Clinical staging: a necessary step in the development of improved animal models of mood disturbance?

Frederick Rohan Walker1,2*, Morgan H. James1,2, Ian B. Hickie3 and Patrick D. McGorry4

1 School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, NSW, Australia
2 Centre for Translational Neuroscience and Mental Health Research, Hunter Medical Research Institute, NSW, Australia
3 Brain and Mind Research Institute, The University of Sydney, Camperdown, NSW, Australia
4 Department of Psychiatry, ORYGEN Youth Health Research Centre, University of Melbourne, VIC, Australia

Abstract

Recently, it has been suggested that the clinical staging approach be considered a serious alternative framework for conceptualising mood related psychopathology. The fundamental difference between clinical staging and the now dominant categorical diagnostic framework is that the entire illness trajectory becomes relevant, as opposed to simply the end-stage. The concept of disease trajectory has significant implications for animal models of psychopathology, and particularly for animal models of depression. This article will introduce and discuss the implications of the clinical staging approach for those undertaking research using animal models of mood disturbance.

Received 11 April 2013; Reviewed 13 May 2013; Revised 26 August 2013; Accepted 26 August 2013; First published online 16 October 2013

Key words: Animal models of depression, clinical staging, depression, mood disorders.

Clinical staging: implications for animal models

The recent release of the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has provoked considerable debate on the strengths and weaknesses of our traditional approaches to clinical and research diagnoses. One of the strongest themes to emerge is the view that existing diagnostic criteria are fundamentally limited by three major factors. First, they are based largely on symptoms presented only by those with severe or persisting illness. While these ‘end-stage’ phenotypes are representative of a subset of patients, they may have very limited application outside of highly-specialised clinical settings. Second, little consideration is given to those early and often sub-threshold symptoms that are more characteristic of the onset phase rather than the persistent course of an illness. Third, the validity of the proposed links between the various symptom-sets and any underlying or differentiating pathophysiologies remains largely unresolved (McGorry et al., 2006).

An alternative view proposed independently by McGorry et al. (2006) and Insel (2007) contends that a clinical staging approach is essential for both enhanced clinical practice and the development of more meaningful clinical and basic research. A fundamental difference of the clinical staging approach is that the entire illness trajectory becomes relevant, as opposed to simply the end-stage – which remains the primary focus of existing diagnostic approaches (McGorry et al., 2006). The clinical aim of the staging concept is to guide the deployment of stage-appropriate (and often early-phase) interventions that have the potential to slow or halt progression to more advanced stages.

By its nature, a clinical staging approach endorses a more dimensional view of psychiatric illness, adding the variables of time course and disease progression to the traditional dimension of illness severity. A significant feature of the staging approach is the recognition that the initial stage of major psychotic and mood disorders is phenotypically similar (Hafner et al., 2005). Indeed, because of the degree of phenotypic overlap it has been suggested that the initial phase of illness be considered as a ‘pluripotential’ rather than disease-specific ‘at risk’ stage (McGorry, 2011). While the clinical utility of adopting this approach is being evaluated (McGorry, 2008), the broad implications that it has for development of relevant animal models for mood disturbance need to be considered. To date, most animal models of mood disturbance have been designed without giving serious consideration to neither what stage of illness has been modelled nor the fact that different phenomena may emerge at different stages of illness. Indeed, a poor fit between the stage of illness and the stage captured by the animal model may have contributed to the clinical failure of several compounds that had exhibited significant promise during pre-clinical testing (Cryan and Slattery, 2007).

* Address for correspondence: Dr F. R. Walker, Room MS306, Medical Sciences Building, University of Newcastle, Callaghan, NSW 2308, Australia.
Tel.: +61 2 4921 5012 Fax: +61 2 4921 5141 Email: Rohan.Walker@newcastle.edu.au
Animal models of mood disturbance – what stage are they at?

There are now a large number of experimental models of depression in rodents. The central feature of almost all of these models is their reliance on repeated exposure to aversive experiences. Amongst the most commonly used models are: repeated social defeat (Berton et al., 2006; Tsankova et al., 2006), repeated social disruption (Herzog et al., 2009), repeated corticosterone administration (Gregus et al., 2005; Zhao et al., 2008), repeated restraint stress (Tynan et al., 2010; Hinwood et al., 2012) and chronic mild stress (Bortolato et al., 2007; Goshen et al., 2008). Each of these models in turn can be combined with developmentally earlier interventions to model early life and adulthood interactions (Hodgson et al., 2001; Gardner et al., 2005). Many of these models are considered, in the presence of appropriately supportive data, to provide valid approximations of the human condition as they produce a symptom set that is highly analogous to that seen individuals with diagnosable depression. Although all symptoms are not routinely measured in all experiments, there are numerous instances in the literature where any of the aforementioned models can be shown to produce robust levels of anhedonia, psychomotor retardation, working memory deficits, anorexia and disturbances in sleep (Willner, 1997, 2005; Yan et al., 2010).

Despite the undeniable ability of standard pre-clinical models of mood psychopathology to elicit what are routinely referred to as ‘depression-like’ symptoms, it is not totally clear that this interpretation is as straightforward as it seems. Specifically, some interpretational uncertainty arises because numerous clinical studies have demonstrated that many symptoms present in patients that are diagnosed with depression (anhedonia, sleep disturbance, irritability, and cognitive disturbance) are also present in the prodromal (pre-diagnosis) stage of the condition.

The concept of consistent prodromal symptoms is not new, and has been extensively investigated, principally due to interest in using prodromal symptoms to predict the emergence of subsequent illness (Hetrick et al., 2008; Kovacs and Lopez-Duran, 2010; Szklo-Coxe et al., 2010; Fusar-Poli et al., 2013). Particularly notable amongst this literature is Fava’s (1990) early study highlighting the consistency with which general anxiety, loss of interest, impaired work performance, fatigue and insomnia appear in individuals that subsequently go on to develop depression. If features such as anhedonia are present in the pre-diagnosis and the post-diagnosis phase of major depression, the critical question for those using standard pre-clinical models and measuring anhedonic behaviour is: which phase of the disorder is this measured symptom actually occurring in?

The mere presence of certain behavioural changes is not the only reason that current animal models are considered to be approximations of the diagnosable condition. Many working within the field consider it to be critical that animals exposed to a particular model also respond in a manner that approximates the way in which patients respond to medication in clinical settings. For example, the validity of a given animal model of depression is predicated not only on its ability to elicit ‘depression-like symptoms’, such as anhedonia, but on whether animals display a marked reduction in this and other symptoms when treated with a selective serotonin reuptake inhibitor or serotonin-noradrenalin reuptake inhibitor (or another accepted antidepressant). Consistent with this thinking, there are now many dozens of articles attesting to the fact that the behavioural disturbances exhibited by animals who have been subjected to a standard model of depression exhibit a marked reduction in these symptoms following treatment with a conventional antidepressant, such as a selective serotonin reuptake inhibitor (Christiansen et al., 2011; Razzoli et al., 2011; Gusmuslu et al., 2013).

Significantly, however, we could not find any clinical literature describing the use of anti-depressants during the pre-diagnosable early stage of what would become major depression. Therefore it is not clear that a reduction in symptoms when treated with an accepted antidepressant is in actual fact a measure of end-stage illness. It is possible that such a reversal may also occur in early stage illness. To be certain that the behaviour(s) exhibited by an animal following exposure to a standard experimental model of depression are genuinely analogous to those seen in individuals with depression, evidence should also be available demonstrating that the clinical and pre-clinical pre-diagnosis phase of the disorder do not respond in a similar way to antidepressants. Obtaining such evidence at the present time represents a major challenge, as metrics capable of effectively discriminating between stage progressions have yet to be developed.

The need to develop indices of stage progression

The development and introduction of metrics or decision matrices that would allow researchers to determine how far a disorder had progressed would be enormously beneficial. Perhaps the best outcome would be that each stage, from moderate behavioural perturbation through to a diagnosable condition, could be uniquely and categorically discriminated from the next, or in lieu of this, a probabilistic estimate could be ascribed to stage progression. Unfortunately, without extensive experimental work it is difficult to know what the best indicators of stage progression will be. Clearly, evaluating the extent to which commonly used and well understood metrics (e.g. sucrose preference) show graded, intensity-dependent changes is an obvious place to begin investigations. Ideally, if sucrose preference did change in a graduated intensity-dependent manner, it may be possible to ascribe particular stages to certain changes in preference scores.
Alternatively, in terms of developing stage metrics capable of differentiating prodromal-like behaviour from diagnosable-like behaviour, it may be useful to look at the approach taken with clinical diagnosis. One of the key aspects of clinically diagnosing the presence of major depression is to identify the continued presence of certain debilitating symptoms for a given period of time (DSM-IV-TR; APA, 2000). At present, the vast majority of animal models assess symptom severity either during the application of aversive experience or immediately after its termination. We could find very few studies that tracked how persistent the depression-like symptoms were following the cessation of aversive experiences. While the suggestion may carry some anthropomorphic bias, it does not seem unreasonable to expect that if a diagnosable condition is being modelled then symptoms should not rapidly resolve following the removal of the aversive stimulus. If rapid symptom dissipation was observed using standard models it may be taken to suggest that they elicit more prodromal-like behaviour. While speculative, a straightforward response to this situation would be to employ repeat cycles of aversive experience, arguably providing a more accurate representation of the life history of those that do eventually develop depression (Kendler et al., 1993; Chapman et al., 2004).

One of the most significant issues in terms of moving forward with the development of metrics capable of detecting modest behavioural disturbances is sample size. Much of the work undertaken thus far using animal models of mood disturbance has made use of group sizes of between 6 and 10 animals per group. This modest number reflects the fact most studies have only been powered to detect relatively large between-group differences. Given the typical variability observed in studies of animal behaviour, it is likely that sample size will have to be increased significantly in order to robustly identify small differences in behaviour that may occur during early phases of disease progression.

Whatever ‘stage-metrics’ are eventually employed, hopefully they will confirm, as many have long assumed, that existing animal models of psychopathology, and particularly animal models of depression, are reasonable models of the end-stage clinical condition. We must, however, be open to the possibility that existing models may represent earlier stages of disease progression than we had originally anticipated.

Are new models required or can existing models be repurposed to accommodate the staging concept?

Application of the staging concept to preclinical modelling of mood disorders raises questions about what models should be used. Can existing models of mood disturbance, such as the repeated restraint stress model, be pressed into service by simply evaluating change earlier in the environmental insult process? If not, it may be the case that specific early (or later) stage models may be more appropriate, models that focus more on the application of specific risk or time-limited factors (e.g. acute stress, sleep deprivation, shifting circadian timing, exposure to infection) or manipulation of quite specific developmental, pharmacological or other biological pathways. The challenge, however, inherent with the introduction of ‘early-stage’ models is that the emergent symptoms may only be loosely associated (phenotypically) with major depression in humans. Further complicating matters, and mirroring clinical reality, early-stage models could produce symptoms of mood disturbance that may in fact be linked equally to other psychiatric syndromes (McGorry, 2011).

Conclusion

Perhaps the greatest utility of animal models to date has been their role in testing the potential therapeutic capacity of novel pharmacological agents. It is now apparent that a range of compounds that appeared to have therapeutic value in animal models of depression has not translated well into the clinic (Cryan and Slattery, 2007). There are a variety of possible explanations for this phenomenon, but one that has not been widely considered may well be a poor fit between the stage of illness in most human subjects (i.e. chronic or recurrent illness) and the stage captured by the animal model.

Fortunately, a firm platform for clinical research in major mood disorders based on the clinical staging approach has now been established (McGorry et al., 2006). The implications of the staging model for the subsequent development of relevant animal models of depression, and potentially other mood disorders, are profound. It will be necessary, first, to state what stage of illness (and observed behaviour or physiological change) is produced in response to a given risk factor and, second, what types of therapeutic strategies are relevant to the various stages of illness progression. Importantly, without the development, introduction and evaluation of stage metrics it will be difficult to fully understand how representative the information is that is currently being generated from existing animal models of mood disturbance. Ultimately, continued development of the staging concept in the field of pre-clinical models of mood disorders has the potential to increase the chance of successful translation of therapies from the lab to personalised clinical practice.

Acknowledgments

This work was supported by project grants from the National Health and Medical Research Council of Australia and the Hunter Medical Research Institute.

Statement of Interest

F.R.W. currently receives research support from the National Health and Medical Research Council of
Australia (NHMRC). M.H.J. has no interests to declare. I.B.H. sits on the National Advisory Council on Mental Health, which reports to the Federal Minister for Mental Health, is a member of BUPA Australia and a Headspace board member. I.B.H. was previously chief executive officer and clinical adviser of Beyondblue, an Australian National Depression Initiative. He has led projects for health professionals and the community supported by governmental, community agency and drug industry partners (Wyeth, Eli Lilly, Servier, Pfizer, Astra-Zeneca) for the identification and management of depression and anxiety. He has served on advisory boards convened by the drug industry in relation to specific antidepressants, including nefazodone, duloxetine, and desvenlafaxine and has participated in a multi-centre clinical trial of agomelatine effects on sleep architecture in depression. I.B.H. is also supported by a National Health and Medical Research Council Australian Medical Research Fellowship. He is supported by a National Health and Medical Research Council and programme grants. P.M. Currently receives research support from the NHMRC and the Colonial Foundation.

References


Szklo-Coxe M, Young T, Peppard PE, Finn LA, Benca RM (2010) Prospective associations of insomnia markers and symptoms...


