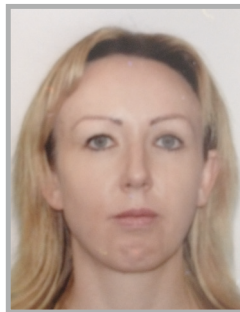


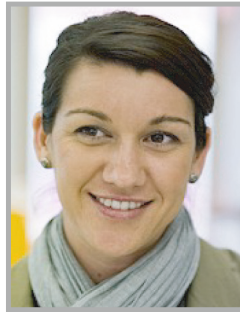
Studying young people at high genetic risk of bipolar disorder: preparing the ground for future prevention and early intervention



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There has been a rapidly growing interest in early intervention and prevention for those at high risk of mental illness, with the hope that such an intervention will either prevent further progression or, at the least, attenuate the ultimate functional and symptomatic impact of these devastating disorders. The major focus of this research effort until now has been in relation to the development of schizophrenia, using the target of those young people at ‘ultra high risk’ (UHR) of psychosis – defined largely in terms of psychotic-like experiences or mild psychotic symptoms in combination with trait features (schizoid or schizotypal) of personality and/or a positive family history. Most follow-up studies of UHR samples have reported ‘transition’ rates to psychosis of between 20 and 40% [1]. There has been evidence of a reduction in such transition rates with various pharmacological and psychological approaches [2], leading to the incorporation of such early intervention programs in national health programs, such as the UK National Health Service.

In recent years there has been increasing interest in analogous studies with bipolar

disorder. The major relevant difference compared with schizophrenia is the lack of a clear target (high-risk) population for early intervention, such as that provided by the schizophrenia UHR group. Unlike schizophrenia, there is no clear prodrome to the onset of bipolar disorder, despite proposals such as that of Skjelstad *et al.* [3], which are largely based on retrospective data.

Aligned with this interest in early intervention for bipolar disorder are recent proposals for a staging model for this condition [4,5]. Such a model posits that the early stages (0: asymptomatic with increased genetic risk; 1a: mild or non-specific symptoms and/or subtle cognitive deficits; and 1b: clear prodromal features) provide potential targets for prevention or early intervention prior to the first episode (stage II), with later stages (IIIa, b, c and IV) representing clinical manifestations of a presumed underlying ‘neuroprogression’. Currently, staging models are limited by their reliance on clinical descriptors, without sufficient clarity of intermediate biological phenotypes (endophenotypes),

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which characterize the pathway to illness, unlike staging models for physical illnesses (e.g., those developed for various cancers), which are premised upon either histology or the extent of tumor spread. Nonetheless, such a heuristic approach to the hypothesized progression of bipolar disorder does provide the potential for focus on early intervention programs.

At present, the challenge for the bipolar disorder field is to elucidate a more fine-grained understanding of the clinical, biological, genetic and neuropsychological features of those putative early stages of the illness (stages 0, 1a and 1b) prior to onset of the first episode (stage II). Calls for large-scale early intervention studies in bipolar disorder [6] should be considered premature, as our current capacity to identify those at risk with any reasonable degree of certainty is extremely limited. Fortunately, in recent years there has been much research energy focused on characterizing those in these early high-risk stages of the illness, although we are only in the very early days of this field. Here, we provide a critical overview of the findings from the emerging research.

There have been two main approaches furthering our understanding of these early stages of bipolar disorder. The first, and most common, design has been the cross-sectional study of those with a family history of bipolar disorder, with the aim of identifying potential trait markers or endophenotypes by comparison with controls from families without bipolar disorder or other serious mental illnesses. In this context, it should be noted that some of these studies have been of young relatives still in the age group at high risk for developing this illness (usually considered to be in the age range of 12–30 years), while other reports include healthy relatives of any age, thereby perhaps including some ‘resilient’ to the illness, as well as those at risk. The second approach (a minority for understandable reasons) is that of prospective longitudinal studies that aim to determine predictors of later transition or ‘conversion’ to bipolar disorder.

Clinical aspects of those at high risk of bipolar disorder

The first question to be addressed here is what proportion of those at high genetic risk for bipolar disorder – usually defined as those with at least one first-degree relative with conservatively appraised DSM-IV bipolar I or II disorder – will in fact develop this condition later on? Population

and family studies (e.g., [7]), which have been mainly comprised of relatives of probands with bipolar I disorder, have reported increased rates of bipolar disorder in first-degree relatives of the order of ten- to 15-fold [7]. A small number of prospective studies have reported on rates of bipolar I disorder in close relatives [8,9]. The recently published 12-year follow-up of the 140 subjects of the Dutch Bipolar Offspring Study (74% of whose parents had bipolar I disorder) has shown that 13% have developed some form of bipolar disorder (mostly bipolar II disorder or cyclothymia) with only a total of 3% developing bipolar I disorder [8]. A recent 16-year follow-up of offspring of bipolar I disorder patients in the US Amish community demonstrated that 7% had developed bipolar I disorder [9].

However, the most striking findings from both the prospective and cross-sectional studies are the high rates of overall psychopathology and the dramatically pleomorphic nature of the clinical presentations. For example, the Dutch study found that at the 12-year follow-up evaluation, 72% had developed at least one lifetime DSM-IV disorder [8]. A total of 54% had experienced some mood disorder (mainly depression), 27% an anxiety disorder, 8% a disruptive behavioral disorder and 25% a substance use disorder (unfortunately there was no control sample for comparison). In one of the major cross-sectional reports – the baseline evaluation from an ongoing longitudinal study – Nurnberger *et al.* reported similar findings [10]. A total of 60% patients had already experienced at least one DSM-IV-defined disorder, with 23% experiencing a major affective disorder (major depressive disorder [MDD] or bipolar disorder), 26% an anxiety disorder and 27% an externalizing disorder (ADHD, disruptive behavior or a substance use disorder). After controlling for potential confounding variables, the rates of affective disorder were found to be significantly higher than in controls. An ongoing prospective Canadian study has also reported similar findings, with increased rates of childhood sleep and anxiety disorders, as well as higher rates of depression and bipolar disorder [11]. Similar pleomorphic findings have also been reported in the baseline evaluation of a Swiss cohort [12].

An intriguing finding reported by both the Duffy [13] and Nurnberger [10] teams has been that prior anxiety disorders increase rates of major affective disorders (MDD and bipolar disorder). Furthermore, in the study by Duffy *et al.*, anxiety

disorders were episodic (rather than ongoing) prior to bipolar disorder in the offspring of the lithium-responsive patients, and later resolved, suggesting that for this group, anxiety may represent a prior presentation of the illness or, at the least, a diathesis towards bipolar disorder. Although there has been speculation that ADHD may represent an alternative presentation or risk factor to bipolar disorder, prospective studies have not confirmed this [14].

Overall, the cross-sectional and prospective studies indicate high rates of psychopathology and a heterogeneous clinical presentation in close relatives of those with bipolar disorder. The finding of particular pertinence to early intervention studies is the replicated finding that those with preceding anxiety disorders in high-risk families may represent a potential target group.

Neuropsychological profile

Although there have been a reasonable number of studies of neuropsychological status in first-degree relatives of those with bipolar disorder, the numbers in each study have been relatively small and few have focused upon the younger at-risk age group [15,16]. Even fewer have examined the predictive capacity of such testing in prospective studies [17]. Accepting these major limitations, there are some suggestions of abnormalities of executive functioning and verbal memory in those at risk of bipolar disorder [15,16]. In one relatively small prospective study, Meyer *et al.* reported that impairment on the Wisconsin Card Sort Test and self-reports of early attentional problems predicted later onset of bipolar disorder [17].

Brain imaging studies

Over the last few years there have been a small but growing number of brain imaging studies of samples at increased genetic risk of bipolar disorder. Such imaging research potentially allows for the capacity to identify abnormal neural substrates, which may represent endophenotypes in those at risk of bipolar disorder. These studies have used structural MRI, diffusion tensor imaging and functional MRI (examining either responses to various paradigms or functional connectivity using resting state data). Some of the major recent findings include: enlarged right inferior frontal gyrus volume [18]; widespread subtle reductions in fractional anisotropy indicative of impaired white matter function [19]; reduced fractional anisotropy in the right anterior limb of

the internal capsule and right uncinate fasciculus [20]); reduced left inferior frontal gyral activation on inhibiting response to fearful faces, suggesting impaired emotional regulation [21]; and greater activation of ventrolateral prefrontal cortex activation in response to emotional distractors [22]. While the field is only just emerging and awaits replication of findings, the results to date indicate both structural and functional dysfunction in brain regions involved in emotional control. Wessa *et al.* have speculated further on the ramifications of such imaging studies for understanding the status of neural networks in these at-risk subjects [23]. As yet, there has only been one study of the predictive capacity of brain imaging findings in this at-risk population. Whalley *et al.* have reported that increased activation of the insula cortex in response to a task involving executive and language processing predicted those who later went on to develop MDD [24]. To confirm potential endophenotypes, individuals at risk for bipolar disorder should ideally be prospectively followed to clarify whether any baseline differences represent true risk markers, or rather compensatory mechanisms, that may help prevent the onset of bipolar disorder.

Early intervention treatment studies

There have only been a handful of treatment studies for individuals at high risk of bipolar disorder. Most have studied subjects with some symptoms, mainly depression, and have utilized pharmacological or psychological approaches. Findling *et al.*, for example, reported on a placebo-controlled study of divalproex, finding no difference compared with placebo [25]. The small number of other pharmacological studies have similarly demonstrated no therapeutic effect [26]. In one of the major psychological intervention studies, Miklowitz *et al.* recently reported on the outcome of family-focused therapy in a randomized controlled trial in 40 at-risk subjects with either bipolar disorder not otherwise specified, MDD or cyclothymia [26]. They reported a more rapid onset of symptoms, more weeks in remission and a more favourable trajectory of mania scores over 1 year with family-focused therapy than that observed in the control group.

Conclusion

Unlike the analogous schizophrenia at-risk research literature, the bipolar disorder field is younger and nascent. Prospective longitudinal studies of large cohorts assessed on multiple

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levels of functioning (clinical, cognitive, social and biological) are needed to provide sufficient power to determine the combination of factors that contribute to the development of bipolar disorder. Nonetheless, there have been important recent clinical and imaging findings, in particular, that suggest potential future clinical applicability.

There are two major potential clinical benefits if this field can deliver upon its promise. The first will be the capacity to predict the risk of future onset of bipolar disorder. This is more likely to be probabilistic rather than definitive, and likely to comprise some multifactorial algorithm of clinical, imaging, genetic and neuropsychological findings [27]. The second will be the development

of focused preventive therapies in this targeted risk population. Successful development of predictive algorithms and early evidence-based interventions would change the face of bipolar disorder management. Watch this space!

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