman DH, Dingemans PM, van de Fliert JR, De Haan L, Linszen DH. Verbal fluency as a possible predictor for psychosis. *Eur Psychiatry* 2010; **25**: 105–10.
 - 46 Riecher-Rossler A, Pflueger MO, Aston J, Borgwardt SJ, Brewer WJ, Gschwandtner U, et al. Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. *Biol Psychiatry* 2009; **66**: 1023–30.
 - 47 Wood SJ, Brewer WJ, Koutsouradis P, Phillips LJ, Francey SM, Proffitt TM, et al. Cognitive decline following psychosis onset. Data from the PACE clinic. *Br J Psychiatry* 2007; **191**: s52–7.
 - 48 Hawkins KA, Keefe R, Christensen B, Addington J, Woods SW, Callahan J, et al. Neuropsychological course in the prodrome and first episode of psychosis: findings from the PRIME North American Double Blind Treatment Study. *Schizophr Res* 2008; **105**: 1–9.
 - 49 Becker HE, Nieman DH, Wiltink S, Dingemans PM, van de Fliert JR, Velthorst E, et al. Neurocognitive functioning before and after the first psychotic episode: does psychosis result in cognitive deterioration? *Psychol Med* 2010; **40**: 1599–606.
 - 50 Balanza-Martinez V, Rubio C, Selva-Vera G, Martinez-Aran A, Sanchez-Moreno J, Salazar-Fraile J, et al. Neurocognitive endophenotypes (endophenocognitotypes) from studies of relatives of bipolar disorder subjects: a systematic review. *Neurosci Biobehav Rev* 2008; **32**: 1426–38.
 - 51 Meyer SE, Carlson GA, Wiggs EA, Martinez PE, Ronsaville DS, Klimes-Dougan B, et al. A prospective study of the association among impaired executive functioning, childhood attentional problems, and the development of bipolar disorder. *Dev Psychopathol* 2004; **16**: 461–76.
 - 52 Sigurdsson E, Fombonne E, Sayal K, Checkley S. Neurodevelopmental antecedents of early-onset bipolar affective disorder. *Br J Psychiatry* 1999; **174**: 121–7.
 - 53 Tiihonen J, Haukka J, Henriksson M, Cannon M, Kieseppa T, Laaksonen I, et al. Premorbid intellectual functioning in bipolar disorder and schizophrenia: results from a cohort study of male conscripts. *Am J Psychiatry* 2005; **162**: 1904–10.
 - 54 Zammit S, Allebeck P, David AS, Dalman C, Hemmingsson T, Lundberg I, et al. A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry* 2004; **61**: 354–60.
 - 55 Olvet DM, Stearns WH, McLaughlin D, Auther AM, Correll CU, Cornblatt BA. Comparing clinical and neurocognitive features of the schizophrenia prodrome to the bipolar prodrome. *Schizophr Res* 2010; **123**: 59–63.
 - 56 Nehra R, Chakrabarti S, Pradhan BK, Khehra N. Comparison of cognitive functions between first- and multi-episode bipolar affective disorders. *J Affect Disord* 2006; **93**: 185–92.
 - 57 Gruber SA, Rosso IM, Yurgelun-Todd D. Neuropsychological performance predicts clinical recovery in bipolar patients. *J Affect Disord* 2008; **105**: 253–60.
 - 58 Seidman LJ, Giuliano AJ, Smith CW, Stone WS, Glatt SJ, Meyer E, et al. Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: results from the Harvard and Hillside Adolescent High Risk Studies. *Schizophr Bull* 2006; **32**: 507–24.
 - 59 Klimes-Dougan B, Ronsaville D, Wiggs EA, Martinez PE. Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. *Biol Psychiatry* 2006; **60**: 957–65.
 - 60 Micco JA, Henin A, Biederman J, Rosenbaum JF, Petty C, Rindlaub LA, et al. Executive functioning in offspring at risk for depression and anxiety. *Depress Anxiety* 2009; **26**: 780–90.
 - 61 Palmer B, Heaton R, Paulsen JS, Kuck J, Braff D, Harris MJ. Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology* 1997; **11**: 437–46.
 - 62 Iverson GL, Brooks BL, Langenecker SA, Young AH. Identifying a cognitive impairment subgroup in adults with mood disorders. *J Affect Disord* 2011; **132**: 360–7.
 - 63 Martino DJ, Strejilevich SA, Scapola M, Igoa A, Marengo E, Ais ED, et al. Heterogeneity in cognitive functioning among patients with bipolar disorder. *J Affect Disord* 2008; **109**: 149–56.
 - 64 Fornito A, Yoon J, Zalesky A, Bullmore ET, Carter CS. General and specific functional connectivity disturbances in first-episode schizophrenia during cognitive control performance. *Biol Psychiatry* 2011; **70**: 64–72.
 - 65 Oertel-Knochel V, Bittner RA, Knochel C, Prvulovic D, Hampel H. Discovery and development of integrative biological markers for schizophrenia. *Progr Neurobiol* 2011; **95**: 686–702.
 - 66 Hetrick S, Parker A, Hickie I, Purcell R, Yung A, McGorry P. Early identification and intervention in depressive disorders: towards a clinical staging model. *Psychother Psychosom* 2008; **77**: 263–70.
 - 67 Kapczinski F, Dias VV, Kauer-Sant'Anna M, Brietzke E, Vazquez GH, Vieta E, et al. The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. *Progr Neuropsychopharmacol Biol Psychiatry* 2009; **33**: 1366–71.
 - 68 Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. *Int J Neuropsychopharmacol* 2009; **12**: 447–58.
 - 69 Fernandes BS, Gama CS, Maria Cereser K, Yatham LN, Fries GR, Colpo G, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. *J Psychiatr Res* 2011; **45**: 995–1004.
 - 70 Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, et al. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neurosci Biobehav Rev* 2011; **35**: 1175–85.
 - 71 Dazzan P, Soulsby B, Mechelli A, Wood SJ, Velakoulis D, Phillips LJ, et al. Volumetric abnormalities predating the onset of schizophrenia and affective psychoses: an MRI study in subjects at ultrahigh risk of psychosis. *Schizophr Bull* 2012; **38**: 1083–91.
 - 72 Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophr Res* 2009; **108**: 104–13.
 - 73 Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *Am J Psychiatry* 2008; **165**: 1015–23.

- 74 Chan RC, Di X, McAlonan GM, Gong QY. Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. *Schizophr Bull* 2011; **37**: 177–88.
- 75 Premkumar P, Kumari V, Corr PJ, Sharma T. Frontal lobe volumes in schizophrenia: effects of stage and duration of illness. *J Psychiatr Res* 2006; **40**: 627–37.
- 76 Mitelman SA, Nikiforova YK, Canfield EL, Hazlett EA, Brickman AM, Shihabuddin L, et al. A longitudinal study of the corpus callosum in chronic schizophrenia. *Schizophr Res* 2009; **114**: 144–53.
- 77 Velakoulis D, Wood SJ, Wong MT, McGorry PD, Yung A, Phillips L, et al. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch Gen Psychiatry* 2006; **63**: 139–49.
- 78 Jung WH, Kim JS, Jang JH, Choi JS, Jung MH, Park JY, et al. Cortical thickness reduction in individuals at ultra-high-risk for psychosis. *Schizophr Bull* 2011; **37**: 839–49.
- 79 Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biol Psychiatry* 2011; **70**: 88–96.
- 80 Jarnum H, Eskildsen SF, Steffensen EG, Lundbye-Christensen S, Simonsen CW, Thomsen IS, et al. Longitudinal MRI study of cortical thickness, perfusion, and metabolite levels in major depressive disorder. *Acta Psychiatr Scand* 2011; **124**: 435–46.
- 81 Pillay SS, Yurgelun-Todd DA, Bonello CM, Lafer B, Fava M, Renshaw PF. A quantitative magnetic resonance imaging study of cerebral and cerebellar gray matter volume in primary unipolar major depression: relationship to treatment response and clinical severity. *Biol Psychiatry* 1997; **42**: 79–84.
- 82 Pillay SS, Renshaw PF, Bonello CM, Lafer BC, Fava M, Yurgelun-Todd D. A quantitative magnetic resonance imaging study of caudate and lenticular nucleus gray matter volume in primary unipolar major depression: relationship to treatment response and clinical severity. *Psychiatr Res* 1998; **84**: 61–74.
- 83 Lacerda AL, Nicoletti MA, Brambilla P, Sassi RB, Mallinger AG, Frank E, et al. Anatomical MRI study of basal ganglia in major depressive disorder. *Psychiatr Res* 2003; **124**: 129–40.
- 84 Portella MJ, de Diego-Adelino J, Gomez-Anson B, Morgan-Ferrando R, Vives Y, Puigdemont D, et al. Ventromedial prefrontal spectroscopic abnormalities over the course of depression: a comparison among first episode, remitted recurrent and chronic patients. *J Psychiatr Res* 2011; **45**: 427–34.
- 85 Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 1996; **93**: 3908–13.
- 86 Sheline YI. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. *Biol Psychiatry* 2000; **48**: 791–800.
- 87 MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, et al. Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc Natl Acad Sci USA* 2003; **100**: 1387–92.
- 88 Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry* 2011; **68**: 675–90.
- 89 Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, et al. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. *Am J Psychiatry* 2002; **159**: 1841–7.
- 90 Brambilla P, Harenski K, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, et al. MRI study of posterior fossa structures and brain ventricles in bipolar patients. *J Psychiatr Res* 2001; **35**: 313–22.
- 91 DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: a pilot study. *Neuropsychopharmacology* 1999; **21**: 63–8.
- 92 Moorhead TW, McKirdy J, Sussmann JE, Hall J, Lawrie SM, Johnstone EC, et al. Progressive gray matter loss in patients with bipolar disorder. *Biol Psychiatry* 2007; **62**: 894–900.
- 93 Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *Br J Psychiatry* 2009; **195**: 194–201.
- 94 Elkis H, Friedman L, Wise A, Meltzer HY. Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. Comparisons with controls or patients with schizophrenia. *Arch Gen Psychiatry* 1995; **52**: 735–46.
- 95 Altshuler LL, Bartzokis G, Grieder T, Curran J, Jimenez T, Leight K, et al. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. *Biol Psychiatry* 2000; **48**: 147–62.
- 96 McDonald C, Bullmore E, Sham P, Chitnis X, Suckling J, MacCabe J, et al. Regional volume deviations of brain structure in schizophrenia and psychotic bipolar disorder. Computational morphometry study. *Br J Psychiatry* 2005; **186**: 369–77.
- 97 Sui J, Pearlson G, Caprihan A, Adali T, Kiehl KA, Liu J, et al. Discriminating schizophrenia and bipolar disorder by fusing fMRI and DTI in a multimodal CCA+ joint ICA model. *Neuroimage* 2011; **57**: 839–55.
- 98 Strakowski SM, Adler CM, DelBello MP. Volumetric MRI studies of mood disorders: do they distinguish unipolar and bipolar disorder? *Bipolar Disord* 2002; **4**: 80–8.
- 99 Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry* 2004; **161**: 1957–66.
- 100 Pettersson-Yeo W, Allen P, Benetti S, McGuire P, Mechelli A. Dysconnectivity in schizophrenia: where are we now? *Neurosci Biobehav Rev* 2011; **35**: 1110–24.
- 101 Friston KJ. The disconnection hypothesis. *Schizophr Res* 1998; **30**: 115–25.
- 102 Kang SS, Sponheim SR, Chafee MV, Macdonald AW. Disrupted functional connectivity for controlled visual processing as a basis for impaired spatial working memory in schizophrenia. *Neuropsychologia* 2011; **49**: 2836–47.
- 103 Rotarska-Jagiela A, van de Ven V, Oertel-Knochel V, Uhlhaas PJ, Vogeley K, Linden DE. Resting-state functional network correlates of psychotic symptoms in schizophrenia. *Schizophr Res* 2010; **117**: 21–30.
- 104 Patel S, Mahon K, Wellington R, Zhang J, Chaplin W, Szeszko PR. A meta-analysis of diffusion tensor imaging studies of the corpus callosum in schizophrenia. *Schizophr Res* 2011; **129**: 149–55.
- 105 Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci USA* 2009; **106**: 1279–84.
- 106 Woodward ND, Rogers B, Heckers S. Functional resting-state networks are differentially affected in schizophrenia. *Schizophr Res* 2011; **130**: 86–93.
- 107 Hasler G, Northoff G. Discovering imaging endophenotypes for major depression. *Molec Psychiatry* 2011; **16**: 604–19.
- 108 Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH. Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biol Psychiatry* 2011; **70**: 327–33.
- 109 Zhang J, Wang J, Wu Q, Kuang W, Huang X, He Y, et al. Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biol Psychiatry* 2011; **70**: 334–42.
- 110 Ongur D, Lundy M, Greenhouse I, Shinn AK, Menon V, Cohen BM, et al. Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Res* 2010; **183**: 59–68.
- 111 Cole MW, Anticevic A, Repovs G, Barch D. Variable global dysconnectivity and individual differences in schizophrenia. *Biol Psychiatry* 2011; **70**: 43–50.
- 112 Kapczynski F, Dias VV, Kauer-Sant'Anna M, Frey BN, Grassi-Oliveira R, Colom F, et al. Clinical implications of a staging model for bipolar disorders. *Exp Rev Neurotherap* 2009; **9**: 957–66.
- 113 Savitz J, Drevets WC. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. *Neurosci Biobehav Rev* 2009; **33**: 699–771.
- 114 Foti DJ, Kotov R, Guey LT, Bromet EJ. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. *Am J Psychiatry* 2010; **167**: 987–93.
- 115 McCabe C, Mishor Z. Antidepressant medications reduce subcortical-cortical resting-state functional connectivity in healthy volunteers. *Neuroimage* 2011; **57**: 1317–23.
- 116 Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry* 2011; **68**: 128–37.
- 117 Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ. Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry* 2008; **165**: 313–20.
- 118 Yatham LN, Kapczynski F, Andreazza AC, Trevor Young L, Lam RW, Kauer-Sant'anna M. Accelerated age-related decrease in brain-derived neurotrophic factor levels in bipolar disorder. *Int J Neuropsychopharmacol* 2009; **12**: 137–9.

- 119** Chakos MH, Lieberman JA, Bilder RM, Borenstein M, Lerner G, Bogerts B, et al. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *Am J Psychiatry* 1994; **151**: 1430–6.
- 120** Owen MJ, O'Donovan MC, Thapar A, Craddock N. Neurodevelopmental hypothesis of schizophrenia. *Br J Psychiatry* 2011; **198**: 173–5.
- 121** Altamura AC, Serati M, Albano A, Paoli RA, Glick ID, Dell'Osso B. An epidemiologic and clinical overview of medical and psychopathological comorbidities in major psychoses. *Eur Arch Psychiatry Clin Neurosci* 2011; **261**: 489–507.
- 122** Payne BR, Lomber SG. Reconstructing functional systems after lesions of cerebral cortex. *Nat Rev Neurosci* 2001; **2**: 911–9.
- 123** Castren E, Rantamaki T. The role of BDNF and its receptors in depression and antidepressant drug action: reactivation of developmental plasticity. *Dev Neurobiol* 2010; **70**: 289–97.
- 124** Schaufelberger MS, Lappin JM, Duran FL, Rosa PG, Uchida RR, Santos LC, et al. Lack of progression of brain abnormalities in first-episode psychosis: a longitudinal magnetic resonance imaging study. *Psychol Med* 2011; **41**: 1677–89.
- 125** Gogtay N. Cortical brain development in schizophrenia: insights from neuroimaging studies in childhood-onset schizophrenia. *Schizophr Bull* 2008; **34**: 30–6.