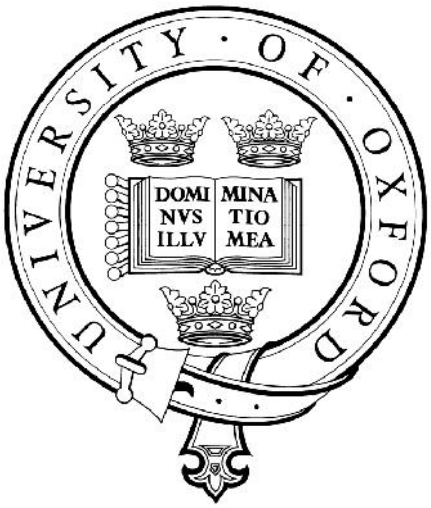
The Broad Bipolar Phenotype: Sampling the Experience of Mood, Stress and Mental Imagery



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The Broad Bipolar Phenotype: Sampling the Experience of Mood, Stress and Mental Imagery

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Abstract

The overarching aim of this thesis was to use an experimental psychopathology approach to investigate mood, stress and mental imagery in the Broad Bipolar Phenotype (BPP), defined by the experience of elevated lifetime hypomania. Daily mood reactions to stress have been well explored in psychosis, but the limited research in BD has produced mixed findings. Holmes, Geddes, Colom and Goodwin (2008) hypothesised that mental imagery in BD may amplify emotion and worsen day to day mood extremes. This thesis investigates volunteers ranging across the continuum of the BPP in relation to key variables from the Holmes et al (2008) model: mood, stress and mental imagery, and brings new methodology to this area. The Mood Disorder Questionnaire (MDQ; Hirschfeld et al., 2000) was used to identify groups with high (N=50; ≥ 7 symptoms) and low (N=60; ≤ 6 symptoms) rates of hypomanic experience i.e. high MDQ and low MDQ. A single investigation was conducted for this thesis (N=110) which is divided into four studies.

Study 1 and 2 tested the hypothesis that high MDQ volunteers would report higher levels of mental imagery compared to low MDQ volunteers. Study 1 (N=61) found that high MDQ volunteers had higher levels of trait mental imagery and intrusive imagery of the future, replicating patient findings. Study 2 (N=49) extended these findings to additional imagery measures.

In a laboratory study, study 3 tested the hypothesis that after an experimental stressor (a traumatic film) high MDQ volunteers would experience more image-based flashback memories to the film than low MDQ volunteers. Volunteers reported any flashback memories to the film via mobile phone Short Message Service (SMS) prompts for six days, plus convergent measures at follow-up. As predicted, compared to the low MDQ group, the high MDQ group experienced significantly more flashback memories to the stressor (on all measures).

Study 4 used an Experience Sampling Method (ESM; momentary assessment sampling over time) to frequently monitor mood and its event-related stress context. Thus, in the context of daily life study 4 sought to explore the role of bipolarity in exacerbating mood reactions, in comparison to other hypothesised contributors: neuroticism and intrusive imagery of the future. SMS mobile-phone messages were sent 10 times a day for 6 days to capture event-related stress ratings and mood ratings. Higher bipolarity (MDQ), neuroticism (EPQN) and intrusive imagery of the future (IFES) were each associated with increased mood reactions over six days, compared to lower levels of these characteristics. In understanding which of these characteristics best accounted for mood reactions, bipolarity (MDQ) best accounted for elated mood reactions, neuroticism did not best account for any moods, intrusive imagery of the future (IFES) best accounted for sad, depressed and anxious mood reactions and both bipolarity and intrusive imagery of the future best accounted for fearful mood reactions.

In summary, the aim of this thesis was to investigate volunteers ranging across the continuum of the BPP in relation to key variables from the Holmes et al (2008) model: mood, stress and mental imagery. As predicted, compared to low MDQ volunteers, the high MDQ group had higher levels of 1) self-reported use of mental imagery, 2) negative flashback memory imagery after an experimental stressor and 3) daily life negative mood reactions to stress. Critically, repeatedly imaging future scenes (IFES), which flash to mind unbidden, was found to show the greatest impact on negative mood reactions in daily life. Mental imagery offers a psychological characteristic which is elevated in volunteers at the higher end of the BPP continuum and also has the potential to be a novel cognitive treatment target in clinical BD samples. For example, targeting flashback memories after a stressor or targeting intrusive imagery of the future may help regulate mood reactions in daily life. This warrants further investigation in patients with BD.

Declaration

I declare that the work presented in this thesis is my own and has not been submitted for any other degree in this or in any other university or institute of learning.

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List of Abbreviations

AIC	Akaike's Information Criterion
ANOVA	Analysis of Variance
ASRM	Altman Self Rating Mania Scale
BD	Bipolar Disorder
BD-I	Bipolar Disorder I
BD-II	Bipolar Disorder II
BD-NOS	Bipolar Disorder Not Otherwise Specified
BSD	Bipolar Spectrum Disorder
BPP	The Broad Bipolar Phenotype
BDI-II	Beck Depression Inventory- 2nd Edition
CBT	Cognitive Behavioural Therapy
DSM-IV	Diagnostic Statistics Manual 4th Edition
EMA	Ecological Momentary Assessment
EPQN	Eysenck Personality Questionnaire, Neuroticism subscale
ESM	Experience Sampling Method
GAD	Generalised Anxiety Disorder
GEE	Generalised Estimating Equation
GLMM	Generalised Linear Mixed Model
HIT	Homograph Interpretation Task
IES-R	Impact of Event Scale- Revised
IFES	Impact of Future Events Scale
IPT	Intrusion Provocation Task
MINI-Plus	Mini International Neuropsychiatric Interview Plus
MDQ	Mood Disorder Questionnaire
NICE	National Institute for Health and Clinical Excellence
PDA	Personal Digital Assistant
PIT	Prospective Imagery Task
PTSD	Posttraumatic Stress Disorder
PWT	Picture Word Task
QIC	Quasilikelihood under the Independence model Criterion
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SMS	Short Message Service
STAI-State	State version of the Spielberger State-Trait Anxiety Inventory
STAI-Trait	Trait version of the Spielberger State-Trait Anxiety Inventory
SUIS	Spontaneous Use of Imagery Scale
UHR	Ultra High Risk
VAS	Visual Analogue Scale

CHAPTER 1

The Broad Bipolar Phenotype: Sampling the Experience of Mood, Stress and Mental Imagery

Background

Overview

This chapter provides a background of the main topics covered in this thesis. Chapter 2 provides a position piece of how mobile phone Short Message Service (SMS) technology can be used to frequently monitor mood in the context of bipolar disorder (BD); chapter 3 describes an overview of the main methods used in this thesis; chapter 4 presents studies 1 and 2; chapter 5 presents study 3; chapter 6 presents a statistical analysis plan used in study 4; chapter 7 presents the full study 4 and finally chapter 8 provides a general discussion of the main findings of this thesis. A full synopsis of this thesis is presented at the end of the current chapter. First, a brief overview of the main topics of this thesis are considered: bipolar disorder; the broad bipolar phenotype; cognitive behavioural approaches to bipolar disorder; mental imagery in psychopathology; mental imagery and bipolar disorder; measuring reactions to stress: the trauma film paradigm; measuring mood reactions to stress; and measuring risk to bipolar disorder.

Bipolar Disorder

Bipolar disorder is a mood disorder characterised by extreme affect, where in its severest form individuals experience episodes of depression and at least one episode of (hypo)mania (DSM-IV; APA, 1). A number of types of BD have been identified, exemplifying the complexity of this disorder: bipolar I, bipolar II, bipolar

disorder not otherwise specified, rapid-cycling and cyclothymia. Population lifetime prevalence is estimated to be 0.6% for bipolar I, 0.4% for bipolar II and 1.4% for sub-threshold BD and 2.4% for the BD spectrum (2). Bipolar disorder has the highest risk of completed suicide out of all psychiatric disorders (3) and is extremely functionally debilitating, with an average of 65.5 days taken off work annually per patient (4).

The Broad Bipolar Phenotype

This thesis takes a continuum approach to studying psychopathology by exploring mood, stress and mental imagery in individuals at-risk to BD who, as outlined below, are believed to be informative of BD proper (5). Much at-risk research in BD has utilised individuals at genetic risk (6). Given that the conversion from subsyndromal BD to the full-blown disorder can not always predicted by heritability (7), alternatives to this approach have been advocated (8, 9). One such approach is the use of analogue groups where non-clinical volunteers are selected on the basis of hypothesised risk to the disorder (10).

Lifetime hypomanic experiences are purported to be one risk factor for BD (11-13); accordingly lifetime hypomania is thought to be indicative of the broad bipolar phenotype (BPP) (12, 14). Indeed, significant hypomanic experience which defines the BPP (15) is endorsed by approximately 20% of young people aged 19-20 (12). Subsyndromal hypomanic experiences in young people are associated with the development of mood and anxiety disorders during adulthood (16) and similarly have been shown to be predictive of future episodes of depression and BD (17). Young people with this BPP present with anxiety and substance misuse comorbidities which parallel those found in clinical populations (14, 18). The investigation of individuals presenting with a BPP, defined in this thesis as the experience of significant lifetime hypomania, has the potential to inform our understanding of psychopathology that is

present in clinical BD. Therefore, the sample selected for investigation in this thesis were individuals ranging across the spectrum of the BPP. The investigation of the BPP allows for studying vulnerability to BD in the absence of broad co-morbidity, the prevalence of chronic depressive symptoms and ongoing mood instability, multiple psychotropic medications and the uncertain but likely damaging effects of multiple severe episodes of illness. Of course, these are certainly characteristics of the full-blown illness itself. However, the aim of this thesis was to explore the experiences of imagery, mood and stress in a vulnerable sample on a continuum of hypomanic experience. This has the exciting potential to allow for conclusions regarding vulnerability markers rather than identifying epiphenomena of the clinical disorder itself. Furthermore, in consideration of the methodology of this thesis (as will be outlined later in this chapter), one intention of this investigation was to use the trauma film paradigm in order to provide a standardised stressor by which to investigate vulnerability to traumatic flashback memories. Any presentation of the aforementioned characteristics in a BD patient may have raised ethical concerns regarding film-viewing.

In this thesis, the Mood Disorder Questionnaire (MDQ; 19) (see later section on: Measuring Risk to Bipolar Disorder) was used to identify individuals ranging across the BPP continuum. In this thesis, the following additional terms will be used synonymously to describe individuals at the higher end of the BPP continuum: high MDQ, high bipolarity, high risk to bipolar disorder; and individuals at the lower end of the BPP continuum: low MDQ, low bipolarity, controls, low risk to bipolar disorder.

Cognitive Behavioural Approaches to Bipolar Disorder: A Need for an Improved Understanding of Mechanisms

Though medication is the foundation of treatment, over 90% of patients with BD experience recurrences during their lifetime (20). Cognitive Behavioural Therapy (CBT) has been advocated as an adjunct to pharmacological approaches, particularly its potential in the long-term management of BD by contributing to the prevention of relapse and recurrence (21). A recent meta-analysis, summarising 12 randomised control trials which explored the impact of CBT on patients with BD, concluded that CBT was beneficial during treatment and post-treatment in reducing relapse, reducing symptoms, and improving functioning (22). However at follow-up, this beneficial effect of CBT was not maintained. Crucially, CBT had little influence on preventing relapse at follow-up. Szentagotai et al (22) proposed that treatment innovations are required if CBT is to succeed as a successful adjunct to medication in the long-term management of BD. This is in accordance with the National Institute for Health and Clinical Excellence (NICE) guidelines which propose that psychological interventions are of benefit in the long-term management of BD, but that these require improvement (23, no. 38, p.33).

In a bid to contribute to an evidence-base for potential future therapeutic innovations for BD, this thesis will investigate a core aspect of the long-term management of BD which is improving day to day variations in mood. This will be achieved by exploring mood reactions to stress in the context of daily life, in individuals ranging across the BPP continuum. Daily life mood management is currently achieved by mood stabilisers, for example, in lithium monotherapy (21). This thesis will investigate what influences mood reactions to daily life stress, in light of identifying influences which are treatment targetable. In addition, this thesis will

explore the salience of mental imagery, a little-explored cognitive process in BD, in light of a recent cognitive model which highlights the potential importance of mental imagery in BD, specifically as an amplifier of bipolar mood (24). This approach would be of interest in terms of therapy development as imagery offers additional CBT treatment targets. Both mood reactions to daily life stress and mental imagery will be investigated in individuals ranging across the continuum of the BPP, as defined by elevated lifetime (hypo)mania to low or no lifetime (hypo)mania.

How might mental imagery be targeted in CBT? The process of targeting mental imagery in CBT could involve the following steps: assessment, formulation, intervention and evaluation. In assessment, the clinician would need to establish whether a client is experiencing any (maladaptive) mental imagery and how such imagery might be problematic for the client, for example the impact of the image on a client's mood or behaviour. Assessing the presence of such imagery could be achieved through verbal enquiry, or by using a paper-pencil based measure, for example, an imagery interview (25). Assessment may not necessarily be a one-time process as assessment can continue throughout the therapeutic period. For example, the client could record their experience of imagery in a diary between clinical sessions, or alternatively, complete imagery-assessment measures in clinical sessions, in order for both the clinician and client to monitor any change that may take place (for example, a reduction in the emotional impact of the imagery, a reduction in the frequency of the image being experienced). For example, through assessment it may become clear that a client with BD frequently and spontaneously experiences a negative image of social isolation. On further enquiry, the client may indicate that the experience of this image renders an increase in anxious mood. As a consequence, in

order to avoid the impact of this image, the client ceases their engagement/attendance of social activities with peers.

In formulation, the information from assessment is collated and a hypothesis is formed, drawing on psychological theory in order to provide a scientific framework for describing the problem (in this case- the experience of maladaptive mental imagery), how it has developed and how it is maintained. Formulation allows for planning an appropriate intervention in order to test the hypothesis that has been formed regarding the client's experience (of mental imagery). In the case of the client described earlier, one could formulate the experience of the client under the cognitive framework provided by the Holmes et al (24) model. The experience of the negative image of social isolation would be hypothesised to amplify the client's anxious mood, rendering the avoidance behavior such as withdrawing from peers. The endeavors to avoid the image and the mood would then perpetuate the frequency of the image of social isolation, thus maintaining the experience of the image and the anxious mood amplification.

There are a variety of interventions for imagery under a CBT framework. These include- imaginal exposure (exposure to the feared stimulus in the client's imagination), imaginal rehearsal (imaging a sequence of events), guided imagery (following an imagery script), Socratic imagery (using Socratic questioning to provoke the client's image and explore their meaning to the client), imagery rescripting (modifying an image to change the meaning associated with it, for example, changing a negative image to a benign image or to creating a new positive image). For this particular client, imagery-rescripting could be used. From the earlier process of formulation, one would hypothesise that changing the valence of the image (into one which is not anxiety provoking) could break the maintenance cycle between

image, mood and behaviour. For example, the image of social isolation could be rescripted into an image of increased connectedness with others, for example, rather than imagining standing at a distance away from a group of peers who are talking, the image could be rescripting into one where the client gradually walks towards their group of peers and eventually joins in with the conversation. As the clinician may assess the client in an on-going manner, it would allow for observing whether the selected intervention is enhancing the changes in mood and behaviour in the direction that was hypothesised during formulation. If assessments indicate that this is not the case, the clinician may have to re-formulate in order to select an optimal intervention for the client.

The average length of CBT can be between 12-20 sessions and in evaluation, the clinician would collate the continuous assessments of their client in order to establish whether the intervention was successful. In this case, collecting information about the frequency of the image of social isolation, the mood and behaviour associated with it, and in turn for the rescripted image, would allow both clinician and client to observe any changes that have occurred over the treatment course. For example, if paper and pencil measures are used in each clinical session, the client may self-report a reduction in anxious mood, a reduction in the experience of the negative image.

As the model on which this thesis is based is a cognitive model, the underlying emphasis in this thesis with regards to potential therapeutic implications is for CBT. However, if the salience of mental imagery as an amplifier of mood states in BD can be established by further research, then its application may not need to be exclusively to CBT. It could be applied to alternative established interventions for BD such as psychoeducation (26) or family-focussed treatment (27), for example, in encouraging

clients and/or their carers to recognise maladaptive mental imagery as a potential amplifier of mood or as a warning signal.

Mental Imagery in Psychopathology

Perceptual information accessed from memory has been coined 'mental imagery', where an individual can imagine autobiographical events from the past, or time-travel forwards by generating a series of never-experienced images by seeing with the mind's eye or hearing with the mind's ear and so forth. In this way, mental imagery differs from verbal thoughts (28, 29). In psychopathology, intrusive affect-laden images prove problematic across a number of illnesses, from anxiety-based disorders (30) to depression (30-32). Targeting such maladaptive mental imagery has proved successful across a range of psychopathology (30).

Despite being highly co-morbid with anxiety (33, 34) BD has failed to capture the interest of the imagery-oriented research community until recently (24). Prior to starting this thesis, only one paper addressed the presence of traumatic intrusions in BD-I patients where 45% of the participants with bipolar I disorder reported experiencing intrusive memories i.e. memories which involved a vivid image of a specific event (35). A second study addressed the role of imagery in retrieving a specific memory in individuals with remitted BD where across the whole sample (which included individuals with remitted unipolar depression), 95% of specific memories that were recalled involved a mental image (36). If mental imagery is a salient cognitive process in BD, its incorporation in therapy may contribute to the innovation that is required from current CBT approaches (22, 23).

Mental Imagery and Bipolar Disorder

Figure 1.1 depicts a recently proposed model from our group (Experimental Psychopathology and Cognitive Therapy, University of Oxford) hypothesising the

role of mental imagery on emotion in BD, informing the basis of this thesis (24). The model purports that mental imagery has a role to play in the emotional volatility that is so characteristic of BD, in that bipolar patients could be especially prone to mental imagery. In particular, mental imagery is believed to act as an amplifier of all mood states: anxiety, depression and (hypo)mania. The top cycle in the model illustrates the role of negative imagery in amplifying anxiety in BD, where internal and/or external triggers are believed to generate a threat-interpretation, fuelling anxious mood which is maintained and increased by the presence of negative imagery . The bottom cycle parallels the top, illustrating how positive imagery might contribute to manic mood elevation. In testing this model, recent research has indicated that the experience of heightened mental imagery (in particular imagery of the future) is associated with BD patients who present with unstable versus stable mood (24).

The diagram pertaining to the Holmes et al model (24) is an illustrative diagram, providing a graphical representation of two emotional states in BD: anxiety and mania (Figure 1.1). It should be noted that Holmes et al (24) hypothesise that mental imagery has the potential to amplify all moods in BD, including depression. For simplicity, depression was not included in this graphical representation of the model. The inclusion of depression, or indeed any other emotional state, would follow the same cycles that are depicted for anxiety and mania. For example, a trigger may increase the presence of depression-associated imagery, fuelling depressed mood. The inclusion of anxiety in this graphical representation is due to the inception of this model which was based on the model for the role of mental imagery in panic disorder (37). This then evolved to include mania in the graphical representation of how imagery could amplify mood in BD.

The implication, therefore, is not that mental imagery is more relevant to anxious mood compared to depressed mood. Given the established association between mental imagery and anxiety (30), imagery may be one cognitive process for understanding anxious mood in BD, in comparison to other cognitive processes such as verbal thinking. Further, there is increasing evidence for an association between mental imagery and depression (25, 31). Therefore, the overarching implication is that mental imagery may be one key cognitive process for understanding mood in BD. Although the diagram illustrates this mood amplification for anxious and manic moods, this is not intended to preclude depression. For example, the model would hypothesise that if negative imagery is triggered by an external or internal influence, this may increase the prevalence of depression-based imagery (for example, an autobiographical image), fuelling and amplifying the experience of depressed mood.

Indeed mental imagery is associated with unipolar depression, and interestingly there is some overlap in the experience of imagery in unipolar depression to BD. First, Holmes et al (24) hypothesised that prospective imagery may be important in BD and may influence goal-orientated behaviour. In an earlier study, flash-forward (prospective) imagery of suicidal acts were identified in remitted unipolar depressed patients (32). This flash-forward suicidal imagery has recently been identified in patients with BD (38). Interestingly, the findings in patients with BD were in line with the Holmes et al model (24) which hypothesises that imagery may be particularly powerful in BD, as patients with BD reported their suicidal images of the future as more compelling compared to patients with unipolar depression. Second, negative autobiographical imagery which is associated with unipolar depression has also been reported in BD (39).

Regardless of whether a depression-based image is a prospective image of a future suicidal act or an autobiographical image from the past, the Holmes et al model (24) hypothesises that the experience of this imagery has the potential to amplify depressed mood. There is also the potential to understand how (depression-based) imagery may differ between unipolar and BD. For example, dysphoria has been associated with a lack of positive prospective imagery (40), whereas the model predicts that positive prospective imagery may be prevalent in BD and amplify manic states, thereby distinguishing mania from depression.

In this thesis, the experience of elevated lifetime hypomania, defined by the term BPP, is intended to be informative of BD, as lifetime hypomania is one (of many) vulnerability factors for the onset of clinical BD (11-13). The model is not intended to equate lifetime hypomania with clinical BD as hypomania is by no means the only route to BD. For example, early experiences of depression are also associated with later onset BD (41).One key symptom which differentiates BD from unipolar depression is the experience of (hypo)mania. Therefore, volunteers ranging on a continuum of the BPP were selected for investigation in this thesis, rather than selecting a sample ranging on a continuum of depressive symptomatology. Interestingly, in studies 1-3 of this thesis, individuals with the BPP reported significantly greater depressive symptoms compared to controls. Utilising individuals who exist on a continuum of hypomanic experience, for the purpose of being informative of clinical BD, has been conducted in previous research (14).

The Holmes et al (24) model may not just be a model of anxiety within bipolar populations as the model hypothesizes that mental imagery has the ability to amplify all mood states, such as mania and depression, in BD. In addition, the wider implications of the model extend beyond anxiety: for example, in hypothesising the

role that mental imagery may have to play in mood instability and suicidality in BD. However, the premise/ conception of the model originated from the fact that anxiety is highly prevalent in BD (42); that it is little understood in BD; that mental imagery is a cognitive process which is well-associated with anxiety; that mental imagery has a powerful impact on emotion; that BD is associated with extreme experiences of emotion; and finally that mental imagery may be one cognitive pathway to the experience of extreme mood states in BD.

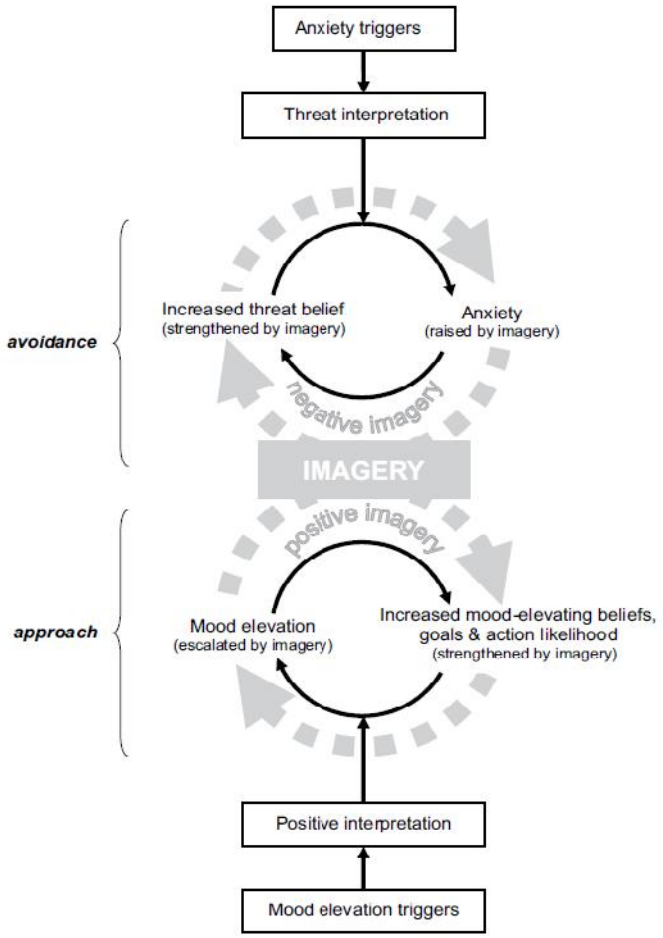
Furthermore, anxiety in BD may not just be due to the prevalence or salience of mental imagery. Simon et al (43), found that greater rumination, which is a verbal cognitive process and quite unlike mental imagery, mediated the relationship between anxiety and suicidality in BD. Therefore, the model is not just a model of anxiety in bipolar populations, but more specifically a model of mental imagery in bipolar populations (and its subsequent contribution to mood amplification, such as the amplification of anxious mood, as well as its potential wider role in mood instability and suicidality).

Examples of other psychological models of BD which also focus on specific aspects of the disorder, rather than attempting to model the whole of BD are briefly provided. First, the BIS/BAS model (44) proposed that individuals with BD have a sensitive BAS, which is responsible for goal-seeking and approach to reward (and linked to positive affect) and a BIS which is sensitive to the experience of punishment i.e. through avoidance (and linked to negative affect). Second, the cognitive model of unipolar depression (45) has been adapted for bipolar disorder. The model for unipolar depression proposed that experiences during childhood can lead to the development of dysfunctional schemas and that events in later life may lead to the activation of these schemas, rendering a production in negative automatic thoughts

and low mood. For BD, Newman et al (46) proposed that the schemas can be bidirectional in that they shift according to mood state, for example, believing one is unlovable (when depressed) to believing that everyone loves them (when (hypo)manic). Lam et al's cognitive model focuses on specific subsets of dysfunctional attitudes regarding goal-pursuit (47). These attitudes are hypothesised to lead to elated mood, where individuals with BD pursue goal related behaviour, enhancing their positive mood state, irrespective of feedback from others. Third, the integrative cognitive model of mood swings and bipolar disorder (48) proposes that (mis)interpretations attributed to internal states prompt attempts to control the internal state through ascent behaviours (increasing activation) or descent behaviours (decreasing activation). These behaviours are hypothesised to trigger further changes in internal states and contribute to the maintenance of symptoms in BD.

This D.Phil. is based on the Holmes et al model of imagery in BD, i.e. that imagery 1) is greater in individuals at the higher end of the BPP continuum and 2) amplifies mood. Chapter 4 of this thesis provides an overview of research exploring mental imagery in BD, which has since emerged from starting this thesis and presents two studies (study 1 and study 2) which investigate whether imagery is greater in individuals with elevated lifetime hypomania versus those with low or no lifetime hypomania utilising laboratory-based measures and experimental tasks. Chapter 5 will explore intrusive imagery in response to a standardised laboratory stressor (a traumatic film). Chapter 7 will test the contribution of imagery to daily mood reactions, in the same sample.

Figure 1.1. A model of the role of mental imagery on emotion within bipolar disorder: imagery amplifies anxiety and mania (24).



In hypothesising about the neural circuitry of this model, the experience of a mental image, either positive or negative, past or prospective, would be expected to elicit activation of brain areas associated with emotion, and this activation would be predicted to be amplified in bipolar samples versus healthy control individuals. What neural circuitry might be relevant here? Neuroimaging studies have indicated that the experience of a mental image renders activation of the visual cortex (49). Imaging studies have found widespread activation of visual, memory and emotion areas when

mental imagery is generated. Specifically, this activation has been found in the middle frontal gyrus, the superior frontal gyrus, the middle occipital cortex, right anterior cingulate cortex and the left inferior parietal cortex (50), as well as the hippocampus, amygdala, entorhinal cortex, parahippocampal cortex and the anterior insula (51, 52).

A meta-analysis of 65 fMRI studies looking at the anatomical coordinates of activation differing between patients with BD and healthy controls, found that during tasks which elicited emotional processing, compared to healthy controls, patients with BD had enhanced activation in the limbic area, including the medial temporal structures (parahippocampal gyrus, hippocampus and amygdala) and basal ganglia (53). Interestingly, a study of emotional processing using a sample of young people scoring high on the MDQ versus those scoring low, indicated that high MDQ volunteers exhibited differential dorsolateral prefrontal cortex and anterior cingulate cortical activation to positive and negative stimuli compared to low MDQ volunteers (54).

Given that limbic activation also occurs when mental imagery is imagined (in healthy controls), one could hypothesise that the experience of a mental image would result in widespread activation of visual, memory and emotion-associated brain areas, and that the activation of the emotion specific regions (the limbic area) would be greater in patients with BD compared to healthy controls. Whether patients with BD have an enhanced activation of the visual cortex, which may potentially render a proneness to experiencing and using mental imagery more so than individuals without an enhanced activation of the visual cortex, remains to be tested.

Measuring Reactions to Stress: The Trauma Film Laboratory Paradigm

In order to investigate whether the BPP confers vulnerability to intrusive negative mental imagery after a stressful event, as hypothesised by Holmes et al (24), chapter 5 utilises the trauma film paradigm as a laboratory-based standardised inducer of intrusive negative mental imagery, hitherto 'flashback memories.' Viewing of the trauma film functions as an experimental analogue of real-life stressors i.e. an analogue trauma in the laboratory. Chapter 5 presents study 3 where the frequency of ensuing flashback memories after viewing the film was compared between individuals with elevated lifetime hypomania versus low lifetime hypomania.

Measuring Mood Reactions to Stress: Experience Sampling Methodology in Daily Life

The Experience Sampling Method (ESM) is an ecological assessment method, allowing for the study of moment-by-moment experiences of participants in their own natural environment. The ESM typically assesses mood and daily-life stress, and the effects of these experiences on variables of interest, for example diagnostic group (55). The ESM is particularly relevant for capturing psychopathology which is believed to change over time within a daily-life context i.e. mood (56). Notably, the ESM has been used to investigate mood reactivity in a number of patient samples where mood reactivity is defined as the extent to which an individual experiences a negative/positive mood reaction to a stressor such as a daily-life event. Patients with depression and psychosis have been found to be more mood reactive to daily-life stressors than their non-clinical counterparts (57-59). Two ESM studies have investigated mood reactions to daily-life stress in (remitted) bipolar patients (60, 61).

Both studies found that patients with BD were not more mood reactive to increasing levels of daily-life stress compared to control volunteers. However, this finding was inconsistent with the authors' hypothesis that compared to controls, individuals with BD would be more mood reactive to stress. It was unclear to the authors why this might be the case, given the extensive ESM findings in patients with psychosis and patients with depression, who have demonstrated greater mood reactivity to stress in comparison to healthy controls (57-59).

Havermans et al (60) used the ESM to compare 38 patients with remitted BD to 38 healthy controls. Participants were asked to report (10 times a day for 6 days) whether they had experienced a positive or negative event and their negative and positive affect at the time of the event. Unexpectedly, there were no differences in mood reactions to stress between patients and controls. However, Havermans et al (60) did find that a sub-sample of patients with a higher number of past depressive episodes experienced more intense negative mood reactions to stressful events compared to controls. Myin-Germeys et al (62) used the ESM to investigate mood reactions to daily-life stress in patients with major depressive disorder (MDD), non-affective psychosis (NAP), and bipolar patients in remission. Patients with MDD and NAP reported significant increases in negative affect and decreases in positive affect compared to healthy controls, in response to increasing levels of stress. This was not the case for negative affect in BD.

Stressful events affect the course of bipolar disorder (BD) and are believed to influence relapse to depressive and manic episodes (63). Mood reactions to such stressors have been hypothesised as one potential mechanism by which this occurs (64). Prior to commencing this thesis, and indeed at present, ESM studies have been unable to demonstrate differences in mood reactions to stress between patients with

BD and controls. This thesis explores which sources of heterogeneity within the BPP, for example mental imagery, influence mood reactions to stress in daily-life. Identification of a salient influence could render a potential CBT treatment target for mood reactions to stress. At the time of starting this thesis, the investigation of a sample vulnerable to BD using the ESM offered a novel approach. Since starting this thesis, ESM studies have emerged using non-clinical samples at-risk of BD; however these studies have not exclusively explored mood reactions to stress. Chapter 7 provides an outline of ESM research in BD and presents study 4. The ESM was adapted for this thesis using mobile phone Short Messages Service (SMS) technology: chapter 2 describes this adaptation and its clinical applicability and chapter 3 outlines the adaptation in light of the research presented in study 4.

Measuring Risk to Bipolar Disorder

The Mood Disorder Questionnaire (MDQ; 19) is a self-report screening tool for BD which assesses lifetime experiences of (hypo)mania and has previously been used to identify vulnerability-markers of the BPP (11, 18, 54). In this thesis the MDQ was used as a measure of 'bipolarity' (i.e. lifetime hypomania experiences which are operastionalised in this thesis as 'the BPP'), rather than screening for BD. Exploring susceptibility to mood, stress and mental imagery in the BPP could be a first step towards understanding if these mood and cognitive processes are ones which contribute to the development of a severe mood disorder.. Lifetime hypomanic symptoms are associated with risk for developing BD (16) and can be used to provide an index of 'bipolarity'. The MDQ was chosen as an index of these lifetime experiences of hypomanic symptoms.

Although there are a lack of studies regarding the prognostic validity of the MDQ, this thesis was not intended to identify individuals who screened for BD

caseness, but instead to identify individuals across the continuum of hypomanic experience. However, it should be noted that a recent review of the MDQ (published after completion of the study design and data collection for this thesis) suggests that the MDQ has a low positive predictive validity (65). That is, there is a low probability of an individual who is identified as having BD by the MDQ, actually having BD. This is particularly problematic for studies where the actual prevalence of BD in the sample is low. For example, in studies where the actual prevalence of BD is approximately 10%, the positive predictive validity was found to be 26.7-33.7% (66, 67). Whereas in samples where the prevalence of BD is higher, 33.1%, the positive predictive value of the MDQ was also found to be higher, 70.8% (68).

In addition, the low positive predictive power of the MDQ is problematic for studies which have used the MDQ as a case-finding tool, where individuals are classed as having BD based on the MDQ alone (65). As a screening measure, the MDQ is an indication of whether an individual might have BD (on the basis of meeting a cut-off which indicates that an individual has had significant lifetime (hypo)manic experiences). Whether an individual actually has BD or not would be established by a follow-up diagnostic interview. Indeed, as a screening measure, the MDQ has a good sensitivity, i.e. a true positive rate of 0.73 and high specificity i.e. a true negative rate of 0.90 (19). Statistically, the correct use of the MDQ, as a screening measure, is not affected by the low positive predictive power of caseness. The positive predictive validity is the most appropriate measure for caseness, rather than the sensitivity and specificity which are appropriate when the MDQ is used as a screening measure. In this thesis, the MDQ was used as an index of bipolarity i.e. a continuum of hypomanic experience, where significant lifetime hypomanic experience was defined as the BPP. Chapter 3 of this thesis provides a detailed

overview of the MDQ including its selection and use in this thesis, as well as discussing the points that have recently been raised by Zimmerman (65) and their implications for this thesis.

Thesis Synopsis

The proposed research aims to compare volunteers with and without the broad bipolar phenotype (high MDQ vs. low MDQ) in relation to key variables from the Holmes et al. (2008) model: mood, stress and mental imagery. A single study was conducted for this thesis (N=110) which is divided into four studies (study 1 and study 2: chapter 4; study 3: chapter 5 and study 4: chapter 6 and chapter 7).

Chapter 2 provides an overview of how mobile phone Short Message Service (SMS) technology can be used in conjunction with ESM approaches to frequently monitor mood in the context of bipolar disorder. This chapter has been accepted for publication (69) and introduces how the experimental ESM paradigm, which is commonly used in research (presented in chapter 6 and 7), can be applied to clinical settings. Since the SMS mood monitoring system has been recently developed in our group, this provides a position piece of how this technology can be harnessed to the clinic as well as experimental psychopathology research.

Chapter 3 provides an overview of the study procedure, particular the main methods used in this thesis: the selection of the MDQ; volunteer sample size and recruitment; the use and novel adaptation of the trauma film paradigm to study mood reactions in the laboratory (study 3: chapter 5); and the use and novel adaptation of the ESM to study mood and stress in daily-life for this thesis.

Chapter 4 presents studies 1 and 2. These studies tested the hypotheses that volunteers with the elevated lifetime hypomania would experience higher levels of mental imagery compared to controls. Study 1 assessed general imagery ability and

intrusive imagery of future events. Study 2 also assessed general imagery ability and intrusive imagery of future events using the same measures as in study 1 and in addition included further measures of general imagery use, future imagery, imagery-based interpretation bias, and an experimental task of emotional reactivity to imagery.

Chapter 5 describes study 3. This study tested the hypothesis that volunteers with elevated lifetime hypomania would experience more frequent image-based flashback memories after an experimental stressor in the laboratory compared to controls. To investigate whether the BPP predicted vulnerability to flashback memories after a stressful event volunteers were exposed to a film designed to meet the Diagnostic and Statistical Manual of Mental Disorders-IV's (DSM-IV) criterion A(1) of psychological trauma (70). Imagery flashback memories to this film footage were tracked over time (six days) using SMS mobile phone technology.

Chapter 6 describes the statistical analysis plan for the ESM study conducted in chapter 7 (study 4). Specifically, it outlines why the traditional approach to analysing ESM data, hierarchical linear modelling, was deemed unsuitable for this data. A description is then provided of the revised statistical approach: Generalized Linear Mixed Model fitted using Generalized Estimating Equations where a logistic function was selected on the basis of the distribution of the data.

Chapter 7 describes study 4. This study investigated the role of bipolarity (MDQ) in exacerbating mood reactions to stress over six days in daily life, in comparison to other hypothesized contributors: neuroticism and intrusive imagery of the future. The ESM was used to assess the association between 1) event-related stress 2) bipolarity, neuroticism and intrusive imagery of the future and 3) the interaction between these and mood reactions to six bipolar-relevant moods: sad, irritable, anxious, depressed, elated and fearful. In addition, we explored which volunteer

characteristic best explained each of the six mood reactions over six days. The ESM was used in conjunction with SMS mobile-phone messages to capture mood and stress data from volunteers over 6 days. Volunteers used text-messaging to provide responses.

Finally, chapter 8 provides an overall discussion of the work from this thesis including limitations and future directions. For an overview of the studies conducted in this thesis, see also Figure 3.2 in chapter 3.

CHAPTER 2

Contemporary Approaches to Frequent Mood Monitoring in Bipolar Disorder

Abstract

Mood fluctuations are problematic in bipolar disorder. Current approaches to frequent monitoring of mood in bipolar disorder are paper diaries and electronic handheld devices. These approaches are limited in several ways, notably in the reliability of the data being collected which is often retrospectively reported. The experience sampling method offers a research paradigm which could be modified for use in clinical settings, to real time frequent mood monitoring. Mobile phone technology has also recently been developed to monitor weekly mood in a bipolar sample, demonstrating successful compliance rates. We propose the use of mobile phone technology as a novel method for frequently monitoring mood in bipolar disorder.

Overview

This chapter provides a review and position statement regarding how mobile phone Short Message Service (SMS) technology can be used in conjunction with an Experience Sampling Method (ESM) to frequently monitor mood in the context of bipolar disorder (BD). This chapter has been accepted for publication (1) and introduces how the experimental ESM paradigm, which is commonly used in research (presented in chapters 6 and 7), can be applied to clinical settings. Since the SMS mood monitoring system has been recently developed in our department (Department of Psychiatry, University of Oxford), this provides a position piece of how this technology can be harnessed to the clinic as well as to experimental psychopathology research.

Mood Fluctuations are Problematic in Bipolar Disorder

Emotional volatility is a characteristic feature of bipolar disorder, but our understanding of problematic mood fluctuations remains limited. Long term chronic mood instability defines a poor clinical outcome for some patients (2-4). In the short term, mood fluctuations can occur frequently when individuals with or without mood disorder react to stressors in their daily lives (5-9). Stressful life events can be particularly tumultuous for patients given their potential to trigger manic or depressive episodes (10-12). Thus, mood volatility in full-blown episodes of mania and depression has the potential to create a persistent state of mood instability between such episodes, for example when patients are euthymic (13, 14). For a case study concerning one variety of fluctuation see Lam and Mansell (15). We need to improve our understanding of such fluctuations.

We argue in this paper that improving the methods by which we collect information on frequent mood fluctuations is key to encourage self-monitoring in

patients and better recognise prodromal symptoms in the prevention of relapse. For example, if a patient's mood is frequently being monitored during the course of maintenance treatment and the responsible clinician recognises a change in mood indicative of a prodrome, then that patient could be invited to see the clinician, as a matter of priority. First, a graphical output of the mood monitoring could be displayed, in order to highlight how the patient's responses to the mood monitoring have indicated that their mood has (recently) changed significantly. Second, in discussion with the patient, the clinician could endeavour to identify reasons for the change in mood. It could be due to an environmental stressor (16) or perhaps after discussion, the patient may reveal that they have not adhered to their medication (17) or may reveal that their sleep has been disrupted.

An appropriate adjunctive psychotherapy could be implemented (18), and in conjunction with a clinician, the patient (and perhaps their caregivers) could be encouraged to recognise that particular environmental stressor as a future potential trigger for mood change (and equipped to manage their response to it).Or the importance of adhering to medication in order to prevent significant changes in mood, or maintaining a regular sleep pattern, could be highlight. Alternatively, if mood monitoring is integrated into on-going treatment, for example, Facilitated Integrated Mood Management (19), then any recognition of prodromal symptoms by the clinician could lead to tailoring the subsequent treatment session to address the change in mood, in the manner described above.

Educating and empowering patients to recognise prodromal trigger/ symptoms is associated with significant clinical improvements in relapse prevention (20). In the first instance, the recognition of prodromal symptoms via mood monitoring may require clinical input i.e. a clinician recognises changes in mood when viewing mood

responses from a patient, and notifies the patient. If patients were able to access graphical outputs of their own mood monitoring, this could further assist in their ability to recognise their own prodromal mood states. If necessary, patients could be encouraged to seek clinical support upon recognition of prodromal symptoms. Alternatively, patients (and their caregivers) may feel equipped to manage such symptoms based on prior psychoeducation.

For the busy clinician, one could even hypothesise about a national or localized SMS monitoring facility, where SMS data from patients is collected. A computerized system could be developed in order to alert this central facility when a patient has experienced a significant change in mood. The central facility could contact the patient prior to contacting formal health services, in order to perform an initial risk-assessment. For example, a patient may have entered in their data incorrectly. However, if the SMS mood data is a reflection of the patient's current mood (i.e. not an error) then the central facility could be responsible for contacting the patient's clinician, or if necessary, emergency services.

Current Approaches to Frequent Mood Monitoring

Mood monitoring in the clinic during psychosocial treatment of bipolar disorder has typically utilised paper mood charts on a weekly basis (21), see for example Colom and Vieta (22). Completion of these mood charts in bipolar disorder has predominantly been retrospective. This may mean recalling mood states after several days or, in the case of Life Charts, after weeks or even months. Such information is liable to recall biases as well as being time consuming for clinicians to review such information (23). Whilst such mood charts continue to be used in bipolar treatment, they could be improved and their limitations render their clinical and research value questionable.

Methods of symptom monitoring in the laboratory may provide clinicians with a more refined method of frequently monitoring mood and provide a constructive adjunct to monitoring outcomes in both psychological and pharmacological treatments. Research paradigms such as ecological momentary assessment (EMA; 24) and the experience sampling method (ESM; 25) involve repeatedly assessing variables of interest over time in the instantaneous context of participants' daily lives. Data are collected prospectively, where participants self-report on mood, stress, thoughts, activities and so forth multiple times a day for up to six days in paper diaries (5, 7, 8). Not only does this methodology allow for charting mood variation within a day and across six days, but it also allows for quantifying 'reactivity.' Specifically, the repeated assessment of variables allows researchers to examine how one variable may change in the relation to another. In mood disorders, the primary interest has been the change in mood in response to daily stressors (26). However, stressful life events may not only be an independent variable which impacts on mood. Stressful life events may in fact be a dependent variable, where mood is the independent variable.

The stress generation hypothesis for unipolar depression (27) purports that individuals with depression will experience more dependent negative life events in that an individual's low mood actively affects the experience of stressful life events. This is specific for life events which are within the individual's control, for example terminating a relationship and not for life events which are outside the control of the individual, for example, the death of a family member. Consequently, the stressful event may exacerbate symptoms and could render relapse into a depressive episode. Therefore, the relationship between stress and mood could be considered to be bi-directional. Research has indicated that this hypothesis can be extended to the experience of bipolar symptomatology (28). Repeated assessment using an ESM

would not only allow for the investigation of daily stressors as an independent variable affecting mood, but would also allow for the investigation of mood as an independent variable affecting experience of daily stressors which are within an individual's control.

Examples of Frequent Mood Monitoring in Bipolar Disorder

In bipolar disorder, Havermans et al (29) used an ESM to compare 38 patients with remitted BD to 38 healthy controls. Participants were asked to report (10 times a day for 6 days) whether they had experienced a positive or negative event and how pleasant, stressful and important the event was. Participants were signalled to respond by a watch which would generate an alarm. The alarm was programmed to generate at random, in 10, 1.5 hour intervals between 7.30am and 10.30 pm for 6 days. Participants then completed a paper diary with their responses and the time at which they completed their responses. Participants indicated whether they had experienced a positive or negative event since the previous watch-alarm and then rated this event on a 1-7 Likert scale for how pleasant (1 'not at all pleasant' to 7 'very pleasant'), stressful (1'not at all stressful' to 7 'very stressful') and important (1 'not at all important' to 7 'very important') the event was. A sub-sample of patients with a higher number of past depressive episodes (4 or more episodes) perceived negative events to be more stressful in comparison to patients with a lower number of past depressive episodes (less than 4 episodes).

Myin-Germeys et al. (2003) used an ESM to investigate mood reactions to daily-life stress in patients with major depressive disorder (N=46), non-affective psychosis (N=42), and bipolar patients in remission (N=38) and healthy controls (N=49). As with Havermans et al (29), participants were signalled to respond at random, in 10, 1.5 hour intervals between 7.30am and 10.30 pm for 6 days by a watch

alarm. Participants then completed a paper diary with their responses and the time at which they completed their responses. For daily-life stress, participants rated their current activity at the time of being signalled on three 1 ‘not at all’ -7 ‘very’ Likert scales in response to: ‘I am not skilled to do this activity’; ‘This activity requires effort’; ‘I would rather do something else’. The mean of these responses formed the stress score. For negative affect, participants rated 4 mood adjectives on 1 ‘not at all’ -7 ‘very’ Likert scales: down, guilty, lonely and anxious. The mean of these formed the negative affect score. Similarly, for positive affect participants rated: happy, cheerful and satisfied and the mean of these formed the positive affect score.

Unlike patients with major depressive disorder and non-affective psychosis, patients with remitted BD did not react differently from healthy controls with regards to negative mood reactions to daily life stress. This result was operationalised by a lack of an interaction effect between group (i.e. BD vs. healthy control) and daily life stress (varying from 1 ‘not at all’ to 7 ‘very’) for the dependent variable (negative affect). That is, BD was not associated with proportionally more negative affect to increasing levels of daily life stress. Conversely, similar to patients with non-affective psychosis, patients with BD did react differently from health controls with regards to positive mood reactions to daily life stress. That is, BD was associated with proportionally less positive affect to increasing levels of daily life stress. Putting mood fluctuations in context (of stress) would be potentially very valuable in the treatment of bipolar disorder. Presently, to our knowledge, these paradigms have not yet been extended for clinical use in symptom monitoring in any mood disorder (26).

As previously stated, refining methods of frequent mood monitoring in bipolar disorder is paramount if relapse signatures are to be identified during and between treatment. In fact mood monitoring may be useful for a variety of reasons, focusing on

‘wellness’ in addition to “pathology”. For example, it could also be useful to help clients to identify what their normal mood fluctuations are like, so that they are able to be aware of and accept a 'bandwidth' of changes in mood, as well as recognising when their mood goes outside this range. The use of paper diaries in EMA and ESM has been criticised, because it assumes the participants’ compliance with the method, when in fact paper diaries can always be completed retrospectively (30). Participants have also been found to complete diary entries ahead of the allotted monitoring-time (31). In a sample of patients who display low compliance to prescribed medication (32), the long training sessions involved with paper and pencil mood charting as well as the increased likelihood of misplacing the charts suggest that paper mood monitoring would be a potential hindrance to clinical work in a bipolar sample.

For these reasons, the use of paper diaries has sometimes been superseded by handheld electronic data collection devices such as personal digital assistants (PDA; 33, 34). Crucially, the reliability of the data is increased because the time at which the participant responds to the monitoring is accurately recorded. But only a few research studies have utilised electronic data collection in bipolar samples (35, 36). Scharer et al (35) described an exciting pre-pilot for 30 patients with Bipolar Disorder where electronic diaries in the form of PDA’s were programmed to resemble the National Institute for Mental Health’s Life Chart Method (LCM). Mood, functional impairment, sleep and medication could be recorded by patients on a daily basis. Sharer et al recommended using electronic diaries in a bid to reduce the data collection and monitoring efforts that are involved when using LCM’s in their original paper forms. Data from the PDA’s could be downloaded onto a desktop computer and printed so that both patient and clinician were able to observe a one month overview of the LCM. Alternatively, data from the PDA’s could be uploaded

electronically by the patient, whereby both patient and clinician could observe an overview of the data electronically, for example, in an email. In a second study, in order to investigate whether daily life mood fluctuations differed according to medication use, an electronic monitoring system, 'ChronoRecord', was used to investigate mood patterns in a sample of bipolar patients who were taking antidepressant medication (N=47) compared to a sample who were not taking antidepressant medication (N=33)(36). Patients reported their mood on a daily basis for 3 months. Over this time period, patients taking antidepressant medication reported depressed mood twice as frequently as patients not taking the medication. The authors suggested that utilising an electronic monitoring system, allowed for the collection of reliable prospective data whereas utilising paper diaries may have run the risk of encouraging retrospective diary-completion (36).

A significant drawback of such electronic handheld devices is the cost: not only in the tool itself but in the development of the necessary software. Consequently any electronic malfunction would also prove costly (30). In less developed societies or at a time when funding for both the health care system and scientific research faces cuts, such methods do not seem widely translatable to the clinic. Lengthy training sessions are also required for electronic devices, which may prove fatal to successful monitoring if participants are not computer literate. Whilst electronic handheld devices resolve the primary problems around frequent data collection using paper diaries, they remain infeasible to wider application in clinical settings.

A 21st Century Approach to Mood Monitoring: Short Message Service (SMS)

Research has provided a way in which mood monitoring can be improved. Using methods such as EMA and ESM, researchers are able to observe detailed variability of mood over time and the reactivity of an individual to a particular context. The premise of EMA and ESM paradigms are to collect multiple assessments in the context of normal daily life. Frequently completing a paper diary or a PDA, i.e. interjecting a foreign data collection instrument into participants' daily lives, may have a major negative impact on the validity of the data. Clinically, the frequent use of socially unusual instruments could render an element of stigmatisation.

Consequently, we advocate utilising participants' own mobile phones as a novel method for frequently monitoring mood in bipolar disorder. This SMS system was recently developed at Oxford University, where the need for an inexpensive and uncomplicated method of frequently collecting mood data in bipolar patients was recognised (23, 37). Participants are signalled by their phones to respond to a question, to which they simply have to text back their response by short message service (SMS). Similar to PDAs, the reliability of data is increased by the ability to record the time at which the participant responds. Mobile phones are very widely used and understood. Little social stigma is attached to the frequent use of mobile phones, thus this method of data collection may have good acceptability. This approach has already been utilised in collecting weekly mood stability data for an average of 36 weeks in a bipolar sample, where, given the 75% compliance rate of weekly texts, it was shown to be a feasible method for the regular assessment of mood over time (23, 38).

Mobile phone SMS technology is by no means the only 21st century approach to frequently monitoring mood in BD. Applications on smart phones are an increasingly popular way for individuals to self-monitor mood, such as the 'optimism' application (39) and the 'mappiness' application (40). These are described in further detail later in this chapter. With the ability to visually chart one's own daily experiences, for example by producing a mood chart on the phone's display screen, such applications have the potential to empower clients with BD in managing and monitoring their own moods. These applications most certainly have an exciting potential in the field of mood monitoring.

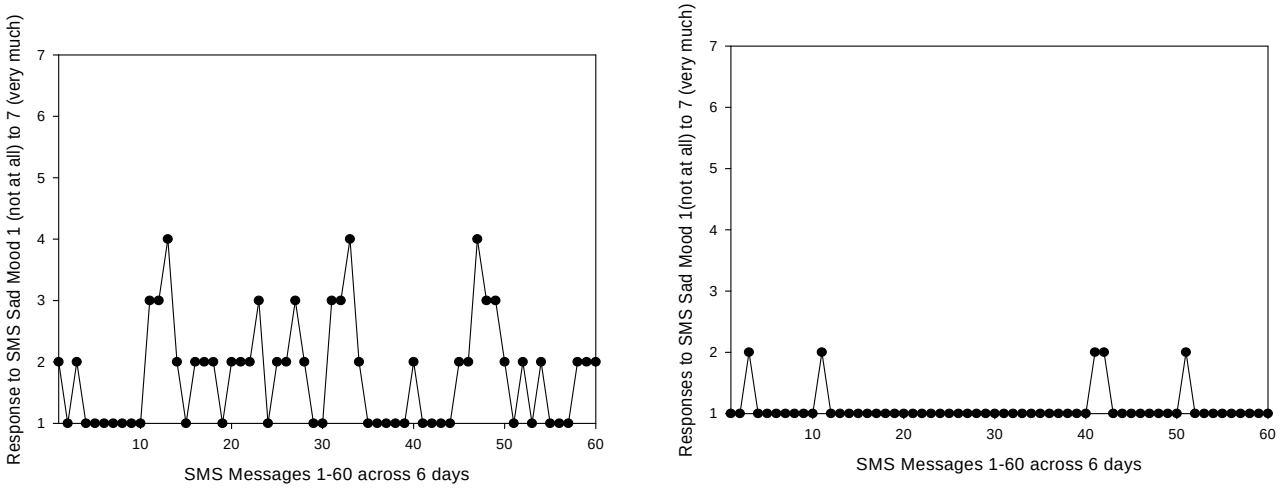
From the Lab to the Clinic: SMS Monitoring in Practice

Presently, the use of mobile phone technology has rarely (and only recently) been employed in conjunction with EMA and ESM paradigms. Studies are beginning to appear which use mobile phone technology with ESM and EMA frameworks. For example Reid et al (41) assert they were the first to utilise mobile phones with ESM. They monitored current activity, mood, responses to negative mood, stresses, alcohol and cannabis use in a sample of 18 adolescents showing a good level of use of the system, though detailed conclusions are precluded by the small sample size. The use of mobile phone technology under an ESM or EMA framework for bipolar disorder is limited. Depp et al (42) used mobile phones with an experience sampling framework to facilitate case management for clients with bipolar disorder and schizophrenia. Other mobile phone programs for mood disorder have recently been developed and are currently being evaluated in clinical trials, for which we eagerly await the results. For a commercially available system for monitoring depression and bipolar disorder, see the "optimism" application which is available on the internet and as an iPhone application (39).This allows users to track their mood and behaviour, observe charts

of their data, identify triggers and plan wellness strategies. Future results from this promise exciting developments.

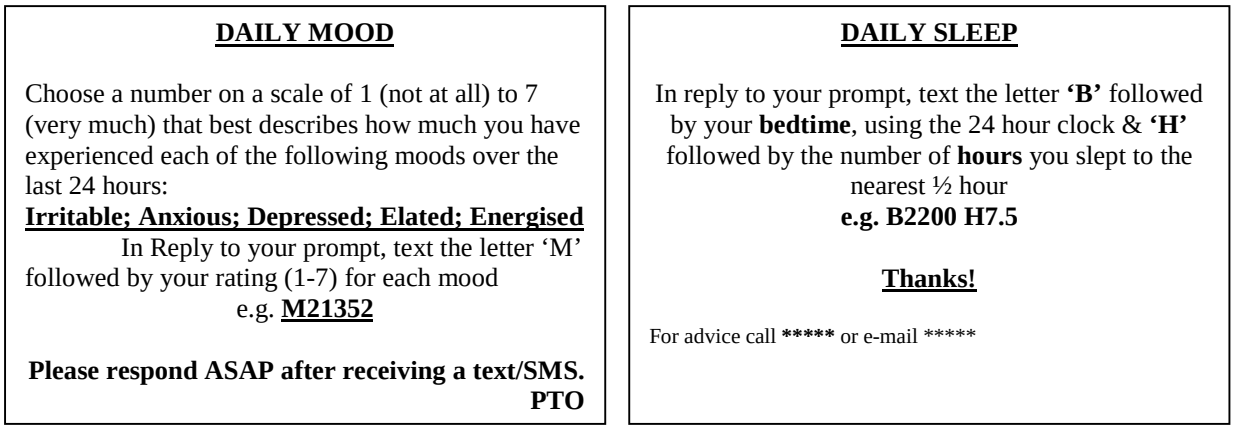
In a clinical environment the intense frequency of the data collection may not be suitable for monitoring bipolar mood over a long period of time. We have piloted the development of an SMS interface that would be more suitable for frequent mood monitoring in a bipolar sample, which allows for charting mood (and any other variable of interest, such as sleep) on a more frequent basis than just weekly. A recent paper from our clinic by Bopp et al (23) provides an example of the SMS interface in action for weekly data using our system, see also Holmes et al (43). Presently, a week-long more intensive ESM study is in progress. Individuals are asked to rate their mood in reference to an adjective, for example 'depressed'. They rate the mood word on a 1-7 Likert scale (anchored from 'not at all' to 'very much') as to what extent they are experiencing the mood at the moment in time that they text back. Participants are prompted to respond 10 times a day for 6 days. For an example of depressed mood ratings over 6 days, please see Figure 2.1 which illustrates one participant with high mood variability and one with a more stable mood profile. Of qualitative interest, participants in the study have spontaneously reported benefits from becoming more aware of their daily mood. Compliance to the SMS interface to date is good with no individuals being unable to complete any responses at all, and 91/97 participants able to complete at least 20% of the total responses (the required amount for inclusion in ESM analysis (44).

Figure 2. 1. Two mood output charts of depressed mood when sampled 10 times daily for 6 days for one participant with high mood variability (left hand side) and one participant showing a clearly stable mood profile (right hand side).



It could be used in tandem with other convergent objective measures e.g. actigraphy for sleep (45). We advocate this approach to be both usable for the participant and feasible for the clinician/researcher. For example, as individuals are familiar with their own phones, only a short 15 minute orientation to the instructions is required. In addition to this, participants are provided with credit card sized instructions to carry with them, which are designed to assist them in responding to the SMS prompts (Figure 2.2).

Figure 2. 2. Credit card sized instructions used to assist users in responding to SMS prompts for daily mood and daily sleep.



Users of this approach text their response to each message they receive, and their reply is automatically captured by central computer system. The investigator can easily generate and interpret a mood chart for visual inspection by the patient and clinician. Mood data is collected 'there and then' so that the mood chart is an accurate as possible reflection of the user's mood during the week. There is no risk of mood charts being lost. Such a chart would prove a useful adjunct to therapy and is akin to a one week cognitive behavioural therapy (CBT) mood chart. Whilst the emphasis of this paper regards mood fluctuations in response to stress, we recognise that there are further bipolar-related variables which could provide richer information in therapy. Mobile phone technology is flexible and could be used to sample other variables of relevance to bipolar disorder in addition to mood such as daily activities (8), goals and planning (46), memories, (47) and intrusive future images (48). Further adaptations of the SMS system could include monitoring a bespoke variety of beliefs, behaviours, thoughts and imagery (49), which tracked over time would provide richer CBT-relevant information.

There is an exciting emergence of new technologies and applications for mood

monitoring. For example, the “mappiness” application on the iPhone (40) allows someone to monitor how their feelings of happiness change according to their environment. One can imagine how technologies such as this could be refined to help people with mood swings e.g. in identifying environmental triggers. We acknowledge that reactions to stressors, whilst an important starting point, may not be the only cause of mood instability. Long-term instabilities in self-regulatory systems could also be caused by multiple systems with conflicting standards (50) whereby no stable mood is reached and the individual oscillates between two mood states. The flexibility of monitoring via mobile phones would allow for clients to provide feedback about their own goals and emotion regulation attempts. Future developments could expand SMS technology, and exploit the opportunity not only for numerical responses but for more qualitative data via written verbal text messages, to test this.

Another useful future development would be to collect situational information at the time of the ESM/EMA mood ratings, in a bid to enhance the utility of the ‘just in time and just in place’ ratings and in better understanding mood fluctuations and relapse signatures. For example, knowledge about situation information from a series of text messages could be reviewed and highlight what situational triggers might lead to a change in mood. Presently we are using the SMS interface to collect information about participants’ stress-context (in conjunction with their mood) by asking them to briefly describe the most important event that has occurred to them since the previous message that was sent to them that day. Participants then rate this event for how pleasant they found it on a Likert scale of 1 (not at all pleasant) to 7 (very pleasant). An example of the former type of event might be “being diagnosed with diabetes” and for a very pleasant event “a meal in a lovely restaurant in Oxford”.

Utilising mobile phone technology may prove to be a practical method of

frequently monitoring mood (and other variables) in bipolar disorder. Mobile phone monitoring improves on the limitations of paper diaries and PDAs that are currently in use, by increasing the reliability of the data being collected and potentially increasing acceptability and frequency of responding in participants. However, there are challenges of using this type of mobile phone monitoring, such as ensuring privacy and security, as personal data could be attributed to a personal contact number. Another issue is that of managing risk if a client, for example, has generated high scores. Clearly, this is a topic which requires clinical sensitivity and ethical decisions at a local level. For an overview see Proudfoot and Nicholas (51) and Shapiro and Bauer (52). This novel approach is intended to aid clinicians and researchers in better recognising prodromal symptoms as well. It is hoped that this system will allow patients to have control over monitoring their own mood variation. Moreover, it forms part of a more computerised vision of improving the care and treatment of people with mental health difficulties (53, 54).

This chapter presents how the ESM can be used in conjunction with mobile phone SMS technology to frequently monitor mood in clinical settings for patients with BD. In this thesis, we utilised the ESM in volunteers ranging across the continuum of the BPP; the selection of these volunteers using the Mood Disorder Questionnaire (MDQ; 55) is outlined in chapter 3. In addition, chapter 3 presents how the ESM was adapted with mobile phone SMS technology for the purposes of use in a research setting. The use of the adapted ESM in a research setting offers an insight into the feasibility of frequent mood monitoring in clinical populations using mobile phones. In addition, chapter 3 also presents how the mobile phone SMS technology was also adapted for use in the trauma film study presented in chapter 5 (study 3).

CHAPTER 3

Study Procedure and Methods

Overview

This thesis takes a continuum approach to studying psychopathology by exploring mood, stress and mental imagery in individuals ranging across the continuum of the broad bipolar phenotype (BPP) who, as outlined below, are believed to be informative of bipolar disorder (BD) proper (1). A single procedure was conducted for this thesis (N=110) which is divided into four studies. All volunteers (N=110) completed the Mood Disorder Questionnaire (MDQ; 2) which was used to identify individuals across the spectrum of the BPP. An overview of the MDQ and how it was used in this thesis is presented in this chapter. The laboratory-based measures and experimental tasks used in study 1 and study 2, which explored whether the experience of mental imagery is greater in individuals scoring high on the MDQ compared to those scoring low, are reported in chapter 4. The novel adaptations of the methods used in study 3: the trauma film paradigm (chapter 5) and study 4: the Experience Sampling Method (chapter 7) are described in this chapter. An overview of the selection of the target sample-size is also provided in this chapter. Finally, a summary of the overall study procedure is described.

The Mood Disorder Questionnaire

Background

One of the most widely studied self-report screening tools for BD is the MDQ (2): a paper-and-pencil tool assessing the experience of lifetime (hypo)mania (Appendix 3.1). The MDQ has been translated into sixteen languages (3) and has been

advocated for use by primary care physicians (4, 5) and for use in secondary care in the U.K. (6, no.38, p.15).

The MDQ is a self-rated screening measure composed of three sections. The first section is a list of thirteen (hypo)manic symptoms. Participants indicate yes or no as to whether they have ever experienced that symptom in their lifetime. The second section is a yes/no question where participants indicate whether any symptoms reported in section 1 co-occurred. The third section assesses the functional impairment of any symptoms reported in question 1. Participants select one of four options: no problem, minor problem, moderate problem, severe problem.

Development and Properties of the MDQ

Hirschfield and colleagues (2) developed the MDQ under the principle that BD was often under-diagnosed (7) and that a brief screening tool may aid clinicians in identifying BD in patients who present with BD-comorbid psychopathology. Thereby treatment could be promptly implemented in individuals who may otherwise be subject to the detrimental consequences of delayed diagnosis (8).

Hirschfeld and colleagues (2) used a receiver operator curve to determine an optimal cut-off score on the MDQ which would successfully identify individuals who screened positive for BD and correctly identify those who did not. An endorsement of seven or more out of thirteen (hypo)manic symptoms (section 1), a positive endorsement of co-occurrence of these symptoms (section 2) and an indication that the symptoms were moderately or severely functionally impairing (section 3), rendered a positive screen. The sensitivity of this cut-off, i.e. patients who screened for bipolar spectrum disorders (BSD) on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) and were correctly identified by the MDQ was 0.73. The specificity i.e. patients who did not screen for BSD on the SCID (9) and were

correctly identified by the MDQ was 0.9. Therefore, the cut-off advocated by Hirschfeld and colleagues (2) indicated that approximately seven out of ten individuals with BD were correctly identified and nine out of ten individuals without BD were correctly identified.

In the general population, using the same cut-offs advocated by Hirschfield and colleagues (2) the sensitivity was much lower (28.1%), however, the specificity was higher (97.2%) i.e. almost all true negatives were correctly screened out by the MDQ (10). In assessing the validity of the MDQ in a UK sample recruited from tertiary services, Twiss et al (11) found that the sensitivity of the MDQ for bipolar I (BD-I) was 0.83 but for bipolar II disorder (BD-II) it was 0.67. Specificity for both was 0.86.

Therefore, the MDQ can be effective for screening out true negatives and has a good sensitivity for correctly screening individuals with BD. However, the sensitivity and specificity of the MDQ is less clear in general populations and for individuals with BD-II disorder. Below, the potential reasons underlying the varying sensitivity and specificity rates found with the MDQ and how this was resolved for this thesis are presented, in light of utilising the MDQ in the most effective way possible for identifying individuals with significant lifetime (hypo)manic experience (individuals with a BPP) and those with low or no significant lifetime (hypo)manic experience (individuals without a BPP).

Disparate Sensitivity and Specificity in the MDQ

The MDQ has been subject to criticism based on the disparate sensitivity and specificity reported across various countries and across various clinical samples (12-18). In particular, the MDQ has satisfactory sensitivity and specificity in clinical populations but not in the general population (16) where the low positive predictive

value of the MDQ suggests that false positives are prevalent in the general population (19, 20). One possible reason for these disparities include the use of preselected patients with mood disorders in clinical studies of the MDQ (21). A second reason is thought to be the irrelevance of the question regarding functional impairment (section 3) in the general population who have little to no contact with clinical services and consequently the experience of functional impairment may be minimal.

The issue of the functional impairment question being used as part of the MDQ optimal cut-off has been highlighted when attempting to use the MDQ as a tool to identify cases of BD-II. Numerous studies have identified the MDQ as a stronger case-identification tool for BD-I compared to BD-II (11, 13, 22-26). For example, Miller et al (22) found that the overall sensitivity of the MDQ was 0.69 for BD-I and 0.30 for BD-II. In Zimmerman et al's 2011 review (27), seven studies were identified which had used the original scoring advocated by Hirschfeld and colleagues (2) and then a broader case identification threshold which included reducing the functional impairment to mild or by eliminating this question all together (15, 19, 22, 23, 25, 28). This improved the sensitivity of the MDQ by more than 30% and reduced its specificity by less than 10%. With the original cut-off advocated by Hirschfeld et al (2) the sensitivity was twice as high in BD-I than BD-II whereas with a modified cut-off the sensitivity was roughly the same.

The argument for modifying or removing the functional impairment item of the MDQ is that despite the DSM-IV definition of a hypomanic episode as one which renders a change in functioning, by definition this change does not confer significant impairment. Consequently, requiring an individual to identify moderate to severe functional impairment may incorrectly screen out individuals with BD-II, bipolar disorder not otherwise specified (BD-NOS) or subsyndromal presentations of BD for

example the BPP (11, 22). Miller et al (22) found that revising the third question regarding functional impairment resulted in an increase in sensitivity from 30% to 70% for BD-II. Specificity only dropped from 67% to 64%. Similarly, Zimmerman et al (21) found that the sensitivity of the MDQ was 65% when using the original scoring but increased 75% when reducing the functional impairment requirement to mild or no impairment.

In addition, Zimmerman (29) recently identified the MDQ as being characterised by a low positive predictive power when used as a case-identification tool, particularly in studies where the prevalence of BD in the sample is low. That is, the probability of the MDQ identifying someone as having BD and that individual actually being diagnosed with BD in samples where the actual prevalence of BD is approximately 10%, is 26.7-33.7% (14, 21). Whereas in a sample where the prevalence of BD is higher, 33.1%, the positive predictive value of the MDQ is also higher 70.8% (12). This issue concerns when the MDQ is (mis)used as a case-identification tool (where the predictive validity is the most relevant measure) versus when the MDQ is correctly used as a screening tool (where the sensitivity is the most relevant measure- not the predictive validity (29). Therefore, studies utilising the MDQ as a case-identification tool must be interpreted with caution, in respect to their relevance to clinical BD. This is discussed in more detail later in this chapter.

It should be noted that using the MDQ as a case-identification tool has the potential to render an over-identification of BD cases, as using it in this way renders a low positive predictive power (29). Therefore lowering the impairment threshold may in the first instance appear to be ill-advised, as this has the potential to lead to greater over-identification of BD when using the MDQ. However, the lowering of the impairment threshold is more suited when the MDQ is utilised more appropriately as

a screening measure, as sensitivity and specificity remain good (26). Lowering the impairment threshold of the MDQ has the benefit of ensuring that individuals presenting with hypomanic experiences for example, in BD-II, BD-NOS and subsyndromal presentations of BD, have a greater likelihood of being screened for. Whilst the experience of depression in BD-II has been found to be highly impairing (30) and depression in children and adolescents with BD-NOS has been found to be as impairing as depression in BD-I (31), it should be noted that lowering the impairment threshold of the MDQ pertains only to the experience of (hypo)mania as this is what the MDQ is designed to capture. That is, to have BD-II and BD-NOS clearly involves impairment but this is attributed to the depressive rather than the (hypo)manic component.

Modifying the MDQ Cut-Off for this Thesis

Research to date suggests that the modification of the MDQ cut-off, particularly in light of the functional impairment section, improves the sensitivity of the MDQ. Such a modification was considered to be pertinent for this thesis given that individuals with a BPP, defined by the experience of significant lifetime hypomania, would not be expected to experience significant functional impairment due to hypomania (for example in BD-II and BD-NOS). That is, hypomania is associated with relatively less functional impairment compared to mania (in BD-I). (Although it should be noted that episodes of depression within BD-II (30) and BD-NOS (31) have been found to be highly impairing).

In a later study, the original authors of the MDQ employed a revised MDQ scoring to investigate predictors of BD risk in a currently depressed patient sample (26). An endorsement of seven out of all 15 questions (symptoms, co-occurrence and severity) generated a positive screen. This rendered the cut-off for the number of

symptoms identified to be a minimum of five. If the number of symptoms identified was seven or above, then the co-occurrence of symptoms and the severity of symptoms did not need to be endorsed. In comparison to the original MDQ paper, this new cut-off increased sensitivity to 87% but lowered specificity to 61% in a patient sample. In the general population sensitivity increased to 57% and specificity lowered to 82% compared to the original MDQ paper in the general population (32). This revised cut-off was also used by Kim et al (25) who found a sensitivity of 0.68 and a specificity of 0.63 for BD diagnosis, whereas it was 0.29 and 0.77 with the original scoring. Therefore, this thesis utilised the scoring approach used by Calabrese et al (26) and Kim et al (25). This approach has the benefit of using a lower threshold for section 3, which is repeatedly being advocated by clinicians and researchers using the MDQ (27).

Alternative Screening Tools

Lifetime hypomanic symptoms are associated with risk for developing BD (33) , accordingly lifetime hypomania is thought to be indicative of the BPP (34, 35). Subsyndromal hypomanic experiences in young people are associated with the development of mood and anxiety disorders during adulthood (33) and similarly have been shown to be predictive of future episodes of depression and BD (36). In this thesis, the MDQ was selected as the most suitable tool to assess this as it was specifically designed to capture whether an individual had experienced significant lifetime (hypo)mania. There are a number of alternative screening instruments for BD (37-41). However, in this thesis, a broad bipolar phenotype was defined as the experience of significant lifetime (hypo)mania symptoms such as hypomanic behaviour and thoughts. The MDQ was specifically designed to capture this, whereas some of the most commonly used alternative screening tools for identifying young

people at-risk of BD do not specifically capture this. The Internal State Scale (42) measures recent mood and cognitions and therefore not any lifetime experiences. The Hypomanic Personality Scale (43) captures personality rather than symptoms. The Hypomania Checklist (44) was developed for increasing sensitivity for BD-II and other subsyndromal experiences however in doing this it excludes any experience of BD-I. In addition, the properties of the MDQ allow for identifying whether an individual has experienced significant lifetime hypomania (a score including and above 7) or not (a score below 7). This rendered it an ideal measure because the BPP in this thesis were identified as those with significant lifetime hypomanic experience and controls were identified as those with low or no significant lifetime hypomanic experience. In addition, the MDQ has been successfully used to identify individuals with and without a BPP in samples similar to that collected in this thesis: a predominantly young sample in Oxford (34, 35).

A recent review of the MDQ (published after study design and data collection for this thesis) draws attention to an interesting concern: the misuse of the MDQ as a case-finding tool rather than as a screening measure (29). Though the MDQ has good sensitivity and specificity (2), Zimmerman argues that in using the MDQ as a case-identification tool, one must take into account the predictive value of that tool- the probability that an individual who is identified as having BD, actually has BD- as the sensitivity and specificity are less appropriate in case-finding (29). Indeed, Zimmerman describes the MDQ as having a low positive predictive value (29). Zimmerman hypothesised that in using the MDQ for case-finding, many individuals who screen positive will in fact present with other psychopathology (to BD). This was exemplified by the finding that individuals screening MDQ positive were more likely have a diagnosis of borderline personality disorder than BD (45).

That the (mis)use of the MDQ as a case-finding tool renders at least in one study, an increased likelihood to be diagnosed with borderline personality disorder rather than BD(45), may not be a criticism of the MDQ per se. First, the MDQ is not designed to be a case-identification tool and therefore its use as such is less likely to be a criticism of the items on the measure itself (given Zimmerman's hypothesis that the MDQ may capture psychopathology other than BD) but in its use by the experimenter/clinician. Second, there is much overlap, controversy and lack of clarity regarding the relationship between borderline personality disorder and BD-II. There are those who argue that borderline personality disorder is part of the bipolar spectrum (46, 47) and those who argue that there is little to no relationship between them (48, 49).

For example, a defining feature of BD-II is hypomania and in testing whether there was a relationship between borderline personality disorder and hypomania, Benazzi (50) found that the greatest overlap was between 'impulsivity' in borderline personality disorder and the 'impulsivity' aspect of hypomania i.e. engaging in risky behavior. Therefore, that is not say that the MDQ (designed for capturing lifetime hypomania) must therefore be accounting for alternate psychopathology such as borderline 'impulsivity', but instead, that there is an unclear association between borderline personality disorder and hypomania, and in using the MDQ as a case-finding tool, there is an increased likelihood for those with borderline personality disorder being identified as having BD. This is further support for the ill-advised case-finding use of the MDQ and not necessarily a criticism of what the MDQ is designed to capture i.e. (hypo)mania. Indeed, if individuals with borderline personality disorder do score highly on the MDQ, this may suggest that there is an overlap (in aspects of hypomania) between borderline and BD.

The use of the MDQ in this thesis is not as a case-identification tool but as an index of whether a volunteer had experienced significant lifetime (hypo)mania or not. To this end, volunteers scoring highly on the MDQ are referred to as: high MDQ and those scoring low as: low MDQ. As Zimmerman rightly advocates: the MDQ should not be used for case identification and therefore in this thesis, high MDQ was not synonymous with having clinical BD. It was of interest to identify individuals with significant lifetime (hypo)manic experiences given that hypomania is associated with the development of BD (34, 51, 52). Conceptually, this thesis refers to those scoring high on the MDQ as individuals presenting with a potential BPP in the same way that previous studies have done (35). Other analogue studies have taken similar approaches in using a measure relevant to clinical BD and hypothesising that those scoring highly may have a vulnerability to the disorder (53). Across all volunteers, the spectrum of the BPP therefore represents the spectrum of significant lifetime (hypo)manic experiences. The original use of the MDQ was such that individuals scoring for significant lifetime (hypo)manic experience would suspected of having a likely bipolar diagnoses, which would be established by a follow-up clinical interview. As Zimmerman rightly argues, it was not intended such that those meeting or surpassing the cut-off could be case-identified as having BD.

Summary

The MDQ was selected as the optimal measure for this thesis. It has previously been noted that no optimal cut-offs have been advocated by the authors (54). When used as a screening measure (i.e. that which was intended by its developers), it may be advisable to lower the impairment threshold cut-off if the clinician is interested in a broader spectrum of bipolarity i.e. if there is an interest in capturing service users with BD-II or BD-NOS (27). There is a potential for an

increase in false positives if this threshold is lowered. However, if clinicians follow correct protocol and proceed with diagnostic interviewing after an individual has screened positive on the MDQ, then this would elucidate whether the individual meets diagnostic criteria for any BD. The danger of false positives would arise if the impairment threshold was lowered and the MDQ simultaneously used as a case-identification tool (i.e. without further diagnostic exploration). In this thesis, the MDQ was utilised to capture the spectrum of experiences of significant (hypo)mania and not as a screening tool for identifying possible BD, nor as a case-finding tool. The scoring techniques utilised by Calabrese et al (26) and Kim et al (25) were used to identify individuals with a history of (hypo)manic symptoms i.e. high MDQ (who endorsed 7 or more items out of all 15 in the MDQ) and those individuals without a history i.e. low MDQ (who endorsed 6 or less items in the MDQ).

In a bid to capture risk (rather than current psychopathology) the Mini International Neuropsychiatric Interview- Plus (MINI-Plus; 55) was used to exclude individuals who presented with current depression and/or (hypo)mania. Individuals presenting with other current or lifetime psychopathology were not excluded as previous research has found that individuals scoring high on the MDQ present with comorbidities which parallel those found in clinical BD populations i.e. current and lifetime psychopathology is a feature of the BPP (35).

Novel Adaptation of the Trauma Film Paradigm (Study 3)

Chapter 5 presents study 3 where the experience of flashback memories in response to a standardised laboratory stressor, a traumatic film, were compared between high and low MDQ volunteers. The novel adaptation of the trauma film paradigm to this thesis is presented below.

Overview

Ethical and practical limitations can prevent the study of real-life trauma. The trauma film paradigm is an established standardised laboratory stressor and its application in study 3 (chapter 5) offers a convergent measure of response to stress which occurs in daily-life. The trauma film paradigm involves showing non-clinical participants a short film with a stressful or traumatic content and meets criterion A1 of the DSM-IV definition of post-traumatic stress disorder i.e. witnessing actual or threatened death or serious injury to another (56). In this light, it can be considered an experimental analogue of real-life trauma.

A popular application of the trauma film paradigm regards monitoring the frequency of flashback memories of the film for approximately one week after film-viewing. Flashback memories are defined as "distressing, re-experiencing of the trauma in the form of intrusive, image-based, sensory-perceptual memories" (57). In the 1960s, Lazarus and colleagues pioneered the use of this paradigm, showing that stress responses (heart rate and skin conductance) were inducible in the laboratory using a stressful film (58). Horowitz and colleagues demonstrated that viewing a film with stressful and/or traumatic content lead to an increase in the hallmark symptom of posttraumatic stress disorder (PTSD): flashback memories (or flashbacks) (59). This was the first indication that a film with traumatic content could be used to experimentally study PTSD symptoms such as flashbacks. Crucially, it also highlights that flashback memories can occur after mildly stressful events (such as an experimental trauma film in the laboratory) as well as after severe ones (such as real-life trauma).

Study 3 of this thesis (chapter 5), investigated whether high MDQ volunteers were susceptible to experiencing flashback memories after an experimental stressor, in comparison to low MDQ volunteers. To this end, the trauma film paradigm was

used as a standardised inducer of negative flashback memories. Flashback memories have been identified as a treatment-targetable cognition across a number of (predominantly) anxiety-based disorders (60-63) and depression (63-65). Bipolar disorder is highly comorbid with anxiety and flashback memories have been little-researched in this sample (66, 67). This will be the first study to use the trauma film paradigm in a BPP sample.

The basic methodology of the trauma film paradigm involves two laboratory sessions separated by approximately one week. In the first session, volunteers complete pre film measures (such as pre-film mood), volunteers watch the trauma film, and immediately after the film post-film measures are completed (such as post-film mood and attention paid to film). Following the first laboratory session, volunteers maintain a paper and pencil diary for one week where volunteers record any flashback memories they experience from the film. At the second laboratory session, approximately one week after film-viewing, volunteers complete follow-up measures (56).

The diary is crucial to the trauma film paradigm as it is the medium by which volunteers record their experience of flashback memories of the film. A paper and pencil diary is given to volunteers after viewing the film. Volunteers record the number of flashbacks experienced including a written description of the flashback at three separate time periods over the course of one week: morning, afternoon and evening. Additional information can also be collected, for example whether the flashback is image or verbal based (68).

Trauma film studies have been used to show how the experience of heightened psychopathology in non-clinical volunteers is related to a higher frequency of flashback memories experienced after viewing a trauma film in the laboratory, for

example in schizotypy (69), depression (70) and trait anxiety (71). Study 3 investigated whether the experience of heightened lifetime (hypo)mania (high MDQ) was associated with a higher frequency of flashback memories after viewing the trauma film, compared to the experience of lower or no lifetime (hypo)mania (low MDQ).

The Adaptation of the Trauma Film Paradigm in this Thesis

A drawback of using paper and pencil diaries is the assumption that participants will complete the diary as instructed. In the case of the trauma film paradigm it is assumed that participants will fill in the diary as soon as they have experienced a flashback of the film. Despite self-reported compliance to the diaries indicating that participants have good compliance (57, 70), there is no objective assessment to ascertain whether a participant filled in the diary as instructed.

In a unique study, Stone and colleagues (72) showed that compliance to paper and pencil diaries was in fact poor. A light sensor inside the diary indicated that participants often filled in the diary en-mass i.e. the day or morning before they were due to return the diary. The authors advocated using methods which would allow for a time-stamp to indicate when participants actually responded, for example a Personal Digital Assistant (PDA). However, a significant limitation of PDA's is the cost to the experimenter as well as the training that must be administered in order for the participant to easily use the device (73).

Hence, a novel approach using mobile phones was developed in order to address the methodological limitations of using the traditional paper and pencil diary. The trauma film paradigm was modified for this thesis, by collecting data regarding flashback memories of the film using participants' own mobile phones. In consultation with a computer programmer a system was developed that would

automatically text-message participants, using Short Messaging Service (SMS), to their personal mobile phones at morning (10.30am) afternoon (3pm) and evening (7.30pm) for 6 days immediately following viewing of the trauma film.

The SMS messages were designed to ask volunteers if they had experienced any flashback memories of the film and if so to report the frequency, content and vividness of any flashbacks (similar to the paper and pencil trauma film diary). Volunteers received the following message to their mobile phones: "Please respond with the number of images, the vividness rating and the image descriptions in the next 15 minutes. Thanks! e.g. 'I4 V7 I saw an old classroom." Volunteers were encouraged to reply within 15 minutes of receiving the message, however, all film-related flashback memories that were reported were included in the analysis. Volunteers replied to the prompt giving details of the number of flashbacks they had experienced since the previous message sent to them, followed by a vividness rating of the flashbacks using a pre-determined 1 (no image at all) to 7 (as clear as normal vision) scale, and finally a 'free-text' description of any flashbacks experienced, such that the experimenter could ascertain that they were flashbacks of the film. Appendix 5.2 provides an example of how flashback memories were defined to participants (note that flashback memories were described as 'intrusions' to participants). Appendix 5.3 provides an example of the instructions that participants were given for how to respond to SMS messages regarding film-related flashbacks. Participants were asked to reply in a particular format, such that the data would be automatically captured by Microsoft Excel.

As this was a novel approach to capturing flashback data after viewing a trauma film in the lab, established convergent measures of flashback memories were utilised at the follow up session: the Impact of Event Scale-Revised (IES-R; 74)

which is a clinical measures of the experience of flashbacks and the Intrusion Provocation Task (IPT; 75) which is a laboratory-based task designed to trigger flashback memories. These convergent measures are described in further detail in Chapter 5.

Novel Adaptation of the Experience Sampling Method (Study 4)

Chapter 7 presents study 4 where the Experience Sampling Method (ESM) was used to investigate which variables influenced mood reactions to daily-life stress. The novel adaptation of the ESM to this thesis is presented below.

Overview

One of the most frequently used momentary assessment methods in psychopathology is the Experience Sampling Method (ESM; 76).The ESM is not limited to one particular technique but can be considered as one approach under the momentary assessment umbrella. A second popular approach which shares similar features to the ESM is Ecological Momentary Assessment (EMA; 77). In this thesis, all approaches will be considered as the ESM. The ESM was used in study 4(chapter 7) to sample the experience of mood and stress in daily-life.

One key concern with the expression of psychological disorders is the functional impairments they render to patients' every-day lives. Such impairments are not always easily replicable in the lab (78, 79). Despite this, patients' mood, behaviour and thoughts are typically assessed by aggregated retrospective self-reports in the clinic and the lab, focusing on general experiences (80). Whilst such approaches have been validated and shown to be reliable (81) they adopt an underlying assumption that such variables are stable when in fact some disorders, notably bipolar disorder, are notorious for their unstable expressions (82, 83).

The ESM addresses such concerns. The crux of the ESM is that it allows for the collection of information such as mood, behaviour and thoughts in way that enhances external validity by investigating individuals in the context of their natural environments (84). This is typically achieved by signaling participants multiple times a day, over the course of several days, to fill out a paper and pencil diary regarding their current mood (for example) and the context in which it occurs. Signaling is traditionally achieved by a watch which is given to participants and set to produce an alarm at random intervals within the day. One of the more popular sampling approaches with the ESM is to signal participants ten times a day over the course of six days (84).

The main limitations of the ESM pertain to the sampling devices used to capture the data, similar to the limitations of the diary method in the trauma film paradigm (73). As previously mentioned, Stone and colleagues (72) demonstrated that retrospective reporting is a significant problem with paper and pencil diaries. Although PDA's were introduced as a resolution, there are a number of limitations with these, for example: the PDA's are reactive in that they are not a device which the participant is accustomed to and therefore the PDA in itself may render altered responses in daily-life; PDA's are expensive for the experimenter; PDA's, and even paper and pencil diaries, are not wholly user friendly and much training is required for the participant (73).

The Adaptation of the Experience Sampling Method in this Thesis

Similar to the adaptation made for the trauma film paradigm, in a bid to address the aforementioned limitations, mobile phones were selected as a novel ESM sampling device by which to capture data in participants' daily lives in study 4 (chapter 7). Utilising mobile phones allow us to address the limitations of ESM

research outlined by Bolger and colleagues (73). Mobile phones may not be reactive as some participants may be relatively familiar with them. Certain demographic characteristics may preclude some individuals from being familiar with mobile phones such as socioeconomic status, age and culture. For example, in an analysis of 400 million SMS text-messages, Ling et al (85) found that adolescents used SMS mobile phone technology more frequently in comparison to other age groups. There is also evidence to suggest that some older persons may also be familiar with mobile phone technology. In 2006, 60% of individuals aged between 65-74 years of age and 36% of people aged over 75 years owned and used mobile phones in the UK (86). However, the familiarity with SMS text-messaging was not assessed and ownership may not be indicative of familiarity.

Mobile phone use may not necessarily be exclusive to particular economic groups or societies. In a survey of 2986 children and adolescents in Germany, in comparison to young people of middle and high socioeconomic status, young people in the low socioeconomic group were more likely to own a mobile phone and use their phone more frequently (87). With regards to cultural differences in mobile phone use, the top ten countries according to mobile phone ownership include four lower middle income countries and three upper middle income countries (88). It should be noted that the rankings did not take into account the proportion of individuals with mobile phones in comparison to the country population.

This research suggests that a variety of individuals may be familiar with SMS mobile phone technology. However, the employment of SMS mobile phone technology may not be suitable for all. This may be due to a number of reasons such as age, socioeconomic status and levels of familiarity with technology. The evidence suggests that for some individuals these factors may not preclude familiarity with

mobile phones. Discussion between patient and clinician should (always) consider the individual requirements of the patient, for example, a patient may be more comfortable with using email to frequently monitor their mood than mobile phone SMS technology (89, 90).

Additionally, they are of no cost to the experimenter (other than in reimbursing the cost of SMS messages) as participants' own mobile phones are used. To this end, they are user-friendly and as a time-stamp is available for outgoing and incoming SMS messages, any retrospective reporting is detectable.

As with previous ESM studies (91), the variables of interest (mood and stress) were captured ten times a day for six days. Volunteers were sent SMS messages at random in ten 1.5 hour time slots between 7.30am and 10.30pm. As a novel ESM sampling device was used, an adaptation of how the data were managed was also devised. Original ESM studies require a participant to have sent at least 20 valid responses in order to be included in the analysis. Invalid responses are defined as a response which is missing (no response given to a prompt) and late (the response was no longer than 15 minutes after the prompt). With the use of SMS mobile phones, additional data management approaches were required. Volunteers' SMS messages may have been filled out incorrectly, for example where the volunteer did not adhere to the instructions such that the SMS message was not interpretable for the experimenter- for example incomplete responses. Volunteers may have sent extra SMS messages which were unprompted, for example SMS responses which could not be attributed to a prompt sent by the computer system. Therefore, out of a possible total of 60 SMS messages, any messages which were invalid, that is: (1) missing, (2) late, (3) incorrect, (4) extra/unprompted were not included in the final analysis. After

taking invalid messages into account, volunteers were required to respond to a minimum of 20 valid responses in order to be included in the final analysis.

Finally, ESM research studies traditionally use hierarchical linear models in their analysis. However, the analyses were also adapted for this thesis due to limitations with hierarchical linear models. This is described in full detail in Chapters 6 and 7.

Volunteer Sample Size

In selecting a final target sample-size, previous research using the Experience Sampling Method (Study 3) has used approximately 50 participants per group, regardless of the number of groups used. To the best of my knowledge, no power calculations were conducted in order to ascertain this figure of 50 participants per group in previously published ESM research (91).

Initial plans hoped to achieve a four group design (200 participants) where high and low MDQ participants would also range across the continuum of risk for anxiety. Anxiety was of interest given its hypothesised role in mental imagery and mood (92). The Eysenck Personality Questionnaire- Neuroticism subscale (EPQN; 93) was selected as a measure to capture anxiety. To this end, it was hoped that participants would fall into one of four vulnerability groups (94), based on their scores on the MDQ (using the cut-offs described above where high MDQ ≥7 and low MDQ ≤6) and median split on the EPQN. There groups were as follows: (1) high MDQ high EPQN; (2) high MDQ low EPQN; (3) low MDQ high EPQN; (4) low MDQ low EPQN.

However, with a median score of five on the EPQN, inspection of the first 55 participants showed that very few participants fell into group 2: high MDQ low EPQN and group 3: low MDQ high EPQN (Table 3.1).

Table 3. 1. Sample size for each of the four vulnerability groups out of a total sample of the first 55 participants recruited

Group 1: High MDQ[a] High EPQN[b]	Group 2: High MDQ Low EPQN	Group 3: Low MDQ High EPQN	Group 4: Low MDQ Low EPQN
20	3	2	30

[a] MDQ = Mood Disorder Questionnaire.

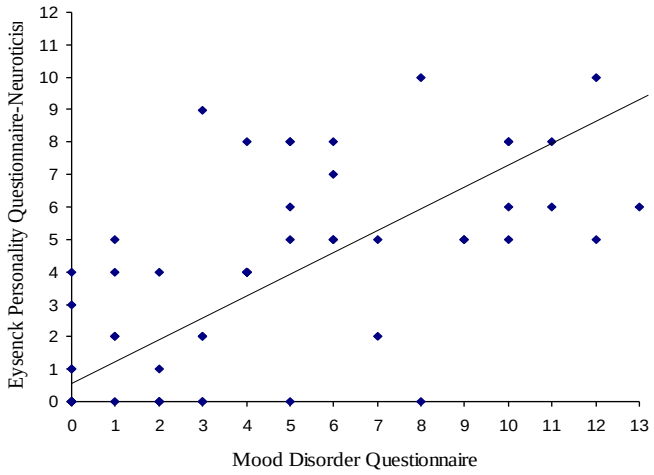
[b] EPQN= Eysenck Personality Questionnaire-Neuroticism subscale.

This unexpected finding was further examined showing a correlation between MDQ and EPQN scores ($r = 0.67$; $p < .001$; $N= 55$) (Figure 3.1). In a larger sample of 4328 first year undergraduate students at the University of Oxford, 614 (14.19%) were in group 1 (high MDQ high EPQN); 250 (5.78%) were in group 2 (high MDQ low EPQN); 1902 (43.94%) were in group 3 (low MDQ high EPQN); and 1562 (36.09%) were in group 4 (low MDQ low EPQN). The proportion of individuals in group 2 in this larger sample (5.78%) reflect the proportion of group 2 volunteers in the first 55 participants of this thesis (5.45%). However, this was not the case for groups 1 (36.36%), 3 (3.64%) and 4 (54.55%) collected in the first 55 participants of this thesis. The dissimilarity in groups 1, 3 and 4 may be due to the nature of the larger sample. This sample was comprised of first year undergraduate students at the University of Oxford who may not be representative of more general samples, such as the first 55 participants tested for this thesis. These findings are unpublished and are part of ongoing data collection, as part of the University of Oxford Student Stress Survey (34).

At this stage of recruitment, it was decided that it would be inappropriate to divide the sample into four groups and a two group design was selected where participants were categorized according to the main variable of interest: the MDQ. This rendered a high MDQ group and a low MDQ group. In accordance with previous

ESM research, the recruitment target was at least 50 participants per group (91).

Figure 3. 1. A scatter plot showing the relationship between MDQ and EPQN scores in the first 55 participants recruited



Study Procedure

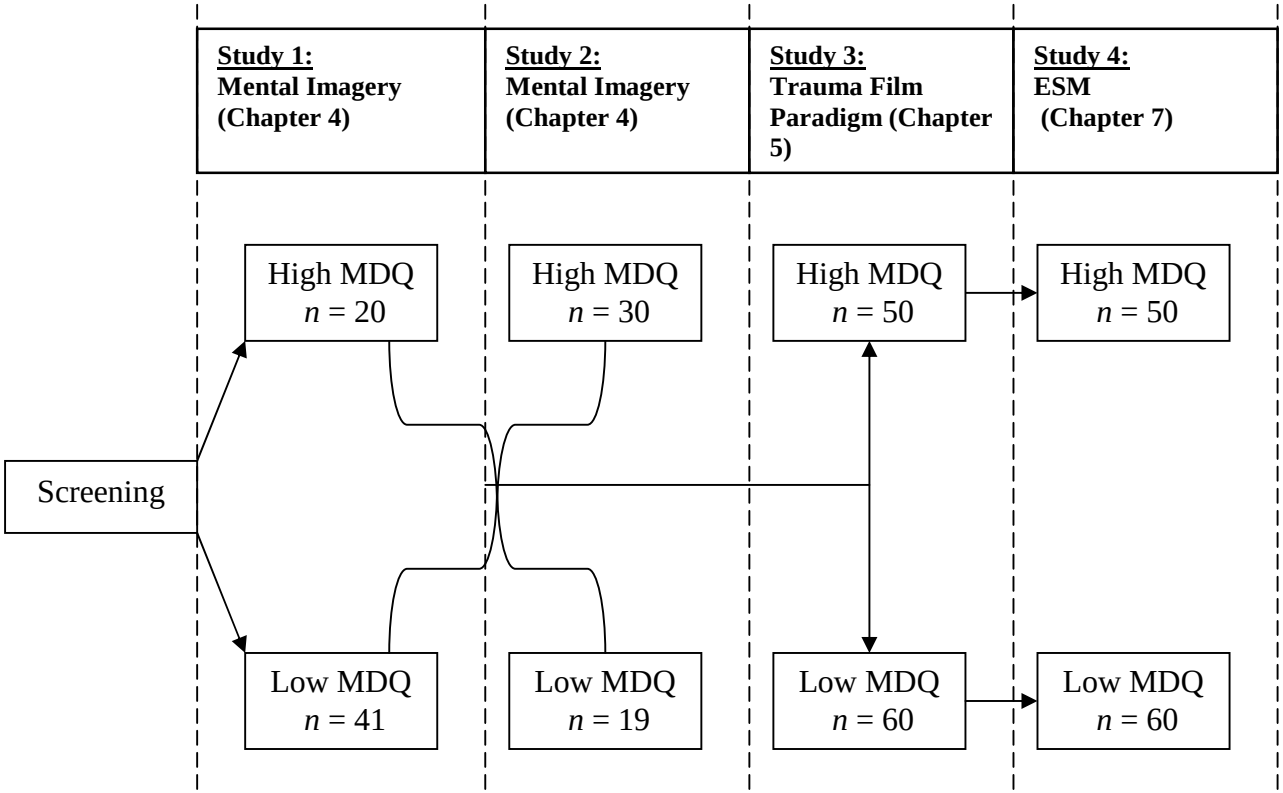
Participants were recruited for a single study. The study was approved by the Central University Research Ethics Committee, University of Oxford (Appendix 3.2). Volunteers were recruited via poster and online advertisements in the local area and universities, seeking those with (high MDQ) and without (low MDQ) hypomanic experience. Please see Appendix 3.3 and 3.4 for an example of posters used.

The inclusion criteria were: (1) aged between 18-65 and evidence thereof; (2) use of a mobile phone; (3) no current depression and/or (hypo)mania. The exclusion criteria were: (1) termination of the trauma film (pertaining to study 3, chapter 5); (2) less than one third of valid SMS mood and stress messages sent i.e. less than 20 out of 60 valid SMS messages (pertaining to Study 4, chapter 6 and 7); (3) unable to attend follow-up session. Appendix 3.5 outlines the participant throughput for the study. Further details of the participant throughput are provided in chapters 4, 5, 6 and 7.

Figure 3.2 provides an outline of the procedure of completed participants (N=110) throughout the study. The experimental methods, measures and protocols

for each study are described in detail in the relevant chapters. The following chapter (chapter 4) presents study 1 and study 2.

Figure 3. 2. Diagram displaying the procedural flow of completed participants (N=110) throughout the study



CHAPTER 4

Study 1 & Study 2: Is the Broad Bipolar Phenotype Associated with a Greater Propensity to Experience Mental Imagery?

The chapter originally presented here cannot currently be made freely available via ORA

CHAPTER 5

Study 3: The Broad Bipolar Phenotype Confers Vulnerability to Flashback Memories after an Experimental Trauma

The chapter originally presented here cannot currently be made freely available via ORA

CHAPTER 6

Statistical Analysis Plan for the Experience Sampling Data

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CHAPTER 7

Study 4: Bipolarity, Neuroticism and Mental Imagery: An Experience Sampling Study of Daily Reactivity to Stress

The chapter originally presented here cannot currently be made freely available via ORA

CHAPTER 8

General Discussion

Overview of the Thesis

The overarching aim of this thesis was to adopt an experimental psychopathology approach to investigate mood reactions and mental imagery in a local sample of volunteers ranging across the continuum of the broad bipolar phenotype (BPP) i.e. those individuals ranging from the experience of elevated lifetime hypomania to low lifetime hypomania. The Mood Disorder Questionnaire (MDQ; (1)) was used to identify groups with high (N=50; ≥ 7 symptoms) and low/no (N=60; ≤ 6 symptoms) rates of lifetime hypomanic experience i.e. 'high MDQ' versus 'low MDQ'. Major and minor life stressors in daily life affect the course of bipolar disorder (BD), and mood reactions to such stressors have been hypothesised as one potential mechanism by which stress affects the course of BD (2, 3). Mood reactions in the context of daily life stress have been well explored in psychosis (4), but the limited research in BD has produced mixed findings (5, 6).

The experience of negative intrusive mental imagery is well established across various anxiety disorders and depression (7) and has a strong impact on emotion (8). The translation of this body of work to intervention development has contributed to successfully targeting mental imagery under cognitive-behavioural frameworks for a number of disorders (9, 10), from PTSD (11) to social phobia (12) and depression (13). At the start of this thesis, only two studies had addressed the experience of mental imagery in BD (14, 15). Tzemou and Birchwood found that 45% of participants with bipolar I disorder reported experiencing intrusive memories i.e. memories which involved a vivid image of a specific event (14). In a study by

Mansell and Lam which investigated the role of imagery in retrieving a specific memory in individuals with remitted BD and remitted unipolar depression, across the whole sample, 95% of specific memories that were recalled involved a mental image (15). Although BD is highly comorbid with anxiety (16), at the time of starting this thesis and indeed at present, our understanding of spontaneously occurring pathological mental imagery as well as mental imagery abilities in BD remains limited.

Holmes, Geddes, Colom and Goodwin (17) hypothesised that mental imagery in BD may amplify mood and contribute to mood instability (see Figure 8.1). This thesis did not study BD patients but instead adopted an analogue approach and compared volunteers with high and low experiences of lifetime hypomania in relation to key variables from the Holmes et al (17) model: mood, stress and mental imagery. Volunteers with significant experience of lifetime hypomania were hypothesised to be informative of clinical BD as lifetime hypomanic experiences are associated with later onset BD (18-20). That is not to say that lifetime hypomania was equated with clinical BD. Early experiences of depression are also associated with later bipolar onset (21), and interestingly, volunteers with significant lifetime hypomania (high MDQ) reported significantly higher depressive symptoms in studies 1-3 of this thesis, compared to control volunteers (low MDQ). Investigating individuals who exist on a continuum of hypomanic experience, for the purpose of being informative (but not predictive) of clinical BD, has been conducted in previous research (22). Specifically, it drew on aspects of the emotion cycles of the model which predict that imagery propensity (1) would be greater in individuals with elevated experiences of lifetime hypomania and (2) that imagery contributes to the amplification of mood states (Figure 8.1). The model by Holmes and colleagues (8) hypothesises that mental

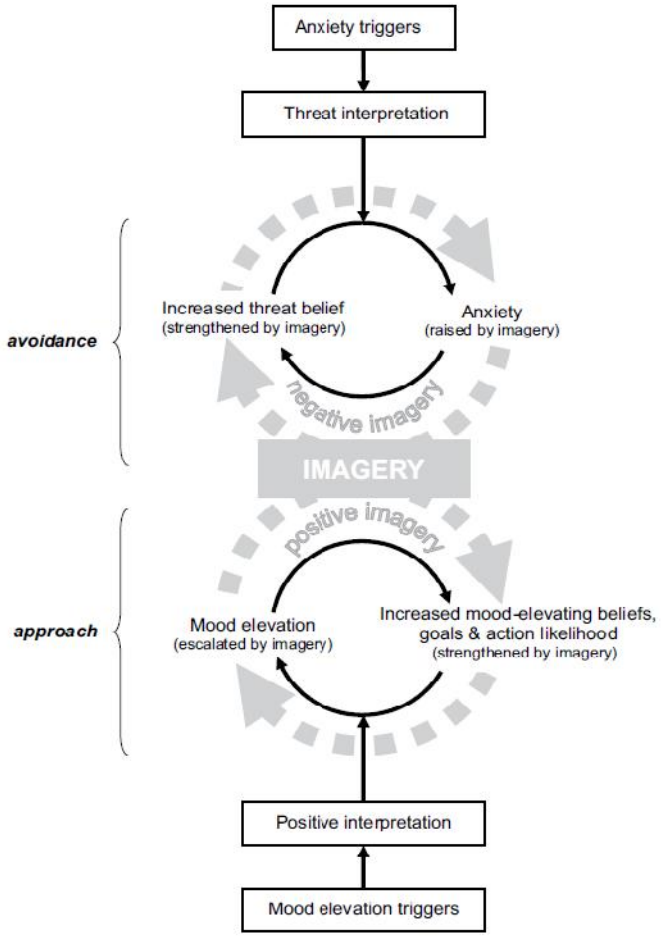
imagery can amplify all mood states in BD. The diagram illustrates this for anxious and manic mood (Figure 8.1). As the diagram is illustrative only, it is not intended to preclude other relevant mood states such as depression.

The amplification of depressed mood might occur, if an individual is triggered by an external or internal influence, perhaps a reminder of a negative autobiographical event such as seeing a photo of an ex-partner. This trigger may exacerbate mental imagery, for example autobiographical images regarding the termination of the relationship and images of being alone. The experience of such imagery would be hypothesised to amplify depressed mood. Furthermore, the wider implications of this model are of relevance to the experience of depressed mood and depression-associated imagery. Holmes et al (17) proposed that prospective imagery is important in BD. Indeed research regarding prospective suicidal imagery processes in depression (23) have been extended to BD (24). Negative intrusive autobiographical imagery has been found to be a characteristic of depression (13) and such imagery has also been reported by patients with BD when describing imagery in depressed episodes (25). Although depression-based imagery was not explored in the BPP in this thesis, there is an exciting potential for future research to examine how such imagery may fuel depressed mood in BD, and how imagery in unipolar depression might differ from imagery in BD.

A large investigation was conducted for this thesis (N=110) which is divided into four studies. Study 1 and study 2 investigated whether self-report trait measures of imagery were greater in individuals with elevated lifetime hypomania compared to those with low lifetime hypomania. Study 3 used the trauma film paradigm to investigate whether individuals with elevated lifetime hypomania experienced greater intrusive imagery (flashbacks) in response to a laboratory stressor (a trauma film) than

individuals with low lifetime hypomania. Study 4 used an Experience Sampling Method (ESM) to test the contribution of bipolarity, neuroticism and mental imagery to daily mood repeatedly sampled in the context of daily life stress.

Figure 8.1. A model of the role of mental imagery on emotion within bipolar disorder illustrating how imagery could amplify anxiety and mania (17).



Main Findings of the Thesis

The findings for each of the four studies are discussed in detail within each relevant chapter: study 1 and 2 (chapter 4), study 3 (chapter 5) and study 4 (chapter 7). In this section, a highlight of the key findings from each study is discussed.

In the current thesis, Study 1 tested the simple hypothesis that high MDQ volunteers would score significantly higher on a measure of general (and non-emotional) imagery use in every day life (Spontaneous Use of Imagery Scale; 26), and on a measure of intrusive imagery of the future (Impact of Future Events Scale;

replicating 27),compared to low MDQ volunteers. As predicted, high MDQ volunteers reported both greater general imagery use and greater (emotional) intrusive imagery of the future compared to low MDQ volunteers. This suggests that individuals at the higher end of the BPP spectrum (versus those at the lower end of the spectrum) may more often use their 'mind's eye' in their daily lives, as well as spontaneously simulating future emotional events using mental imagery. For example, before getting dressed to go out, high MDQ volunteers may use more mental imagery to imagine what they would look like in different combinations of clothes (SUIS) and may experience images popping into their head of how they look and/or people's reaction to their outfit, over the course of the day (IFES). While the current IFES finding replicated an earlier result in a similar sample (27), in the same study Deeprose et al did not find a difference between high and low MDQ volunteers on the SUIS. The reason underlying this difference remains unclear. Understanding the role of general mental imagery use in individuals ranging across the continuum of risk for bipolarity requires further investigation, where it may be of benefit to use experimental tasks such as mental rotation (28) as well as self-report measures such as the SUIS.

Study 2 sought to replicate study 1 (particularly given the discrepancy on the SUIS between study 1 and Deeprose et al (27)). Further it extended it to include additional measures of general imagery use (Verbal vs. Imagery VAS), future imagery (PIT), imagery-based interpretation bias (HIT) , and an experimental task of emotional reactivity to pictures (PWT). In study 2, high MDQ volunteers again reported both greater general imagery use (SUIS) and intrusive imagery of the future (IFES) compared to low MDQ volunteers, replicating study 1. Novel results showed that imagery of self-generated future events (PIT) were reported to have a greater

impact on high MDQ volunteers compared to low MDQ volunteers. Specifically, compared to low MDQ volunteers, high MDQ volunteers were more likely to believe that their negative future images would come true, and felt more as if they were actually experiencing the negative/positive future event when imagining it. Finally, high MDQ volunteers scores indicated that they were more emotionally reactive to negative picture-word combinations (PWT) compared to low MDQ volunteers. Further, they reported greater self-involvement when combining the picture and word (i.e. high MDQ volunteers reported feeling more as if their mental image of combining the picture and word in their mind was actually happening). Together, the findings from the PIT and the PWT suggest that mental imagery propensity in high MDQ volunteers has the potential to be particularly unpleasant. For example, imagining a future scenario where 'people will think you're a failure' has the ability to make high MDQ volunteers, compared to low MDQ, more likely to believe that the image will occur in real-life. Thus, in summary, in study 1 and study 2, the experience of elevated lifetime hypomania was associated with the heightened experience of various types of mental imagery compared to with the experience of low or no lifetime hypomania. The findings from study 1 and 2 are consistent with the Holmes et al model which predicts that imagery propensity is greater in individuals across the bipolar spectrum. The findings from study 1 and 2 suggest replication and extension to a clinical BD sample.

Study 3 examined whether vulnerability to a specific type of mental imagery after a traumatic stressor, intrusive negative imagery (henceforth flashback memories), was associated with the experience of elevated lifetime hypomania. Study 3 tested the hypothesis that high MDQ volunteers would experience more frequent image-based flashback memories after an experimental stressor in the laboratory

compared to low MDQ volunteers. Volunteers were exposed to a film designed to meet the Diagnostic and Statistical Manual of Mental Disorders-IV's (DSM-IV) criterion A(1) of psychological trauma (29). Image-based flashback memories to this film footage were tracked over six days using Short Message Service (SMS) mobile phone technology. Although high and low MDQ volunteers experienced a similar mood reaction at the time of watching the film, the ensuing impact of the film over the subsequent six days on flashback memories was strikingly different: high MDQ volunteers, compared to low MDQ volunteers, reported experiencing almost twice as many flashback memories to the film. This finding was supported by convergent measures at follow up (Impact of Events Scale-Revised (IES-R; 30) and Intrusion Provocation Task (IPT; 31). This is consistent with Holmes et al (17) who hypothesised that individuals with BD will experience heightened intrusive negative mental imagery after a stressful event. The findings from study 3 suggest that an individual at the higher end of the BPP continuum who experiences a stressful (traumatic) event such as a road traffic accident is likely to be repeatedly haunted by the event through spontaneous intrusive mental imagery e.g. experiencing a flashback of an oncoming vehicle heading towards them at great speed. Again, future investigation should be extended from the non-clinical BPP sample used in this thesis to a clinical BD group, in particular with regards to intrusive mental imagery after a naturally occurring stressor (rather than an experimental stressor). It also suggests that those individuals higher on the BPP spectrum may be more affected by horror movies and upsetting scenes on the television.

Further findings from this study found that compared to the low MDQ group, the high MDQ group reported engaging in more safety and avoidance behaviours relating to the traumatic content of the film in the subsequent six days. For example,

compared to low MDQ volunteers, high MDQ volunteers rated “I have been more aware and take greater care when crossing the road” and “I have been more aware of wearing a seatbelt” as being more true, in the six days following film-viewing. This is consistent with the Holmes et al model (17) where negative imagery is hypothesised to strengthen the belief that there is a real threat, increasing the likelihood of avoidance behaviour. Further investigation is required in order to test the causal impact (which was not assessed in study 3) of intrusive negative mental imagery on safety and avoidance behaviours.

In addition, exploratory multiple regressions revealed that neuroticism was the strongest predictor of flashback memories, on two measures of flashback memories: SMS Flashback memories and the IES-R. This is consistent with the notion that there is a strong and established relationship between anxiety and intrusive mental imagery such as flashbacks (32). However, this finding suggests that vulnerability to neuroticism within the BPP renders a susceptibility to experiencing flashback memories after an analogue trauma, rather than hypomanic-vulnerability rendering a susceptibility to flashback memories. Interestingly, high MDQ volunteers reported significantly higher neuroticism than low MDQ volunteers in studies 1-3 of this thesis. It could be that elevated neuroticism within the high MDQ group rendered a susceptibility to experiencing frequent flashback memories after an experimental stressor, in the six days following the film, in comparison to low MDQ volunteers (who in turn reported lower neuroticism). In order to elucidate whether a vulnerability to neuroticism versus a combined vulnerability to both MDQ and neuroticism renders increased susceptibility to flashback memories a four group design could be adopted. Individuals varying in both MDQ and neuroticism (i.e. high MDQ, high neuroticism; low MDQ high neuroticism; low MDQ high neuroticism; low MDQ low neuroticism)

could be exposed to the trauma film and their flashback memories monitored for six days.For example, if neuroticism is crucial to the development of flashback memories (in comparison to hypomania) then the low MDQ high neuroticism group would be predicted to experience more flashback memories to the film in comparison to the high MDQ low neuroticism group. However, if both vulnerability to hypomania and neuroticism are necessary for a powerful susceptibility to flashback memory development then the high MDQ high neuroticism group would be expected to experience more flashback memories than the low MDQ high neuroticism group.

In study 3, the experience of elevated lifetime hypomania was associated with an increased reaction to a laboratory stressor (a trauma film), where the outcome variable of interest was image-based flashback memories to the film. However, while it is important to test reactions in the controlled environment of the laboratory, it is also important to test reactions in daily life. Therefore, study 4 investigated whether mood reactions to everyday stressors which occur in daily life differed across the BPP. Study 4 investigated the role of bipolarity (MDQ) in exacerbating mood reactions to stress over six days in daily life, in comparison to other hypothesized contributors: neuroticism (EPQN) (33) and intrusive imagery of the future (IFES) (34). An Experience Sampling Method (ESM) was used to assess the association between mood reactions and 1) daily stress, henceforth: ‘event-related stress’ 2) bipolarity, neuroticism and intrusive imagery of the future 3) the independent interactions between event-related stress and bipolarity, neuroticism and intrusive imagery of the future. Mood reactions were assessed with six bipolar-relevant moods: sad, irritable, anxious, depressed, elated and fearful. In addition, study 4 explored which volunteer characteristics best explained each of the six mood reactions over six days i.e. bipolarity, neuroticism and intrusive imagery of the future. The ESM data

were collected by SMS mobile-phone messages to capture mood and stress ratings from volunteers ten times a day over 6 days. For statistical reasons (which are outlined in chapter 7), volunteers were considered as one group and were not dichotomised into high and low MDQ, as in studies 1-3. Within a sample ranging across the continuum of risk for BD, higher bipolarity (MDQ), neuroticism (EPQN) and intrusive imagery of the future (IFES) were each associated with various increased mood reactions to event-related stress over six days in daily life. In understanding which of these characteristics best accounted for mood reactions, a model including bipolarity (MDQ) and event-related stress provided the best fit for elated mood reactions. Neuroticism (EPQN) did not best explain any mood, and a model including intrusive imagery of the future (IFES) and event-related stress best accounted for sad, depressed and anxious mood reactions in daily life. These findings are consistent with the overarching prediction of the Holmes et al model (17) which hypothesises that high imagery levels will worsen day to day mood extremes. Repeatedly imaging future scenes after stressful events in daily life, for example imagining the disastrous consequences of missing a bus, could have a significant impact on emotion, more so than an individual's trait bipolarity or neuroticism. It provides a suggestion of a cognitive mechanism by which emotion is elicited i.e. intrusive future imagery.

The next part of the discussion consolidates a selection of the main findings between chapters. In studies 1 and 2, which were both laboratory-based, the high and low MDQ groups differed on their experience of intrusive imagery of the future. In study 4, these frequent spontaneous future images were found to have the strongest impact on negative mood reactions which occurred outside the laboratory, in daily life. In study 3, neuroticism was found to be the strongest predictor of experiencing

image-based flashback memories to the (traumatic) film over the course of the same six days in which mood reactions were captured. Indeed, the high MDQ group reported higher neuroticism across studies 1-3, compared to the low MDQ group. However, in study 4, although higher neuroticism exacerbated mood reactions in daily life, neuroticism did not significantly affect daily mood reactions captured over six days in comparison to intrusive imagery of the future and bipolarity.

Implications of this Thesis

Theory Implications

The results of this thesis supported the model proposed by Holmes et al (17) in that 1) the experience of bipolarity was associated with high imagery susceptibility (study 1 and study 2); 2) the experience of image-based flashback memories was higher after an (experimental) stressor (study 3); 3) daily life negative mood reactions to stress were associated with intrusive imagery of the future (study 4).

Since starting this thesis, emerging clinical (15, 25, 34-36) and non-clinical research (27, 37) has implicated mental imagery as a potentially prevalent cognitive process in patients with BD and in individuals who score high on measures of hypomanic experiences, compared to control individuals, as described in chapter 4 of this thesis. This thesis thus serves to add to these emerging findings.

Study 1 and Study 2. Higher susceptibility to mental imagery in individuals with greater lifetime hypomania (as demonstrated in study 1 and study 2) is of particular interest, as mental imagery is thought to have a special relationship with emotion (38-40). There is some indication that individuals with higher mental imagery ability are more prone to developing fears and phobias compared to individuals with lower imagery ability (41). Study 1 and 2 demonstrated imagery susceptibility in individuals at the higher end of the continuum of the BPP (high MDQ). Mental imagery may

therefore be appropriate to explore as one (cognitive) risk factor for BD, if the experience of extreme emotion is in fact exacerbated by imagery, as opposed to heightened mental imagery being an epiphenomenon of clinical BD.

Across both study 1 and study 2, intrusive imagery of the future (measured by the IFES) was almost twice as high in volunteers with elevated lifetime hypomania versus those with low or no lifetime hypomania. In study 2, both negative and positive self-generated imagery of the future (as ascertained by the PIT) were found to have a more compelling effect on high MDQ volunteers i.e. they felt more as though they were actually experiencing the positive/negative future event when imagining it, and felt as though imagined negative future events were more likely to come true. This 'persuasive' effect of frequently imagining future events (be they intrusive or self-generated) could be detrimental when considering that at a neural level mental imagery processes overlap with perception (42) such that imagery (of the future) may be responded to or acted upon as though it were real (43, 44). For example, mental imagery regarding future suicidal acts was found to be associated with a strong desire to act on the image in patients with BD, compared to those with unipolar depression (36). Although suicidal imagery was not specifically addressed in this thesis, the findings from study 2 tentatively suggest that the compelling nature of negative future images may be present in sub-clinical samples i.e. individuals with elevated experiences of lifetime hypomania.

Interestingly, craving-associated imagery of craved substances in substance misuse have been suggested to contribute to desire and actual substance misuse (45, 46). Substance misuse is prevalent in the bipolar spectrum (47); compelling mental imagery of the future may also be one cognitive risk factor for substance misuse in BD. Likewise, the compelling nature of positive future imagery could be

advantageous i.e. in goal attainment. For example, risk for hypomania in the general population has been associated with a heightened pursuit of goals (48). Compelling positive future imagery may exacerbate and fuel goal pursuit in individuals at-risk for BD. For example, having a manuscript successfully accepted for publication in a high impact journal, such as 'Nature', could trigger positive future imagery such as seeing oneself receive the 'Nobel-prize' in front of an applauding audience of peers and colleagues. Such imagery could fuel the desire to work excessively for long hours in a bid to achieve this illustrious goal!

Study 3. Stressful life events are thought to affect the course of BD by increasing risk of relapse and triggering onset (3). Hypothesised contributors to this process (i.e. manic relapse) are events which disrupt sleep (49) and events which render goal dysregulation (50). Johnson proposed that negative life events can also precede episodes of depression (3). In study 3, after an experimental stressor (a trauma film), intrusive images i.e. flashback memories were more frequent in individuals with elevated lifetime hypomania compared to those with low or no lifetime hypomania. This finding was especially interesting given that the increase in state negative mood after the experimental stressor itself (i.e. across the film) was no different across all volunteers. This would suggest that individuals at-risk for BD have a unique susceptibility to being haunted by image-based flashback memories after a stressful event. Further, this might be driven by processes other than state mood changes in response to the actual stressor (51)- perhaps a potential possibility includes memory consolidation processes.

While the current study is in a non-clinical context, it may be of interest to consider potential clinical implications. Stressful experiences at the early stages of BD may prove detrimental and contribute to the development of BD. For example,

traumatic events such as physical abuse during childhood are associated with an earlier onset and more severe course of BD (52). Frequent image-based flashback memories may serve to haunt individuals at-risk for BD after an early stressful experience, or indeed adult trauma, with an amplifying effect on emotion (17), increasing the likelihood of full-blown PTSD which is estimated to be prevalent in up to 40% of patients with BD (53). Gregory et al (25) found that negative intrusive imagery was associated with euthymia in a sample of euthymic patients with BD (in comparison to hypomania which was associated with vivid enjoyable images of the future). Image-based flashback memories could contribute to the pathways by which negative life events render onset and (potentially) relapse of emotional reactions and full-blown bipolar episodes. The causal relationship between an image-based flashback memory to a stressor and emotional reaction (in a BPP sample) remains to be tested.

Bipolar disorder is highly comorbid with anxiety (16) and in the current sample MDQ was moderately correlated with neuroticism ($r=0.60$, $p<0.001$). The findings from study 3, regarding the higher frequency of flashback memories in the high MDQ group, fit into a larger body of research which have identified intrusive mental imagery (described as image-based flashback memories in this thesis) across various anxiety disorders: PTSD (11); social phobia (12); agoraphobia (54); obsessive-compulsive disorder (55) and spider phobia (56).

Study 4. In support of the overarching prediction of the Holmes et al model (17) i.e. that high imagery levels will worsen day-to-day mood extremes, in a sample selecting across the continuum of the BPP, high levels of intrusive imagery of the future were associated with exacerbated negative mood reactions in the context of daily life. This included anxious mood, which has been specifically identified as vulnerable to

amplification by mental imagery in the Holmes et al model (17), as well as sad, depressed and fearful mood reactions. This proposed amplification effect of using imagery in daily life is particularly interesting as the experience of heightened imagery is hypothesised to contribute to mood instability. In fact, as previously discussed, intrusive imagery of the future was found to be heightened in BD patients who had been designated with long-term unstable mood versus those with stable mood (34). Laboratory studies, outside of the context of BD, demonstrate that using mental imagery compared to verbal strategies can amplify bipolar-relevant moods such as depressed, anxious and positive mood (8, 38, 57, 58). Study 4 demonstrated a related amplification effect (of sad, depressed, anxious and fearful moods) in the context of daily life.

ESM studies conducted in clinical BD have produced mixed findings with regards to the relationship between daily mood and daily stress (5, 6). For example, both Myin-Germeys et al (5) and Havermans et al (6) found that across all participants (which included those with remitted BD and healthy controls) higher daily life stress was associated with higher negative affect. However, in both studies, patients with remitted BD did not react differently to healthy controls with regards to their negative mood reactions to daily life stress. Study 4 raises the intriguing possibility that differential experiences of daily mood and stress in BD may not necessarily be due to diagnostic category per se (i.e. BD versus healthy control) but may be accounted for by underlying cognitive processes such as levels of intrusive imagery of the future.

Research Implications

The comparison between mental imagery susceptibility and verbal thoughts in the BPP and clinical BD samples remains to be tested. In addition, a wider battery of mental imagery measures (other than self-report measures as was used in studies 1

and 2) could elucidate whether mental imagery proneness exists at a cognitive level in BPP and clinical BD samples, for example mental rotation tasks (28).

Study 3 and study 4 demonstrated the feasibility of using SMS mobile phone technology (participants' own mobile phones) as a data collection tool in replacement of paper diaries. Paper diaries have been criticised for their inability to account for retrospective reporting, and handheld computerised devices are not ideal due to their expense and the training required for volunteers to use them (59). Specifically, in the current thesis, mobile phones were shown to be a feasible and novel data collection tool for the ESM, in sampling multiple times a day over six days (60). In addition, SMS was also shown to be a feasible and novel method for capturing data about flashback memories in the trauma film paradigm, again rather than a paper diary. Mobile phones are emerging as a data collection tool in the ESM paradigm however, instead of using SMS technology, researchers have verbally telephoned volunteers multiple times a day (61). SMS might appear to be more economic. Recently, SMS technology has been used in conjunction with an ESM, however this was for the purpose of capturing marketing information about using mobile phones more generally (62). In addition, Depp et al piloted SMS technology in an ESM framework to facilitate case management in a sample of patients with schizophrenia (63). To my knowledge, this is the first study to use SMS mobile phone technology as a mood and stress monitoring device under an ESM framework within the context of BD. The overarching research implication suggests that SMS mobile phone technology has the potential to be widely applied in replacement of paper diaries in both research settings (for example in future trauma film studies and ESM studies) and clinical settings (facilitating case management in range of patient groups), as outlined in chapter 2 of this thesis.

A key research implication from study 4 is the formulation of a new statistical approach for analysing ESM mood and stress data. As outlined in chapters 6 and 7, the non-normal distribution of mood data in this study was noted, and in fact this occurred in a variety of previously published ESM data (5, 64-71). I have made the suggestion in this thesis that such data are not amenable to the hierarchical linear models which have traditionally been used to analyse this data (72). The formulation of a Generalised Linear Mixed Model with a logistic link function was deemed more suited to the distribution of the mood data, and in fact would be more suited to the distribution of the data reported in previously published ESM studies. In fact similar approaches to the analysis used in study 4 have recently been utilised in ESM research (73, 74). Gindre and Swendsen (74) used hierarchical and nonlinear (Bernoulli) models in analysing the differences in daily life routines and activities in a sample of individuals who met lifetime criteria for (hypo)mania compared to healthy controls. Ben-Zeev and colleagues (73) used generalized linear models with a Bernoulli sampling model and logit link function to analyse predictors of having a persecutory ideation in daily life (versus not having any persecutory ideations) in a sample of individuals with schizophrenia and schizoaffective disorder. The statistical approach to the ESM data used in this thesis is by no means posited to be *the* best solution for ESM data, instead this analytic approach is presented as as *a* better solution for such data than current traditional methods (64).

In study 4, the ESM pleasantness scale where volunteers rated 1 for ‘not at all pleasant’ and 7 for ‘very pleasant’ rendered, in some volunteers, a response-bias. On occasion, volunteers would rate a series of six 1’s for each of the six moods (i.e. indicating that they did not experience any negative mood at the time of the SMS message) and then following that, rated a ‘1’ for pleasantness (i.e.. indicating that the

most important event that they described was not at all pleasant; see figure 7.3 [top left] of chapter 7). In line with previous ESM research (64) this pleasantness score is then reverse scored to give an indication of stress where 1 represents 'not at all stressed' and 7 indicates 'very stressed' (64). Repeatedly pressing the number '1' on mobile phone key pads may be prone to this type of error in ESM research as the repeated pressing of the numbers 2-7 encompassed only 13 (0.34%) out of the 3864 valid SMS messages sent by volunteers whereas the repeated pressing of the number 1 encompassed 289 (7.5%) of the valid SMS responses. The implication for future research would be to reverse the pleasantness scale in order to limit any response bias. This has in fact been addressed in the design of an upcoming experiment using the ESM to capture mood and stress data in a clinical BD population whereby volunteers will be asked to report how stressful the event is (rather than how pleasant) and each item on the scale will be anchored the opposite way around: 1= not at all stressful, 2= slightly stressful, 3= fairly stressful, 4= moderately stressful, 5= particularly stressful, 6= very stressful and 7=extremely stressful.

Potential Clinical Implications

The experimental psychopathology non-clinical sample used in this investigation is believed to be informative / predictive of BD (specifically the high MDQ group). Although further research and replication is required regarding the experience of mental imagery, mood and stress in clinical BD, it is possible to draw some interesting potential clinical implications from the research conducted in this thesis.

A recent meta-analysis, which included 12 randomised control trials exploring the effect of CBT on patients with BD, found that CBT was beneficial during treatment and post-treatment in reducing relapse, reducing symptoms, and improving

functioning (75). This finding is consistent with an earlier review of 18 randomised control trials of psychotherapy for BD, which proposed that CBT was most effective to BD patients who were in a recovery period (76). However, the meta-analysis revealed that at follow-up, CBT had little influence on preventing relapse. Szentagotai et al (75) proposed that treatment innovations are required if CBT is to succeed as a successful adjunct to medication in the long-term management of BD, consistent with the National Institute for Health and Clinical Excellence (NICE) guidelines which also proposed that psychological interventions are of benefit in the long-term management of BD, but that these require improvement (77, no. 38, p.33). How could traditional CBT be improved? One way might be to tailor it better to the processing style of individuals with BD i.e. an imagery rather than verbal processing style.

In this thesis, mental imagery was shown to be a salient feature of high MDQ volunteers, compared to low MDQ. Specifically, image-based flashback memories of an experimental stressor (a trauma film) were exacerbated in the high MDQ group. Such image-based intrusions have been successful targeted in CBT for PTSD (11) and indeed in imagery re-scripting for depressed patients (78). Such interventions could be extended to BD, particularly as PTSD is variously estimated to be prevalent in up to 40% of patients with BD (53).

In addition, intrusive imagery of the future was associated with the amplification of negative mood reactions in daily life. A potential next step in the innovation of CBT for BD could consider further investigating how intrusive mental imagery of the future might worsen day to day mood extremes in daily life and how such imagery of the future might be effectively targeted. Imagery re-scripting techniques have aided treatment for the emotional lability of borderline personality disorder (79). Targeting flashback memories via imagery exposure has been

successful in CBT (11, 78) and such a wide variety of imagery techniques have the potential to be translated to targeting flashforward imagery in BD.

Furthermore, if the salience of mental imagery as an amplifier of mood states in BD can be established by further research, then its application to therapy may not need to be exclusively under a CBT framework, for example, it could be applied to alternative established interventions for BD such as psychoeducation (80) or family-focussed treatment (81) in assisting clients in recognising intrusive imagery of the future as a potential amplifier of mood or warning signal.

Finally, a position piece was provided (in chapter 2) and demonstrated feasibility (in chapter 7) of using SMS mobile phone technological as a daily mood and stress monitoring tool in a predominantly young sample ranging across the continuum of the BPP. Previously, weekly mood monitoring in an adult sample of patients with BD was found to be feasible using SMS mobile phone technology (82). More recently, in a small sample of patients with BD-I and BD-II, a Facilitated Integrated Mood Management program was developed which incorporated 5 sessions of psychoeducation treatment with daily mood and sleep monitoring using SMS mobile phone technology (as well as the option to use e-mail), and weekly monitoring of depressive and manic symptoms (83). Patients were found to be compliant with both daily and weekly monitoring as well as reporting an increase in their awareness of mood management strategies over the course of the program. It was suggested that weekly discussions regarding the patients' daily mood fluctuations (as indicated by the electronic monitoring) may have contributed to improvements in mood management strategies. In fact, part of the long-term management of BD involves managing mood in a bid to prevent relapse and recurrence which can be triggered by a variety of stressors (84). It would appear that the use of SMS mobile phone

technology as a mood monitoring device in BD has the potential to be utilised as both as assessment tool (of day to day fluctuations and their context) and a treatment tool (in facilitating discussions leading to improved mood management strategies). In addition, the use of SMS monitoring could hold a particularly pertinent advantage for younger clients, in engaging them in the clinic and preventing drop-out, as using a mobile phone may be less stigmatising than other methods such as a paper-diary (85).

Limitations of the Research Presented in the Thesis

The limitations for each study are outlined in the respective chapters. Following, is an outline of the general limitations of this investigation. Volunteers were selected on the basis of representing the continuum of the BPP (elevated lifetime hypomania) versus being at low or no risk (low/no lifetime hypomania) on the basis of a screening tool: the MDQ. However, although we have an understanding of the longitudinal course of early elevated hypomanic experiences, where early subsyndromal hypomanic experiences predict the onset of mood and anxiety disorders in adulthood (86), the specific longitudinal course of those who screen positive on the MDQ remains to be investigated. Therefore, it is unknown how many of our sample at the higher end of the BPP spectrum would go on to develop BD. Axis-I diagnoses in our sample indicated that the high MDQ group reported comorbidities which parallel those found in clinical BD populations (87) and in previous studies which have used the MDQ to identify individuals in the context of the BPP, for example a higher prevalence of anxiety disorders compared to low MDQ individuals (22). This suggests that there may be some merit to studying individuals who score high on the MDQ with regards to being informative/ predictive of BD. However, it is necessary that future research explores the longitudinal course of the MDQ in a bid to establish its sensitivity and specificity in capturing risk for BD. Alternatively, convergent

measures of bipolarity could also be used such as the Hypomanic Personality Scale (HPS; 88).

This investigation was conducted in a non-clinical (albeit clinically informative) sample and therefore the generalisabilty of the findings to a clinical BD sample are limited. However, showing the trauma film (as was conducted in study 3) to a clinical sample may be ethically inadvisable. Further, in regarding generalisabilty, approximately half of the sample in this investigation was from the student population in Oxford. First year undergraduates in Oxford have been found to have a higher prevalence of high MDQ scores (4%) to what might otherwise be expected in a similar university (Stanford University, USA; 1.7%) (19). Finally, the sample were predominantly young. However, three distinct ages of onset have been identified for BD (17, 27 and 46 years) and our sample predominantly fall across the earlier part of this range (89). Therefore, it may be possible to draw conclusions about a predominantly young sample selected on the basis of the MDQ, specifically, and possible to tentatively conclude that the findings in this thesis may be informative/predictive of the earlier stages of BD, rather than exclusive epiphenomena of the full-blown disease.

The laboratory-based questionnaire measures, experimental tasks and SMS data collection used in this investigation relied on self-report and consequently the impact of demand cannot be ignored, for example, high MDQ volunteers may have a general tendency to score highly on any measure. However, it should be noted that this group did not score consistently higher on all measures e.g. the verbal processing style VAS in study 2. The use of convergent measures in future studies which are less susceptible to the effects of demand could be utilised to support the overarching findings of this thesis. For example, Holmes et al (17) proposed that negative mental

imagery amplifies mood in BD, such as anxious mood. Physiological measures of anxiety such as heart rate (90), salivary cortisol (91), skin conductance (92) could be monitored whilst, for example, asking volunteers to imagine negative images of the future (such as with the PIT). Neuroimaging methods could also be used to establish whether emotional mental imagery is associated with particular brain areas versus non-emotional imagery (93).

Finally, the nature of this investigation does not permit a causal conclusion i.e. that the experience of elevated lifetime hypomania causes heightened mental imagery processing (or indeed vice versa). However, Holmes et al (17) utilise a vicious cycle to describe the relationship between mental imagery and mood. A more complex longitudinal study would be required to tease apart the causality an bi-directional nature of this relationship.

Future Directions and Conclusions

Future directions for research have been highlighted in the relevant chapters. One broad and interesting direction for future research would be to demonstrate how the momentary experience of mental imagery may directly impact on mood in daily life. This could be achieved by using an ESM design to investigate the frequency of image-based flashback memories after a standardised experimental stressor (such as the trauma film) or even a film designed to induce positive and/or flashforward imagery (94). Images could be captured multiple times a day over a period of six days using SMS mobile phone technology alongside ratings of mood. This would allow us to causally determine whether the experience of an intrusive image to the experimental stressor amplified negative mood in comparison to when a volunteer reports no experience of an intrusive image.

A recurring finding in this investigation was the salience of intrusive imagery of the future in volunteers scoring high on the MDQ. It appears that this predominantly young sample “can’t stop imagining the future” and this future imagining is associated with negative mood reactions in daily life. Intrusive negative imagery of the past has been extensively studied across a number of anxiety disorders and depression (32). Intrusive imagery of the future and its relevance in the context of BD warrants further exploration. In a bid to understand whether heightened mental imagery is a cognitive process which confers susceptibility to severe psychopathology, comparisons could be made between a clinical sample with BD, first-degree family memories at-risk, individuals with the BPP and healthy controls.

Furthermore, mental imagery processes overlap with perception (42), such that imagery may be responded to or acted upon as though it were real (43, 44). However, the biological basis of mental imagery in psychopathology is not well understood. A biological understanding of mental imagery in psychopathology could serve to complement findings from self-report questionnaires. In addition, little is known about the developmental role of mental imagery in psychopathology. Further research could include whether, for example, genetic vulnerability (95) or developmental factors such as maternal postnatal depression (96) and so forth may be among the multitude of factors to impact on mental imagery and/or bipolarity within wider development i.e. the potential expression of psychopathology in adolescence/ adulthood. Finally, this thesis did not examine intrusive mania-associated mental imagery in the BPP (17): only a trauma film study was used (study 3). It would be of interest to experimentally understand how mania-based mental imagery (such as an image of oneself receiving a prestigious award) may contribute to extreme mood

amplification in the context of BD, for example, by using a mania rather than trauma inducing film (97).

In summary, the work in this thesis has sampled the experience of mood, stress and mental imagery in the laboratory and in daily life, in individuals ranging across the continuum of the BPP. Following, is an anecdotal example which attempts to summarise the main findings of this thesis, and is based on a character who has a greater lifetime experience of hypomania. 'Claire' is on her way to catch a bus to an important interview, no more anxious than would be expected for what is currently a mildly stressful situation (study 4). Whilst walking to the bus-stop she receives a call from a friend and upon seeing their name pop up on her phone screen, she immediately visualises her friend's face in her mind's eye (SUIS). After the conversation, Claire recalls that her friends have arranged a post-interview celebration in a restaurant. Claire generates an image of walking into the restaurant that evening, seeing her friends' eager anticipatory faces and then the ensuing disappointment when she imagines telling them that the interview did not go well. Believing that this negative future image might indeed come true, she contacts a friend and asks him to cancel any dining plans until after the interview results (PIT). Claire turns a corner and realises that the bus she intended to board has just departed. This is extremely stressful to Claire as now she has little hope of arriving for her interview on time. Claire is then plagued by intrusive images of the future (IFES): seeing herself rush into the interview room flustered and unprepared; imagining her interviewers unimpressed faces; imagining that the interviewers tell her that she has not been successful due to her late arrival; seeing herself calling her parents and hearing the disappointment in their voices; imagining herself having to spend hours searching for another job and preparing for another interview. Triggered by the stress of missing the

bus and overwhelmed by frequent images of the worse possible future outcomes popping into her mind, Claire is more sad, depressed and anxious than she was before (study 4). Fortunately, a second bus quickly arrives and Claire feels less negative, although she is not as calm as she was when walking to the bus stop earlier (study 4). On stepping off the bus, Claire witnesses a car collide with a cyclist on the other side of the road. The cyclist is visibly badly injured. Seeing that many people are going to the cyclist's aid, Claire proceeds to her interview. The interview goes tolerably and Claire leaves to meet her friends. However, she is haunted by the accident she saw earlier despite not deliberately thinking about it: sounds of the collision pop into her head, unwanted images of the impact between the cyclist and the car spontaneously appear in her mind's eye… (Study 3). Four weeks later, Claire is still experiencing flashbacks to the accident she witnessed and sub-clinical PTSD symptoms.

Claire's day would be a difficult day for anyone to face. However, her lifetime experiences of hypomania, for example, 'being more self-confident than usual,' needing 'much less sleep than usual,' doing things that 'other people might have thought were excessive, foolish, or risky' have rendered this day more difficult compared to someone without these lifetime experiences. Siddharta Guatama (Buddha, 563-483 B.C.) once said "do not dwell in the past, do not dream of the future, concentrate the mind on the present moment." The findings from this thesis suggest that the propensity towards experiencing past (flashbacks) and future (flashforwards) imagery in individuals with a greater history of lifetime hypomania could present a real problem regarding concentrating their minds "on the present moment" and have ensuing emotional consequences.

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APPENDICES

The appendices originally presented here cannot currently be made freely available via ORA