THE DEMANDS OF COMORBIDITY: IMPLICATIONS FOR THE EXPLANATION AND

CLASSIFICATION OF MENTAL DISORDER

Amie M. Sinden

A thesis submitted to Victoria University of Wellington

in fulfilment of the requirements for the degree of

Master of Science

Victoria University of Wellington

2014

Acknowledgements

Abstract

A central goal of psychiatric classification is to assist in the assessment and treatment of those who experience mental disorder. This challenge takes on greater significance in complex cases, especially given the high prevalence of psychiatric comorbidity. High rates of comorbidity also challenge the validity of current psychiatric nosology. Etiological classification has been promoted as an alternative to improve the state of psychiatric diagnosis. However, comorbidity makes specific conceptual, explanatory and methodological demands of any such classification strategy. In this thesis, a demand for coherent and integrative explanation of comorbidity acts as a standard by which to assess the strength of different causal models of mental disorder and their resultant concepts. Integrative pluralism is presented as an epistemological framework well-suited to the complexity of this scientific challenge.

Table of Contents

Introduction

Psychiatric comorbidity presents both challenges and opportunities. For those who experience multiple mental disorders, comorbidity acts as a marker of poorer prognosis and poorer treatment outcomes. For clinicians and researchers its high prevalence is as an indicator that psychiatric nosology could be improved.

One strategy to improve nosology, and the practice of diagnosis which follows from it, is to move to classification based in etiological theory or causal models of mental disorder. Causal understanding offers the potential to more effectively intervene for the purpose of prevention or treatment of mental disorder. In the spirit of scientific realism, causal explanation may also bring concepts of mental disorder closer to reality or the "truth", thus improving the ultimate validity of diagnosis.

However, mental disorder appears recalcitrant to simple causal explanations and as will be argued, the phenomena of comorbidity in particular demands especially high explanatory coherence and integration from models of mental disorder. Thus, the nature of comorbidity has implications for future nosological strategies.

It may be that the nature of mental disorder is so causally heterogeneous, not only in its causes but in its causal structures, that one disorder cannot be easily discriminated from another. In this instance comorbidity would cease to exist as a real phenomenon and hold little explanatory value. If this is the case then classification of mental disorders cannot proceed on the basis of aetiology and instead may turn to a basis in pragmatism and empiricism in order to meet ethical goals.

Alternatively it may be that the nature of mental disorder is homogeneous enough in causal structure to be etiologically discriminable, one disorder from another, and from normality. In this case comorbidity would gain explanatory value and classification could proceed on an etiological basis in accordance with realist assumptions. Such models could be

used to advance the treatment and prevention of comorbid disorder – a particularly important goal.

Of course it is also feasible that mental disorders differ significantly in their causal structure, inhabiting different zones along a continuum of structural homogeneity to heterogeneity. With this continuum in mind, the concept of comorbidity is put to work to assess the resilience of different models of mental disorder to comorbidity's explanatory demands. In this way, implications for future classificatory approaches are considered.

Chapter One sets out evidence and reasoning for why comorbidity is a phenomenon worth consideration and argues for standards of explanation that follow from its ethical demands. Chapter Two then reviews the coining of the term *comorbidity* and the historical context of its conceptual development. Chapter Three discusses several different concepts of comorbidity, including comorbidity at the population versus the individual level. Then concepts of comorbidity stemming from physical medicine are discussed before critique of concepts of mental disorder as described in the Diagnostic and Statistical Manual-5th edition (DSM-5, American Psychiatric Association [APA], 2013). Following this, various models of mental disorder are explored: latent construct and pathogenetic models are reviewed in Chapter Four; Chapter Five presents a pathophysiological model; and in Chapter Six, integrative and network models of mental disorder are considered. The thesis concludes with a brief summary of implications for classification, causal models, theoretical and epistemological strategies, that follow from their examination through the lens of comorbidity.

Chapter One - Why Comorbidity Has Something Important To Say

Despite psychiatric comorbidity's theoretical and methodological significance (Bogenschutz & Nurnberg, 2000), its most important consequence is the distress and disability it brings to those who experience comorbid mental disorders. It is this concern which directs the arguments of this thesis.

Data from the US National Comorbidity Survey (NCS) indicate that 14% of the population have a lifetime history of three or more mental disorders. This group is estimated to share more than half of the total population's prevalence of lifetime mental disorder (Kessler et al., 1994). These results were reinforced by findings from the Australian 2007 National Survey of Mental Health and Wellbeing (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009), where one in four people who met criteria for a 12-month ICD-10 (International Classification of Diseases, World Health Organization, 1992) diagnosis, were also diagnosable with a comorbid disorder.

Increased severity, disability, distress, recurrence and health burden are all strongly related to comorbidity (Andrews, Slade, & Issakidis, 2002; Gadermann, Alonso, Vilagut, Zaslavsky, & Kessler, 2012; Kessler, Chiu, Demler, & Walters, 2005; Maj, 2005a). The National Comorbidity Survey – Replication study (NCS-R) demonstrated that although mental disorder is quite prevalent within the community, serious cases occur "among a relatively small proportion of cases with high comorbidity" (Kessler et al., 2005, p. 617).

Evidence also suggests that those who experience serious mental health conditions have both inequitable access to physical health services and significantly higher mortality rates (Phelan, Stradins, & Morrison, 2001; Prince, Patel, Saxena, Maj, & et al., 2007). This may occur for a number of reasons. Comorbidity may reduce participation in treatment, may reduce treatment effectiveness or may require additional treatment provision. It may also increase the likelihood for an insidious chronic course, with a lower probability of recovery.

A comprehensive literature review by Fenton, Blyler, and Heinssen (1997) indicated that comorbid alcohol and drug abuse was a strong predictor of "noncompliance" with pharmaceutical treatment for schizophrenia and an important factor to address when seeking to improve treatment adherence. The well-cited STAR*D study evaluated the outcomes of citalopram treatment for depression in participants drawn from psychiatric and primary care settings. Those with comorbid psychiatric disorders (especially anxiety and drug abuse), as well as those with comorbid medical disorders, had reduced rates of remission from depression following treatment than those with a single diagnosis (Trivedi et al., 2006).

A study investigating outcomes from treatment with either antidepressant medication or structured psychotherapy in a group of low-income women indicated similarly poorer results for those with comorbidity. In this instance, of the full sample who met criteria for depression, 33% also met criteria for comorbid post-traumatic stress disorder (PTSD). While treatment with either medication or psychotherapy resulted in improvements of depression for both groups, the group with comorbid PTSD experienced more distress and impairment at a one year follow up. Although treatment did reduce symptoms of depression in the comorbid group, the authors suggested that provision of treatment for PTSD, especially in the context of interpersonal violence, may additionally assist in alleviating depression (Green, Krupnick, & Chung, 2006). Finally, a 12-year prospective study of participants with anxiety disorders including generalised anxiety disorder (GAD), social phobia and panic disorder, also demonstrated reduced recovery and higher recurrence with the presence of psychiatric comorbidity (Bruce et al., 2005). Here, comorbidity between anxiety disorders and major depression or substance abuse, as well as comorbidity within the investigated anxiety disorders, acted as a predictor of poorer clinical course.

In fact, the high incidence of depression as a comorbid disorder, may explain a significant portion of the decrease in life satisfaction associated with comorbidity (Meyer,

Rumpf, Hapke, & John, 2004). 78.5% of those meeting criteria for a 12-month diagnosis of major depressive disorder (MDD) were diagnosed with another comorbid disorder, with MDD considered primary in only a small proportion of cases (Kessler et al., 2003).

Explanations for Poorer Outcomes

Such evidence points to poorer outcomes from a variety of treatments for those who experience comorbidity, in a number of different combinations, across a range of disorders. Potential reasons for such outcomes include the stigma associated with multiple diagnoses, a lack of understanding about the causal interactions that bring about comorbidity, and the use of homogeneous or "pure" samples in treatment efficacy research.

Stigma associated with a mental disorder diagnosis is worse for those who receive comorbid diagnoses than those with a single mental disorder diagnosis or chronic physical condition. An international study found that this was the case for those with comorbid anxiety and mood disorders across both developed and developing countries (Alonso et al., 2008). However, while stigma may have some role in explaining why those with comorbidity experience poorer outcomes, either with or without treatment, a more important factor is likely to be current lack of understanding of how disorders causally interact, and therefore, a lack of guidance in treating such complex cases.

Findings from a substantial meta-analysis of randomised controlled trials (RCT's) of treatment outcome for anxiety disorders, illustrates this well (Olatunji, Cisler, & Tolin, 2010). Various types of treatments (cognitive behaviour therapy [CBT], dynamic therapy, pharmaceutical treatment with and without CBT, and mindfulness) were included in this study. Contrary to expectations based on previous anxiety comorbidity literature (such as the findings above by Bruce et al., 2005), higher levels of comorbidity did not necessarily predict lower treatment effect. It was found that comorbidity in the context of mixed anxiety had a negative relationship with treatment effectiveness, whereas a significant positive treatment

effect was observed for overall comorbidity with panic disorder, PTSD and obsessive compulsive disorder (OCD). Here, "overall comorbidity" was any anxiety disorder comorbid with any other non-anxiety disorder. Most studies however, excluded schizophrenia and bipolar disorders.

From these findings the authors concluded that such effects may indicate one disorder's causal or symptom dominance over the other comorbid disorder. An alternative interpretation is that, given a large portion of RCT's included in the analysis were CBT interventions, and the mechanisms by which CBT brings about change is unclear (Shafran et al., 2009), treatment effect may have been relatively non-specific to disorder type. In addition, while treatment effect size may have been similar for those with comorbidity, resultant well-being itself may still have been generally worse. In any case, "the findings also highlight a clear need for additional research examining the nature of the influence of comorbidity on treatment outcome of anxiety disorders" (p. 651).

One area where causal interactions between disorders are slightly less opaque is that of "dual diagnosis". However, even here multiple mechanisms and associations are posited to simultaneously drive comorbidity between depression and substance use (Swendsen & Merikangas, 2000). A study that investigated the outcomes of integrated and intensive treatment for those with severe and chronic alcoholism, found differential associations between alcohol use and comorbid psychiatric disorders (Wagner et al., 2004). Whereas personality disorder acted as a strong predictor of both treatment drop out and relapse, comorbidity with mood and anxiety disorders did not. Additionally, comorbid mood disorders remitted more quickly than anxiety disorders with continued abstinence. However, the authors emphasised a need to directly address both alcohol use and depression through long-term, integrated treatment in order for change to be effected in the lives of these individuals. Indeed a systematic literature review by Schulte, Meier, and Stirling (2011) indicated that

client satisfaction was higher for those dual diagnosis clients who received integrated dual diagnosis treatment than for those dual diagnosis clients who received standard treatment without an integrated dual focus.

Thus, it appears a lack of coherent models accounting for the causal relationships between disorders is an impediment to the development of integrated care of comorbid disorders. Moreover, concepts of what distinguishes one disorder from another in comorbid presentations would also be improved if such models existed. Such clarity may serve to improve clients' understanding of the rationale for particular treatment approaches or simply focus treatment on factors that will make a bigger functional improvement.

For those with severe mental health difficulties (schizophrenia, bipolar disorder and severe depressive or anxiety disorders) a focus on collaborative care may be just as important. Lee, Crowther, Keating, and Kulkarni (2013) identified consumers' and carers' engagement in treatment and service decisions as crucial to addressing "comorbidities" such as homelessness, addiction, physical illness, unemployment and forensic issues. These difficulties frequently form barriers to treatment for severe psychiatric disorders. Comorbidities such as homelessness and unemployment also serve as a reminder that causal interactions are likely to occur at multiple levels, from biological through to socio-political.

Such evidence of poorer outcomes for those who experience comorbidity is likely related to an inadequate understanding of the causal interactions that bring about mental disorder. Additionally, development of effective treatments for those with comorbid disorders may be inhibited through the use of homogenous or pure samples in treatment efficacy research. More broadly, this issue relates to the applicability of research findings to the clinic environment.

The use of homogenous or pure disorder samples in research has been recognised as a problem for the treatment of comorbidity since the term's inception (Feinstein, 1970). Hyman

(2010) cites the DSM's role in both scientific and regulatory domains as central in

determining the use of pure samples for drug registration and clinical trials. The concepts of

disorders as laid down in nosology, therefore, have obvious implications for treatment.

Maj (2005b) links "unwarranted polypharmacy" with the artificial splitting of clients'

holistic presentations into disorder categories (p. 182). A practice of polypharmacy for

complex cases does indeed seem to be on the rise. While some drug combinations have

evidential support, "many are of unproven efficacy" (Mojtabai & Olfson, 2010, p. 26). For

example, polypharmacy for bipolar disorder has increased dramatically despite a lack of

evidence in support of its effectiveness (Sachs, Peters, Sylvia, & Grunze, 2014). Weinstock et

al. (2014) reported that in a sample of patients with bipolar disorder presenting for hospital

admission, 36% met criteria for complex polypharmacy of four or more medications. Those

who did were more likely to be female, in a depressive state, with a comorbid anxiety

disorder, and a history of suicide attempt. Use of multiple medications without the backing of

specific empirical evidence could be based upon two possible beliefs: that the biological

causes of distress will be addressed with the administration of an additional pharmaceutical

agent; or in the absence of such a causal presumption, trial and error is an acceptable strategy.

When faced with a client in serious distress, in the absence of readily available treatment

guidance that maps well onto a particular presentation, it is understandable that clinicians turn

to either internally held causal models of mental disorder or their experience of "what's

worked in the past". In either case it is obvious that clearer understanding of the causal

processes at work would clarify treatment choices.

In contrast, beliefs that CBT efficacy research is similarly dominated by the use of

homogeneous samples are arguably unfounded. Shafran et al. (2009) reported that RCT

efficacy research using comorbid samples has increased in recent times. Additionally, they

argued that, when clinicians are allowed some flexibility to address comorbidity, RCT results

do generalise well to the clinical population. Here, non-specific therapist effects appeared less important than improving the delivery of treatment protocols. Yet at the same time, the mechanisms for change in CBT treatments remain unclear (Shafran et al., 2009), alongside the causal interactions within and between disorders.

Thus, when it comes to comorbidity, although the research base may be improving, much is left to the clinician to decide how treatment proceeds. This appears to be the case with either medication or psychotherapy treatment. Knowledge is certainly growing regarding general and specific risk factors alongside the effects of mediators and moderators of mental disorder. Generic etiological models, such as those by Kendler and Gardner (2011) regarding the development of depression in women, help in understanding how specific disorders may be caused. However, in order to understand and effectively treat comorbidity, it appears that a more detailed understanding is required. There is a need to move beyond explanations that operate at the level of "multiple mechanisms of comorbidity are likely to be simultaneously active" (Swendsen & Merikangas, 2000, p. 173). This means finding methods that identify which particular factors are most active in bringing about a particular client's presentation and referring to theory and evidence that demonstrates how intervention may assist.

These findings clarify an important ethical goal - to improve outcomes for those who live with the highest burden of mental health difficulties, the comorbid population. Such a goal certainly has implications for broader service delivery as well as clinical practice and research objectives. One strategy to meet this goal is to improve the causal understanding of mental disorder. Through an understanding of cause and effect we may improve treatment, allow more accurate prognosis and intervene to prevent mental disorder. Clear knowledge objectives spring from the ethical goal to improve outcomes for those who experience

comorbidity. It is these knowledge objectives that form the focus of this thesis, alongside their application to the work of clinicians and researchers via classification.

Ethical Driver Shapes Knowledge Objectives

Comorbidity's consistently high prevalence since the introduction of DSM-III (APA, 1980) indicates that it is not an anomaly. Instead comorbidity demands improvements in our concepts, models and classification of mental disorder. At the same time it opens a door into the complexity of mental disorder, which in turn suggests that responding to its challenges will be no small undertaking. It is towards this complexity that our concepts, theories and methods should turn.

The ethical goal to improve outcomes for those with comorbid disorders consequently demands an improvement to the state of scientific knowledge. In particular, this ethical goal demands coherent concepts and explanations of comorbidity:

1. In order for the individual experiencing mental disorder (and those involved in their care) to make sense of their experience;

2. For the development of effective treatments and interventions;

3. For the clinician to adequately carry out the roles of assessment, communication and application of treatment with the client.

Conceptual and explanatory coherence.

As will be demonstrated, concepts of comorbidity are intrinsically tied to concepts of mental disorder. These concepts relate to what mental disorder is and what it is not; what differentiates mental disorders from one another; and what distinguishes mental disorder from normality and from more general problems in living. Much literature exists regarding concepts of mental disorder (First, 2012; Phillips et al., 2012a; Wakefield, 1992; Zachar & Kendler, 2007). Central to the debate is causal explanation. Irrespective of how implicit or

undeveloped, causal explanation shapes the concept of mental disorder from which the concept of comorbidity follows.

Arguably the most prominent conceptualisation of mental disorder is Jerome Wakefield's harmful dysfunction (HD) analysis (Wakefield, 1992, 2007). Under this concept, mental disorder is caused by a failure of a mechanism to fulfil its natural function or evolved purpose. Causal models are also prevalent in folk psychology concepts of mental disorder. For example the above study by Swendsen and Merikangas (2000) cited the adage "drinking to forget" as a common-sense explanation for why alcohol is often used in the context of psychological difficulties (p. 185). This thesis examines concepts of comorbidity as a means to give insight into current and alternative models of mental disorder.

As discussed above, causal understanding is important for a number of reasons. It helps to make sense of a client's experience, it increases the likelihood of developing effective treatment or intervention, and it presents a rationale to client and clinician for particular treatment approaches. It is important to remember however that causal models are representations of the world (Sloman, 2005). Their presentation of cause and effect may exist at different levels of detail or different granularities. They may be relatively simple or encompass multiple causal factors. They may demonstrate a link between cause and effect with high certainty or instead model risk associations probabilistically[1]. They may hold across a range of background conditions taking the more absolute form of universal laws. Alternatively they may be more conditional upon other factors, as is the case with INUS[2] conditions. Indeed it is these types of complex and conditional causal pathways that seem to characterise mental disorder.

---

[1] Statistically generated risk models are included under this and following discussions of causal models.

[2] These are conditions where a cause alone is Insufficient to bring about an effect, but is a Necessary part of an Unnecessary but Sufficient set of conditions that may bring about an effect (Meehl, 2001; Sloman, 2005).

Just as causal models and explanations may have different features, they may also be of varying quality. Drawing on philosophy of science and epidemiological literature, Kendler (2012) compiled seven criteria by which to assess an explanation:

1. Strength – reflects a causal variable's[3] effect size. A strong explanation will account for a large amount of the variance observed.

2. Causal confidence – the certainty with which a causal variable is demonstrated to alter the outcome, as opposed to an association through non-causal mechanisms.

3. Generalizability – the robustness of the causal variable in bringing about an effect across a range of background conditions. Strength and generalizability are often related.

4. Specificity – the extent to which a causal variable is involved in bringing about one effect but not another, for example anxiety but not depression.

5. Manipulability – the ability to manipulate the causal variable in order to change the outcome. Indicates the potential for successful treatment.

6. Proximity – the proximity of the variable in the causal pathway towards the outcome. Distal causes do not reflect foundational causes; this is dependent upon the nature of the causal chain.

7. Generativity – the potential for "fruitful etiological understanding" being stimulated by this causal variable. (p. 14.)

Kendler (2012) suggests that unlike some diseases, such as cystic fibrosis, which can appeal to solely genetic causes to sufficiently meet all explanatory criteria, mental disorders must appeal to multiple factors, across multiple levels in order to be adequately explained. In their pursuit to build viable models of mental disorder and comorbidity that hold across

---

[3] These explanatory criteria are applied to singular causal variables, risk factors, constructs, broad explanations and models of mental disorder and comorbidity, so the term "causal variable" should be interpreted in its broadest form.

populations or large samples, researchers may be most interested in criteria such as strength, generalizability and generativity. Clinicians instead may prioritise specificity, proximity and manipulability, in order to tailor assessment and treatment to clients' needs. Thus explanatory priorities may differ according to the desired goal.

Particularly important in explanations and models of comorbidity is a need for coherence. Within coherence lies a demand for integrative explanation. The above criteria of strength and generalizability (Kendler, 2012) somewhat relate to explanatory coherence as an expression of consistency between variables and effect. Yet, it is the way in which explanations and models interact or hold together that is of particular significance for understanding comorbidity. In this instance, the concept of coherence operates at a level one step removed from the data, coming to instead characterise the types of relationships and properties operating within and between causal models.

Thagard (1989) frames explanatory coherence as based in the logical properties of propositions (in this case causal hypotheses and models), their relation to the data or effects they seek to explain, and their relation to other propositions. This means that the propositions derived from a theory are logically consistent, exhibit relations of symmetry, and refer to causal mechanisms that enable each other and interact to produce relevant phenomena. If an etiological classification system is eventually proposed, it needs to demonstrate internal and external coherence. In line with Thagard's principles of coherence (1989), that means that the causal hypotheses of mental disorder upon which classification is based, account for the data, agree with each other, and fit together or converge to form a consistent explanatory system. Thagard states that simplicity is also desirable, in that coherence is weakened with the addition of more and more hypotheses. As suggested, it may be the case that some disorders have relatively simple causal structures, whereas others are best explained by very complex causal models.

While coherence is desirable for explanations of individual mental disorders, it is especially relevant for comorbidity. This is because comorbidity occurs as either an intersection or overlap of mental disorders. Comorbidity also requires its own explanations of for example, why depression and substance use so regularly co-occur and what the predominant mechanisms might be that bring about this phenomenon. These explanations should also cohere with explanations of the individual disorders rather than contradicting them. If mental disorders are conceptualised as causal structures then their explanatory frameworks need to similarly intersect or overlap in order to maintain coherence with the observed phenomena of comorbidity.

If this is the case then it is likely that explanations and models will need to be explicated at a level of detail that makes apparent the interactions between causal systems or causal pathways that bring about comorbidity. The requirement to construct coherent explanations makes particular demands when seeking an integrative understanding of comorbidity. The granularity required of causal models may differ depending on the nature of each disorder and the way that disorders interact.

Such integrative and coherent explanation may be especially useful in guiding treatment choices for both the client and clinician. For example, prioritisation of treatment to target the most distressing symptoms may be a useful strategy in some instances of comorbidity. In other instances, targeting broader causal factors that underlie multiple symptoms may be preferred. Such choices rely on integrative and coherent explanation of mental disorder and comorbidity. In short, they require a good enough understanding of a causal system that effective treatments may be developed to change an effect, and then clinically applied to foster well-being for the client. At this time, we lack such an understanding.

Methods attuned to the demands of comorbidity.

The development of coherent, integrative explanations of comorbidity is dependent upon research and clinical methods that are attuned to comorbidity's particular demands.

Through research, models and concepts of mental disorder may be improved. In the spirit of scientific realism, this means that representations may more closely approximate an objective "truth" or "reality". In the spirit of scientific pragmatism this means that models are more responsive to our goals (Zachar, 2014). Neither is mutually exclusive. In either instance, if comorbidity is considered an important phenomenon requiring explanation then methods need to be adopted that will generate explanations and models for understanding comorbid disorders and the kinds of comorbidity that are observed. Research is also required that investigates the effectiveness of treatment for more common instances of comorbid disorders and different kinds of comorbidity.

Given the likely complexity of this task, simplification is a viable strategy. As discussed, however, a certain level of detail is likely required to gain integrative understanding. Group studies and traditional experimental and quasi experimental methods that look to deconstruct, if not reduce, causal systems into their component parts are essential tools. When dealing with emergent phenomena however, Pennington (2014) suggests that the act of reconstruction is just as important.

Reconstructive methods enable the testing of a reductive model to see whether it reproduces the emergent phenomena it seeks to explain. Such methods include neural network simulations, analysis of brain functional and structural connectivity (Pennington, 2014), as well as dynamical network modelling of systems beyond the brain (Barabási, 2011; Mitchell, 2009).

Classification forms an important link between the research base of more general models and the clinical practice of applying such models to the individual. While

classification attends to conceptual demands, assessment and diagnostic methods that follow from classification form the method by which those concepts are applied to the clinical and research contexts. These methods need to be responsive to the demands of matching the individual client to the group level disorder.

As will be argued, the current descriptive classification method attends poorly to comorbidity's ethical demands for improved outcomes, and its knowledge demands for coherent, integrative explanation. The DSM's atheoretical approach does not exclude etiological theory; instead it leaves the door open for clinicians to use their own causal theories. As a result comorbid presentations are likely conceptualised in a subjective and idiosyncratic fashion by clinicians who often work with heavy caseloads under considerable time pressure. If classification is able to be grounded in explicit concepts and causal models of mental disorder this will offer a basis for explicit concepts and models of comorbidity to also be developed. As discussed, conceptual clarity and explanatory coherence would therefore assist clinicians with assessment, communication and treatment planning.

As regards the pursuit of classification, comorbidity poses a significant additional question – is mental disorder so inherently heterogeneous that it cannot be adequately classified, except perhaps on a largely pragmatic basis? Alternatively, is currently observed comorbidity an outcome of a poor classification system, which can be rectified with a more robust etiological framework? This dialogue is also explored in the coming chapters.

Chapter Two reviews a history of comorbidity and sets the scene within which current concepts of comorbidity were developed. These concepts are explored in Chapter Three. Alternative and potential future models of mental disorder are then discussed in following chapters, in light of the ethical goals and knowledge objectives identified in this first chapter. A short conclusion summarises the findings and proposes suggestions for future consideration.

Chapter Two - The Creation of Psychiatric Comorbidity

First Use of the Term Comorbidity

The term *comorbidity* was coined with regard to internal medicine in an article by Feinstein (1970) entitled "The pre-therapeutic classification of co-morbidity in chronic disease." Here comorbidity was defined as "… any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" (p. 457). Feinstein used lung cancer as an example of an index disease that might exist alongside comorbid coronary artery disease or pneumonia. Written 45 years ago, this article voices issues of continued relevance to psychiatric comorbidity: the importance of understanding comorbidity at both individual and population levels; the difficulty of attributing cause in complex comorbid cases; and the implications of comorbidity for the application of research to the clinical context.

In outlining the functional effects of comorbidity for the patient, such as potential earlier detection, increased symptom severity and likely poorer prognosis, Feinstein emphasised the impact that comorbidity may have on an individual's life experience. He also noted possible therapeutic implications such as the withholding of intervention due to a comorbid condition, and post-therapeutic outcomes such as an inability to work due to the comorbid condition. He highlighted some of the diagnostic challenges for the clinician when encountering comorbidity in a patient. Here, as in much internal medicine, diagnosis and cause are assumed to be inextricably linked through the identification of a pathological disease process. Feinstein argued that ascertaining cause in the context of chronic diseases was particularly challenging as patients tended to present with a diverse array of symptoms and signs, in addition to variation in the sequence and timing of such symptoms. He called for both clinical reasoning and statistical research to play a role in decisions regarding treatment of patients with comorbid diseases. Thus a particular emphasis was placed on the importance

of identifying comorbidity for the purpose of creating comparable groups in order to

investigate treatment efficacy. Questioning the relevance of research using 'pure' samples to

the clinical care of those with comorbid diseases, he said:

> By excluding patients with associated diseases from trials of therapy for a particular
>
> disease, statisticians can design the trial to contain a presumably 'homogenous'
>
> population, but the results achieved in these 'purified' circumstances cannot be
>
> extrapolated to the heterogeneous world of clinical reality. (Feinstein, 1970, p. 456)
>
> Kaplan and Feinstein (1974) later suggested a system by which to classify different

types of comorbidity, differentiating diagnostic, prognostic and pathogenic comorbidity.

Diagnostic comorbidity captured the challenge of distinguishing between diseases that shared

common symptoms, prognostic comorbidity conferred increased risk of adverse future events

due to the presence of a comorbid disease or the combination of the two diseases, and

pathogenic comorbidity signified a likely causal relationship existing between the two

diseases.

These seminal articles provided a basis by which to consider comorbidity as it related

to psychopathology. They set the stage for psychiatric comorbidity having significant "real-

life" effects for patients as well as practice implications for the clinician. This discussion also

highlighted the challenge that comorbidity poses for the application of homogenous group

research to the individual within a clinical setting. In addition, while it was acknowledged

that overlapping symptoms and complex chronology characterised comorbid presentations,

the term was explicitly conceptualised as two or more co-occurring but distinct disease

processes.

Development of the DSM-III

Throughout the 1960's and 1970's the validity of psychiatric nosology and diagnosis

was increasingly questioned (Brown & Barlow, 1992; First, 2012; Klerman, 1990; Rosenhan,

1973; Szasz, 1960). This included challenges to the ideological dominance of the medical model in relation to psychiatry. Such accounts emphasised the adverse consequences of psychiatric diagnosis such as labelling and dehumanisation, questioned the extended reach of mental health practice beyond psychopathology into problems in living, and cited a growing evidence base from the psychological domain for the validity of dimensional models of psychological functioning (Brown & Barlow, 1992; Klerman, 1990). Furthermore, growing evidence from within the psychiatric domain dating back to the 1930's indicated that psychiatric diagnostic practices were variant between clinicians, and thus unreliable (First, 2012). The most influential of studies was that of Kendell et al. (1971), commonly referred to as the "US-UK study". Using videotaped cases, the study demonstrated that the conceptualisations of schizophrenia, manic-depressive illness and personality disorder varied significantly between British and American psychologists, and thus so too did diagnosis of these disorders.

Robins and Guze (1970) proposed criteria that if met, would reliably and validly diagnose schizophrenia. This laid a theoretical pathway for the paradigm shift that was to come. Improving diagnostic reliability was a high priority for good reason; validity is unattainable without reliable measurement (Spitzer & Fleiss, 1974). Furthermore, the adoption of Cohen's *kappa* technique marked a statistical development that enabled the quantitative ascertainment of inter-clinician agreement (Spitzer, Cohen, & Fleiss, 1967)**.** Reliability was also a direct concern in and of itself, given evidence of discrepant conceptualisations and diagnostic practice.

It was within this context that the DSM-III was developed and later published (APA, 1980). This publication formalised a paradigm shift in psychiatric classification that had been gaining momentum over the previous decade. While it carried from its preceding editions a primary goal of clinical usefulness, it departed from the DSM-II (APA, 1968) in a number of

important ways: the use of operationalised diagnostic criteria; the promotion of an

atheoretical descriptive approach; and the inclusion of a biopsychosocial perspective in the

form of multi-axial diagnosis (First, 2012).

The groundwork and evidence base for a shift to operationalised diagnostic criteria

had been successfully laid down within the research domain during the 1970's, and with it,

the promise of improved reliability. In particular the discovery of medications such as

chlorpromazine, lithium and imipramine warranted the need for clear diagnostic criteria, in

order to assemble homogenous samples for research into the efficacy of these pharmaceutical

treatments for different clinical presentations (First, 2012). In 1972 the "Feighner criteria"

were published outlining criteria for 15 psychiatric illnesses, with supporting evidence from

clinical, family and follow up studies (Feighner et al., 1972). The intention of the Feighner

criteria was to provide a framework to facilitate communication between researchers and

allow comparison of findings across research studies. The criteria were presented as tentative

and open to change in light of new evidence. From the outset, this framed classification and

nosology as a scientific pursuit founded in iterative improvement. These diagnostic sets were

then revised and a further ten disorders added during the development of the Research

Diagnostic Criteria (RDC, Spitzer, Endicott & Robbins, 1975). These criteria sets formed the

basis of the operationalised diagnoses subsequently published in the DSM-III in 1980. Field

trials of the criteria sets indicated their viability for use in clinical settings and improved

reliability in comparison to DSM-II diagnoses (Spitzer, Forman, & Nee, 1979).

The second conceptual change brought about by the DSM-III was a move away from

the psychodynamic explanations that formed the basis of earlier editions, to an atheoretical

descriptive approach. First (2012) describes Spitzer's motivation for this politically

unpopular move as being primarily grounded in a wish to avoid endorsing explanations that

lacked evidence, rather than a desire to avoid etiologically based classification per se.

Another benefit of the descriptive stance however, allowed adoption of the DSM-III for use by practitioners from a range of different theoretical perspectives including psychiatrists, psychologists and psychoanalysts (APA, 1980). This again reflected the broadening social and scientific context in which psychiatric classification was resident. Similarly, the inclusion of a multiaxial diagnosis allowed the DSM-III to adopt a biopsychosocial approach. Although the manual recommended the evaluation of physical, psychosocial and adaptive functioning for the purpose of treatment planning and prognosis, First (2012) argued that it was also included to counter arguments that evaluation was a solely diagnostic enterprise. "Thus, the decision to include a multiaxial system was as much about reacting to criticism as it was about innovation" (p. 135).

The resulting success of the DSM-III and its adoption as a foundational text for clinical, research, educational and public health purposes speaks to its many strengths. Its operationalised approach and use of the relatively new *kappa* technique signalled an innovative change. In addition, decisions were founded upon a substantial research evidence base in conjunction with field trials that demonstrated clinical feasibility. It reliably improved distinction between diagnostic categories and enabled a stronger basis for researching treatment efficacy and applying this knowledge to the clinical context. It improved inter-rater reliability, allowing for more valid psychiatric diagnosis while enabling better comparison across research studies. It also avoided endorsement of etiological theories that lacked supporting evidence. Crucially, it added legitimacy to psychiatric classification and diagnosis in the face of the substantial challenges detailed earlier. At the same time, it acknowledged its fallibility, stating that although data-driven, the interpretations of those on the committees were influential in shaping the text (APA, 1980). Furthermore, the original Feighner criteria which had played an important role in the inception of operationalising diagnostic criteria, was founded upon a realisation that iterative improvement would be made with accumulation

of evidence and knowledge (Feighner et al., 1972). The problem of reification however was perhaps an unforeseen consequence.

The Problem of Reification

In its success the DSM-III became perhaps too influential. The priority to increase reliability was coupled with an intention to create a shared language for communication about mental disorder. However, this language came to dominate concepts of mental disorders within clinical, research and public health settings. Despite the caveat in its introduction that diagnostic categories were not intended to specify discrete entities, these categories nonetheless became reified (Clegg, 2012; Jacobs & Cohen, 2012; Widiger & Shea, 1991). This reification remained a problem for the following editions of the DSM. Hyman (2010) described reification as a problem affecting a range of users including those within clinical, scientific, legal and other non-clinical communities: "…cautionary statements within the DSM-IV (APA, 1994), if read at all, provide little protection among many communities of users against reification of the disorders listed within" (p. 158).

Reification in this instance can be understood as a process in which mental constructs, such as the descriptive diagnostic categories outlined in DSM-III and following editions, are considered objectively real (Murphy, 2006). Gannon (1984) argued that this process of reification focused clinicians' attention to the diagnostic category rather than the behavioural components of an individual's presentation, leading to an increased risk of dehumanisation through diagnosis. Similarly, Jablensky (1991) called for clinicians to employ a "middle ground" perspective that optimised the rigour of operationalised criteria while maintaining a person-centric approach. In doing so he implored the avoidance of reification in favour of "epistemological openness."

Reification was likely supported by the following factors: concepts and beliefs regarding the nature of mental disorder founded in the medical model; essentialist cognitive

biases; and a tautological relationship between the nomenclature and research methods for group selection.

Concepts of mental disorder prevalent within the medical model.

Successes in the latter half of 19th century medicine identified autopsy and bacteriological correlates with mental syndromes such as Alzheimer's disease and syphilis, leading to an assumed underlying biological cause for the psychotic disorders among others. This causal assumption served as the basis for treatments such as insulin coma and electroconvulsive therapy. However, following World War II many psychiatrists found success in the use of psychodynamic principles to explain and treat war-related trauma. The medical model, with its conceptualisation of mental disorder as discrete categories originating from biological cause, was questioned. Although both DSM-I (APA, 1952) and DSM-II documents were organised in a hierarchical manner according to medical model classification practice, a psychodynamic undertone prevailed regarding many non-organic disorder descriptions, with explanations founded in psychopathology as a reaction to the environment rather than an outcome of biological properties. Increased interest in mental health from the social sciences also broadened perspectives relating to concepts of mental disorder, and alongside this, other professions such as clinical psychologists and psychiatric social workers began working with those experiencing mental illness (Brown & Barlow, 1992; Clegg, 2012; Klerman, 1990).

Interest in psychiatric classification was revitalised in the 1970's in response to the challenges facing psychiatry as described earlier, leading to the eventual publication of the DSM-III. Those involved in the Feighner criteria (Feighner et al., 1972) and RDC (Spitzer, Endicott, & Robbins, 1975), among others, were dubbed "neo-Kraepelinians." Emil Kraepelin (1826 – 1926) prioritised description of signs, symptoms and developmental course in his classification protocols. It is argued that alongside an explicit desire to improve

diagnosis through reliable classification based in evidence, the neo-Kraepelinians also emphasised eventual biological explanation of mental disorder (Brown & Barlow, 1992; Jacobs & Cohen, 2012; Klerman, 1990). Guze (1982) planted mental disorder firmly within the medical domain, naming epidemiology alongside neurobiology as the two realms in which scientific progress would be made within the field of psychiatry. He stated that "psychiatry wants to reidentify with its medical base, by committing itself anew to that quintessential medical activity: diagnosing illness" (Guze, 1982, p. 7). While others have more recently argued that the medical model shares much in common with the biopsychosocial model (Murphy, 2006), the prioritisation of biological cause as the principle explanatory device and level of choice for intervention was evident in other ways. First (2012) for example, points to the failure of the multiaxial system, surely the DSM-III's strongest indicator of alignment with broader psychosocial principles, as being due to its low clinical utility. A complementary explanation may be that if the cause of mental disorder is understood to be biological and the prescribed treatment consequentially addresses that level of explanation, then the benefit of measuring functioning in other domains of life is relatively limited.

Whether the explanation of a mental disorder is analogous to discrete categories, such as bacterial disease, or more multifactorial chronic illness, such as hypertension, conceptualisation of mental disorder within the medical model leant itself to the reification of diagnostic categories. The dominant part these categories played in implicitly shaping cognitive and socially shared concepts of mental disorder, likely overshadowed explicit knowledge of the descriptive status of DSM-III diagnostic constructs, its atheoretical stance, and the accompanying disclaimers that reminded users that diagnostic categories were not discrete entities (Hyman, 2010).

Psychological essentialism.

Along these lines, Peter Zachar (2000, 2014) highlighted the role of an essentialist

bias in the reification of psychiatric disorders. Eloquently described by Gelman (2004),

psychological essentialism can be understood as "the view that certain categories have an

underlying reality or true nature that one cannot observe directly but that gives an object its

identity, and is responsible for other similarities that category members share" (p. 404).

Within the medical model there is a tendency to view mental disorders as "natural

kinds" or "essences" (Hyman, 2010; Kendell & Jablensky, 2003; Zachar, 2000). These are

entities with fixed internal properties that are both necessary and sufficient to define their

membership to the category of natural kind or essence (Kendler, Zachar, & Craver, 2011;

Zachar, 2000). Examples of natural kinds often come from physics and chemistry, such as

elements of the periodic table: all gold atoms have 79 protons and all atoms with 79 protons

are gold atoms. Within the medical model, natural kind assumptions dominated, especially in

the form of "disease realism". Here diseases are construed as internal biological explanations

for observed syndromes that are considered objective departures from adaptive functioning

(Kendell & Jablensky, 2003). Zachar (2000) argued that diseases are not natural kinds, citing

tuberculosis as an example where the effects of the bacterium in its host is dependent upon

many factors, making the outcomes relational rather than inherent to the properties of the

bacterium. Although knowledge of a disease's causal mechanisms often gives diagnosis high

predictive validity and reliability, it does not make it a natural kind. A mechanistic biological

explanation, despite its power and stability, does not entirely discount relational properties

external to itself. It is important to recognise that Zachar's concerns regarding natural kinds

exist outside the debate regarding reductionism of mental states. Instead, Zachar highlighted

the extent to which our concepts of mental disorders simplify their properties and underlying

causal explanations due to a cognitive bias towards essentialism. Zachar also similarly

critiqued tendencies to regard psychological constructs, such as traits or syndromes, as natural kinds. Thus, he regarded psychiatric diagnoses as frequently falling foul to *representational, causal and placeholder* essentialist biases.

Representational essentialism refers to how categories of human construction, such as race, are often construed as accurate reflections of natural kinds. *Causal essentialism* denotes a tendency to view causal relationships or mechanisms that result in category-typical, observable characteristics, as natural kinds. *Placeholder essentialism* indicates a belief that a causal essence underlies observable characteristics, and therefore category membership, in the absence of knowledge of the actual causal process. Substantial evidence suggests essentialism is a cognitive heuristic that acts in quite fundamental ways from at least pre-school age, assisting in the learning and generalisation of language and knowledge, as well as supporting reasoning about internal properties and cause. It appears particularly relevant as a reasoning heuristic regarding acquisition of scientific knowledge (Gelman, 2004).

This evidence also supports the notion that psychological essentialism likely played a role in the reification of DSM-III diagnoses. Psychiatric disorders, although based on the best evidence available, were descriptive categories constructed through agreement by committee. Nonetheless, disorders such as depression and schizophrenia were reified and interpreted as categories that objectively existed in reality. In the context of the medical model, biological causes were readily generated based on twin studies that portrayed the role of genetic factors as pivotal in the development of these highly specified disorders (Kendler, 1996). Thus, although the DSM-III emphasised its descriptive, atheoretical stance, its actual use within the broader research and clinical context meant the nosology was readily coupled with nascent causal theories and hope of full mechanistic explanation in due course. The representational, causal and placeholder cognitive biases of psychological essentialism appear actively at work in the oft-bemoaned process of psychiatric diagnosis reification.

The reciprocal influence of research method.

A final factor in the reification of diagnostic categories is the tautological relationship between classification and research methods. Some methods require the use of comparable groups to test hypotheses. Clear definition of criteria used to determine group selection is also required when comparing findings across different studies. Diagnostic criteria as outlined in classification systems such as the DSM, provides much needed guidance and enables sample consistency between different research programmes. Structured diagnostic interviews provide even greater consistency and assurance that other sources of sampling error such as interviewer bias, is minimised. However, diagnostic criteria need not be the sole or dominant determinant of group selection. Indeed research that extends to include participants with characteristics beyond diagnostic criteria boundaries is necessary to expand understanding of the limitations and weaknesses of classification systems.

Kendell and Jablensky (2003) addressed the implications of diagnostic criteria on research in their classic paper regarding the validity and utility of psychiatric diagnoses. They again applauded the improved reliability that DSM-III allowed research, identifying that its level of accurate description also facilitated replication studies. However, they questioned its eventual use, especially by grant-giving agencies and scientific journals, for pressuring researchers to define their participants using the descriptive diagnostic criteria of the DSM system. Such policies were particularly dangerous for etiological research, especially if the validity of syndromes was questionable. Kendell and Jablensky went so far as to suggest that political considerations were overriding scientific interests:

> The widespread use of a single definition has many advantages, but researchers must be free to use other definitions if they wish, if only because that is how the shortcomings of the standard definition are most likely to be overcome. (2003, p.10)

Hyman (2010) also argued that DSM classification had too much influence over the work of scientific and regulatory bodies. He cited an example where investigation into treatments for the negative symptoms of schizophrenia was stymied due to exclusion of cognitive symptoms from the DSM-IV definition of schizophrenia. The extensive use of homogeneous samples in research and clinical trials not only inadvertently reinforced DSM's concepts and categories, but potentially impeded treatment development, thus negatively impacting on the lives of those it intended to improve.

Reification summary.

The process of reification, or construal of diagnostic constructs as objectively real, was encouraged by mechanisms of social, cognitive and methodological origin. These included conceptualisations of mental disorders within the medical model as being natural kinds, likely due to underlying biological processes that in time would be identified, confirming the validity of diagnostic categories. Such conceptualisations and understandings were supported by psychological essentialism; a bias that evidence suggests is in operation at a fundamental cognitive level in both children and adults. Reification of DSM diagnoses was also reinforced by the wide publication and funding of research that recruited participants based on diagnostic criteria. Research involving pure disorder samples was likely quite effective in reinforcing reified diagnostic categories. How the publication of the DSM-III and its accompanying reification affected the concept of comorbidity is discussed next.

The Creation of Psychiatric Comorbidity

With the uptake of DSM-III in both clinical and research domains it became apparent many individuals met criteria for multiple disorders. This was a problem the multiaxial approach only partially addressed. Within the context of the genesis of DSM-III and its revision, the concept of comorbidity worked its way into psychiatry and psychology from the

medical and epidemiological literature (Klerman, 1990) and became a concept central to debates regarding psychiatric diagnosis from the mid 1980's onwards.

Within clinical settings the diversity and prevalence of comorbidity became evident (Barlow, DiNardo, Vermilyea, Vermilyea, & Blanchard, 1986; Mezzich, Ahn, Fabrega, & Pilkonis, 1990) and continued to be so (Brown, Campbell, Lehman, Grisham, & Mancill, 2001). However, clinical samples are unlikely to provide the best estimates of comorbidity prevalence. Often called Berksonian or clinical ascertainment bias (Berkson, 1946; Bogenschutz & Nurnberg, 2000), it has been well established that those who have two or more disorders are more likely to present for treatment, and therefore the use of clinical populations to calculate prevalence can often overestimate comorbidity in comparison to community population data.

Nonetheless, a number of large-scale epidemiological studies confirmed that psychiatric disorders co-occurred at rates that were higher than expected by chance, that is, higher than expected given the base rate occurrence of a disorder in its pure form within the community. Epidemiological data also highlighted a general tendency toward psychiatric comorbidity: diagnosis with any one disorder increased the likelihood of receiving a diagnosis for almost any other disorder (Boyd et al., 1984; Regier, Burke, & Burke, 1990). Later research utilising DSM-IV criteria, such as the National Comorbidity Survey (NCS), replicated these findings of high comorbidity across diagnostic categories (Kessler et al., 1994). So too did the National Comorbidity Survey Replication study (NCS-R), which estimated that 22% of the population meet criteria for two diagnoses, and 23% for three or more diagnoses (Kessler et al., 2005).

The effects of the DSM-III on the incidence and concept of psychiatric comorbidity were both direct and indirect. The change from DSM-II to this descriptive, categorical and atheoretical classification system significantly increased the incidence of comorbidity

(Frances, Widiger, & Fyer, 1990), again bringing to light an issue that challenged the validity of psychiatric nosology, but this time from within. Despite this challenge, to a certain extent the reification that accompanied the concept of mental disorders, also accompanied the concept of comorbidity.

Direct effects of the DSM-III on comorbidity.

Frances, Widiger and Fyer (1990) laid out nine ways in which the DSM-III and DSM-III-R increased the likelihood of comorbidity, a number of which are relevant to this discussion. Some of their critiques resonated with earlier criticisms regarding the validity of psychiatric diagnosis. They reported that increased coverage in the DSM-III had extended psychiatry's scope of practice. They also suggested that categorical classification could artifactually create comorbidity where none existed if the phenomena were actually dimensional in structure. In addition, they stated that splitting broadly defined categories into more finely-grained diagnostic groups also increased the rate of comorbid diagnoses.

Importantly their analysis also revealed that changes in diagnostic method accounted for much of the observed increase in rates of comorbidity. The diagnosis of multiple disorders if different conditions presented together was encouraged in the DSM-III and DSM-III-R, leading to less emphasis on differential diagnosis. This led to increased comorbidity, especially in instances of co-occurring conditions on different axes such as depression and personality disorder. The decision to remove a number of exclusionary criteria in DSM-III-R, although based on reasonable grounds, also led to increased comorbidity. So too did the lowering of thresholds in DSM-III regarding duration, impairment, severity and frequency of symptoms. Decisions regarding level of impairment also became vastly more complicated in the case of comorbid diagnoses where it was often unclear whether one disorder caused more distress than another, or whether the combined constellation of symptoms was responsible. Overlap between criteria items in different diagnostic sets also increased comorbidity, but

Frances et al. (1990) pointed out that "if the constructs of anxiety and depression overlap, then perhaps the criteria sets should as well" (p. 48).

Frances et al. (1990) remained cognisant of the pragmatic choices involved in designing classification systems, emphasising that while certain decisions may have been responsible for increasing comorbidity, they were made to offset other undesired effects or assumptions. For example, they acknowledged that while a multiaxial system reduced the attention given by the clinician or researcher to differential diagnosis, it also allowed for a more complete descriptive picture of the individual, which may benefit both clinical practice and research. In the case of anxiety and affective disorders they suggested that dimensional measures may be more informative with nominal cut-off points to be utilised only when homogenous samples were required for research.

In summary, their analysis revealed a number of issues that flowed directly from the classification system into diagnostic practice. This led, for better or worse, to an increase in rates of comorbidity. The concept of psychiatric comorbidity thus took shape as a result of the appearance and use of DSM-III. Some of the implicit assumptions underlying concepts of mental disorder that were associated with the classificatory change also accompanied the concept of comorbidity.

Reification of comorbidity.

While comorbidity served as a reminder that improvements in validity had not necessarily accompanied gains in reliability, it somewhat ironically, also became an entity unto itself. To an extent, the concept of comorbidity was also reified alongside the diagnostic categories that were at least in part responsible for its creation (Lilienfeld, Waldman, & Israel, 1994). Comorbidity in accordance with DSM nosology, referred to "the assignment of more than one diagnosis to an individual to account for symptoms of illness occurring during a

given period of time" (First, Spitzer, & Williams, 1990, p. 83). As such, it was in all regards a construct that again became associated with an objective reality.

Assumptions inherent in the medical model, regarding causes of comorbidity, were carried across to the fields of psychiatry and psychopathology with the adoption of the term from general medicine. Whether highly comorbid conditions, such as depression and generalised anxiety disorder were considered a natural kind is up for debate, but the influence of the medical, disease-driven model is evident in the following examples.

Even in the most recent DSM-5 (APA, 2013) some disorders are considered dominant to others. For example the symptoms of major depression may be better explained by schizoaffective disorder or schizophrenia. The hierarchy of disorders evident in the structure of the nosology follows a long tradition of hierarchical organisation within medical and biological classification (Klerman, 1990), which has given some diagnoses such as organic and psychotic disorders, explanatory dominance over others such as anxiety and mood disorders.

While evidence for shared genetic factors between highly comorbid disorders exists (Kendler, 1996), beliefs inherent within the medical model about the fundamental influence of biological cause has prioritised biological explanations over other possible causes such as environmental factors. In particular, the conceptualisation of depression as a biologically-based disease became well-entrenched, particularly with the availability of moderately efficacious pharmacological treatment (Coppen, Shaw & Farrell, 1963). Given that depression presented as highly comorbid with a number of other disorders (Mezzich et al., 1990), this may have contributed to the reification of comorbid diagnoses as co-occurring disease processes.

More recently, comorbidity has been construed as an indicator of phenotypic heterogeneity. Here comorbid diagnoses are interpreted as spurious (Bogenschutz &

Nurnberg, 2000). Instead a gene or group of genes are understood to be the fundamental cause of a range of phenotypic expressions, including comorbid presentations. While it may be acknowledged that environmental factors mediate phenotypic outcome, they appear to be of less explanatory importance. In contrast, an alternative interpretation consistent with a biopsychosocial medical model, is that both biological and environmental factors are causal, with not one level of explanation claiming fundamental importance (Kendler, 2012; Murphy, 2006).

An example like this illustrates how essentialist biases might impact on interpretations of comorbidity. *Representational essentialism* may lead to the reification of either comorbid diagnoses in general, or specific comorbid combinations. *Causal essentialism* may encourage existing evidence of shared genetic or biological factors to be interpreted as dominant explanations for comorbid presentations. Finally, *placeholder essentialism* may support a belief that one day etiological classification based in an understanding of biological processes such as genetics or neuro-circuitry will lead to the elimination or significant reduction of comorbidity.

Already, a number of concepts of comorbidity have surfaced in this discussion. These include: comorbidity as two distinct disease processes; comorbidity as due to a shared fundamental cause; comorbidity as a marker of vulnerability; comorbidity as an indicator of a specific treatment approach; comorbidity as a challenge to the validity of psychiatric diagnosis; comorbidity as a concept created by the DSM-III and its progeny; and comorbidity as a signifier of multicausal complexity.

These concepts are often opposing, and if not, certainly lack consensus and clarity. The following chapter will investigate the most influential contemporary concepts of comorbidity, and unwrap how each is based within a differing concept of mental disorder. For the moment it is important to acknowledge that notwithstanding this disagreement and

confusion, neither the DSM-IV nor DSM-5, despite self-acclaimed goals of clinical utility,

attempt to offer guidance regarding interpreting or working with the concept of comorbidity

in the clinical setting. While the nosology stands silently by, the outcome for those who meet

criteria for multiple disorders is an accumulation of separate diagnoses that neglect to

integrate their symptoms into a meaningful whole and do little to help make sense of their

singular life experience.

Chapter Three - Concepts of Comorbidity

Introduction

Comorbidity's multiple meanings reflects both the variety of professions engaged in mental health care and the complexities of conceptualising mental disorder. Even within disciplines, concepts may differ across settings. A comorbid diagnosis of depressive and substance use disorders may have different meanings for those who regularly encounter it in emergency and detoxification settings versus practitioners working with those whose conditions are stabilised but chronic (Piotrowski, 2007).

Given the scope of this thesis, psychiatric and psychological contributions are the primary perspectives explored. A choice to exclude social or constructivist perspectives of comorbidity was made due to limited space rather than judgment that these approaches lack validity. Even within only these fields, concepts of comorbidity can be wide and varied, which can decrease clarity. Krueger and Markon (2006) concur, stating that "the problem is that the term itself is broad enough to encompass too many conceptually distinct phenomena" (p. 4). This represents both a challenge and an opportunity to make the underlying assumptions of various conceptualisations of psychiatric comorbidity explicit. This chapter and the following chapters are an attempt to utilise distilled conceptualisations of comorbidity to appraise different models of mental disorder. However, before investigating models of mental disorder a conceptual crossroads is visited, that of comorbidity at the individual versus population level.

Individual Versus Population Conceptualisations

The term comorbidity has distinct meanings at the population and individual levels, raising important challenges and implications. For example, Lilienfeld et al. (1994) suggested that comorbidity as a term should be separately referred to as *co-variation* at the population level, and *co-occurrence* at the individual level. To review, covariance of disorders is the

tendency for some disorders to occur together within a population at a higher rate than predicted by the product of the base rates of the individual disorders. It is this pattern of co-variation that may be interpreted as indicative of a vulnerable population or as a nosological flaw.

Comorbidity as an indicator of vulnerable or multimorbid populations.

High comorbidity of physical conditions and diseases in populations of older persons has a range of implications across clinical, epidemiological and public health contexts (Pincus, Tew Jr, & First, 2004; van den Akker, Buntinx, & Knottnerus, 1996). This instance of high comorbidity or multimorbidity, supports the notion of a vulnerable population of older persons. Similar examples include the very young or immunosuppressed. Evidence of disproportionately high comorbidity of psychiatric disorders within a relatively small percentage of people, may indicate a similarly vulnerable population (Zachar, 2009). Epidemiological research supports this hypothesis.

As discussed in Chapter One, it is estimated that just 14% of the population have a lifetime history of three or more mental disorders. This group is estimated to share more than half of the total population's prevalence of lifetime mental disorder (Kessler et al., 1994). Severity, recurrence and health burden are also all strongly related to comorbidity (Gadermann et al., 2012; Kessler et al., 2005; Maj, 2005a). The National Comorbidity Survey – Replication study (NCS-R) demonstrated that although mental disorder is quite prevalent within the community, serious cases occur "among a relatively small proportion of cases with high comorbidity" (Kessler et al., 2005, p. 617).

Comorbidity as an indicator of a nosological problem.

Alternatively, evidence of high comorbidity, especially amongst community samples may suggest that psychiatric nosology is incorrectly parsing mental disorders from one

another or from normality. Conceptual subtexts to this hypothesis include that of subthreshold comorbidity and comorbidity across developmental trajectories.

Categorical diagnostic cut-off criteria such as the number, duration or frequency of symptoms experienced, may artifactually lower estimates of prevalence of mental disorder within epidemiological studies. Diagnostic thresholds may also underestimate the effect that comorbid subthreshold syndromes or symptoms have on overall severity and disability. For example, analysis of data from the Zurich Cohort prospective and longitudinal study, suggested that it was the co-occurrence of anxiety and depressive symptomatology, rather than a presentation of symptoms at above diagnostic threshold, which was associated with symptom severity. The authors interpreted these finding as supporting the incorporation of dimensional approaches to classification protocol (Preisig, Merikangas, & Angst, 2001). Hence categorical diagnosis may artifactually change how we study, understand and represent the nature of mental disorder, as well as the phenomena of comorbidity.

Comorbidity at the population level may also assist in formulating hypotheses regarding disorder development and aetiology. Developmental patterns of sequential versus cumulative comorbidity (Moffitt et al., 2007), also referred to as heterotypic versus homotypic comorbidity (Angold, Costello, & Erkanli, 1999), may be of particular use. Whereas homotypic or cumulative comorbidity refers to continuity or recurrence of the same disorder over time, sequential or heterotypic comorbidity refers to patterns of co-variation between different disorders across time. While homotypic comorbidity may indicate a population that experiences chronic or recurrent bouts of mental disorder across a lifetime, heterotypic comorbidity instead suggests that a disorder may manifest differently across time. Thus heterotypic comorbidity potentially undermines classification based on descriptive rather than etiological principles.

Co-occurrence of disorders at the individual level has distinct implications of its own.

Individual level.

Those with comorbid psychiatric diagnoses present with more symptoms and greater symptom complexity. This has diagnostic, prognostic and therapeutic implications for the individual and their clinician. However, the descriptive status of nomenclature does little to coherently explain an individual's comorbid presentation or offer guidance for treatment. In addition, a poorer research base regarding treatment efficacy in comorbid samples may go as far as to discriminate against adequate service provision for these individuals.

Unfortunately, little research has been conducted into the effect of comorbid diagnosis on patients' or clients' experiences of the psychiatric diagnostic process. It is unknown whether comorbid diagnosis reduces or enhances a person's ability to make sense of his or her own subjective experience. Although not strictly a psychiatric or psychological condition, an account of twenty people's experiences with fibromyalgia might give some insight:

> Participants described enduring the course of a 'giant mess' of unpleasant symptoms, some of which were understood to be symptoms of fibromyalgia and some the interactive or parallel effects of comorbid illness. The respondents also demonstrated their considerable efforts at imposing order and sense on complexity and multiplicity, in terms of the instability of their symptoms. (Dennis, Larkin, & Derbyshire, 2013, p. 736).

By definition those with comorbid diagnoses generally experience a broader array of signs and symptoms that fail to fit one set of diagnostic criteria. These presentations are hence often more complex than pure cases in addition to being more severe, imparting greater health burden and poorer prognosis (Feinstein, 1970; Gadermann et al., 2012; Maj, 2005a). The presentation of overlapping symptom clusters also brings increased diagnostic complexity. The issue of clinical complexity has important implications for the clinician, especially when trying to discern a chronological pathway responsible for the current

presentation, which may assist in making primary and secondary causal distinctions (Kessler & Price, 1993).

In addition, psychiatric classification and diagnosis often fails to assist communication with clients or guide clinical reasoning and treatment planning. Supplementary to the negative effects of labelling that may result from psychiatric diagnosis, assignment of comorbid diagnosis can increase confusion. For example, in regards to developmental delay in children, where comorbidity is very high, it may be more useful to use specific descriptions of a child's strengths and weaknesses than multiple diagnostic categories, when conceptualising a client's presentation and communicating clinical findings with parents and teachers (Kaplan, Dewey, Crawford, & Wilson, 2001). Similarly, conceptualisation and explanation of comorbid depression and anxiety as resulting from a singular broad dimension of psychological functioning, may be more comprehensible and more accurate (Krueger, 2008).

Part of the rationale behind the DSM-IV and DSM-5's stance for using multiple diagnoses is to enable a richer characterisation of presenting symptoms. However, multiple diagnoses may instead obscure the focus of treatment (Pincus et al., 2004). This is especially pertinent given the lack of clarity or consensus regarding how comorbid disorders emerge, interact, and affect treatment. Given these conceptual challenges, and a lack of evidential guidance, clinicians often turn to their own conceptualisations and habits in order to decide which diagnoses are the most important or relevant in any particular case (Pincus et al., 2004). This lack of guidance is a very real problem given estimates that more than one third of those presenting at psychiatric outpatient settings meet criteria for three or more disorders (Zimmerman & Mattia, 1999). In fact, similar concerns have been expressed in the domain of physical medicine regarding the complications and unsuitability of applying multiple, best-

practice treatment guidelines, to older persons experiencing multimorbidity (Hughes, McMurdo, & Guthrie, 2013).

Again, some of these difficulties arise from the dominance of classical research design, which utilises pure cases or homogeneous samples to assess treatment efficacy. The exclusion of comorbid cases from treatment efficacy research results in findings that generalise poorly to clinical populations (Jensen, 2003; Krueger, 2008). Consequently such research is of limited value in guiding clinicians' decisions regarding treatment. Furthermore, when translated into clinical guidelines, it appears more onus is placed upon the clinician to make the correct causal distinctions in order to follow the appropriate treatment plan. For example, the National Institute for Health and Clinical Excellence (NICE) guidelines for depression in adults instructs:

> When depression is accompanied by symptoms of anxiety, the first priority should usually be to treat the depression. When the person has an anxiety disorder and comorbid depression or depressive symptoms … consider treating the anxiety disorder first (since effective treatment of the anxiety disorder will often improve the depression or the depressive symptoms). (NICE, 2009, p. 18)

This is a case in which a non-hierarchical, descriptive classification framework offers little assistance. The guideline itself is also unclear whether treatment for depression or anxiety should be prioritised based upon causal primacy as indicated by symptom duration, symptom severity or symptom distress. In such situations, clinicians must return to their own training, experience and conceptualisations of mental disorder and comorbidity, in order to decide which path of treatment to follow for a particular individual.

However, nor would a purely evidence based approach likely serve clinicians well, simply because it may create extreme complexity in clinical decision making given the considerable descriptive, if not causal heterogeneity observed in clinical practice (Pincus,

2012). This problem raises issues of agreement over mental disorder constructs and how well research data applies to clinical cases. If a very high standard of treatment efficacy evidence was required, alongside a very good match of descriptors or indicators between client, sample and construct, this would raise the complexity of clinical research and care immensely, potentially transforming it into an algorithmic rather than person-centred enterprise. The challenge therefore, is not for nosology and research to attend to every possible individual permutation of presentation, but to attend to comorbidity in a way that provides greater conceptual clarity and explanatory power.

It could be argued that the failure of the classification system to address comorbidity in a meaningful way, a lack of systematic guidance regarding integrated treatment approaches for complex comorbid and multimorbid presentations, and a reliance upon pure sample research design in treatment efficacy studies, effectively represents a form of discrimination against a population of individuals who are particularly vulnerable to psychiatric and psychological distress. Support of this perspective exists by way of significant and damning evidence, that those who experience serious mental health conditions, have both inequitable access to physical health services and significantly higher mortality rates (Phelan et al., 2001; Prince et al., 2007).

Integration across individual - population levels.

Incompatibility between treatment efficacy research and clinical practice raises a number of questions. How well does an individual's experience of mental disorder map onto concepts of mental disorder as characterised by group averages? What precisely might be lost in translation between these two levels? Are significant gaps in understanding created by mental disorders being the focus of explanation rather than the individual? Alternatively, would a focus on explanation of individuals' causal sequences and presentations render an incomprehensible melange of idiosyncratic causes and symptoms? Furthermore, why is the

client or patient's experience of diagnosis and treatment so neglected in the psychiatric and psychological literature?

These questions are inescapable when addressing the phenomena of psychiatric comorbidity. In many ways, this crossroads between the individual and population or group level also highlights a crossroads between concepts, explanations and method. It signals not only that our nosology needs improvement, but also, that whatever solutions we find need to coherently integrate back and forth across the population, group and disorder level to be applied at the individual and clinical practice level.

Outside of clinical practice, literature and research regarding comorbidity is generally focused at the population or disorder level. It is therefore important to keep in mind the need for inter-level integration in the following exploration of concepts of comorbidity. Concepts of comorbidity in relation to physical medicine and status quo DSM-5 models of disorder are described, prior to analysis in following chapters of alternative models of mental disorder in light of comorbidity and its explanatory and conceptual requirements.

Concepts of Comorbidity Within Physical Medicine

Even within physical medicine the word comorbidity has taken on a multitude of different representations. The term refers to a range of phenomena that exist along a spectrum of etiological implications, from descriptive to causal (Zachar & Kendler, 2007). Comorbidity may refer to co-existing medical conditions that do not share a causal basis, or to a more general susceptibility to disease, or to comorbid diseases that directly share causal mechanisms. It is also a term that refers to both the degree of disability in an individual person as well as that of a specific population, such as older persons. Additionally, the concept has implications for public health care service delivery and budgeting (van den Akker et al., 1996). In fact, a variety of terms that bear relation to comorbidity have gained currency in medicine: multimorbidity, patient complexity and morbidity burden to name a

few. Yet it often remains unclear how these terms and concepts are related (Valderas, Starfield, Sibbald, Salisbury, & Roland, 2009).

A call for more precise use of the varying constructs prevails in internal medicine in order to better address the goals of different contexts. Thus the meaning of comorbidity, or its replacement concepts, should differ depending on whether the goals are related to clinical, epidemiological or public health research. In clinical settings constructs should be formed based on their ability to guide patient management. In specialist care the term comorbidity may serve well, but in primary care, multimorbidity may be more appropriate. In epidemiological research both terms have utility, especially in relation to chronology and mapping etiological pathways. In public health, patient complexity and overall disease burden gain more relevance for summarising and quantifying the cost of service provision (Valderas et al., 2009). Thus the term comorbidity in the current day remains highly reflective of its socio-cultural context.

Undoubtedly the medical model has broadened significantly since Feinstein's coining of the term in the 1970's. Alongside acceptance that a multitude of factors, ranging from biological to political, impact upon the health of individuals and populations (Valderas et al., 2009), a more nuanced understanding of disease aetiology has developed. This may be due in part to the prioritisation of chronic and age-related conditions such as diabetes and cardiovascular illness (Ministry of Health, 2014).

Valderas et al. (2009) described four models of etiological association between medical conditions. These models are adapted from the work of Neale and Kendler (1995), who proposed six etiological models for comorbidity between multifactorial disorders within the domain of psychiatry. The four models proposed by Valderas et al. (2009) are: direct causation, associated risk factors, heterogeneity, and independence.
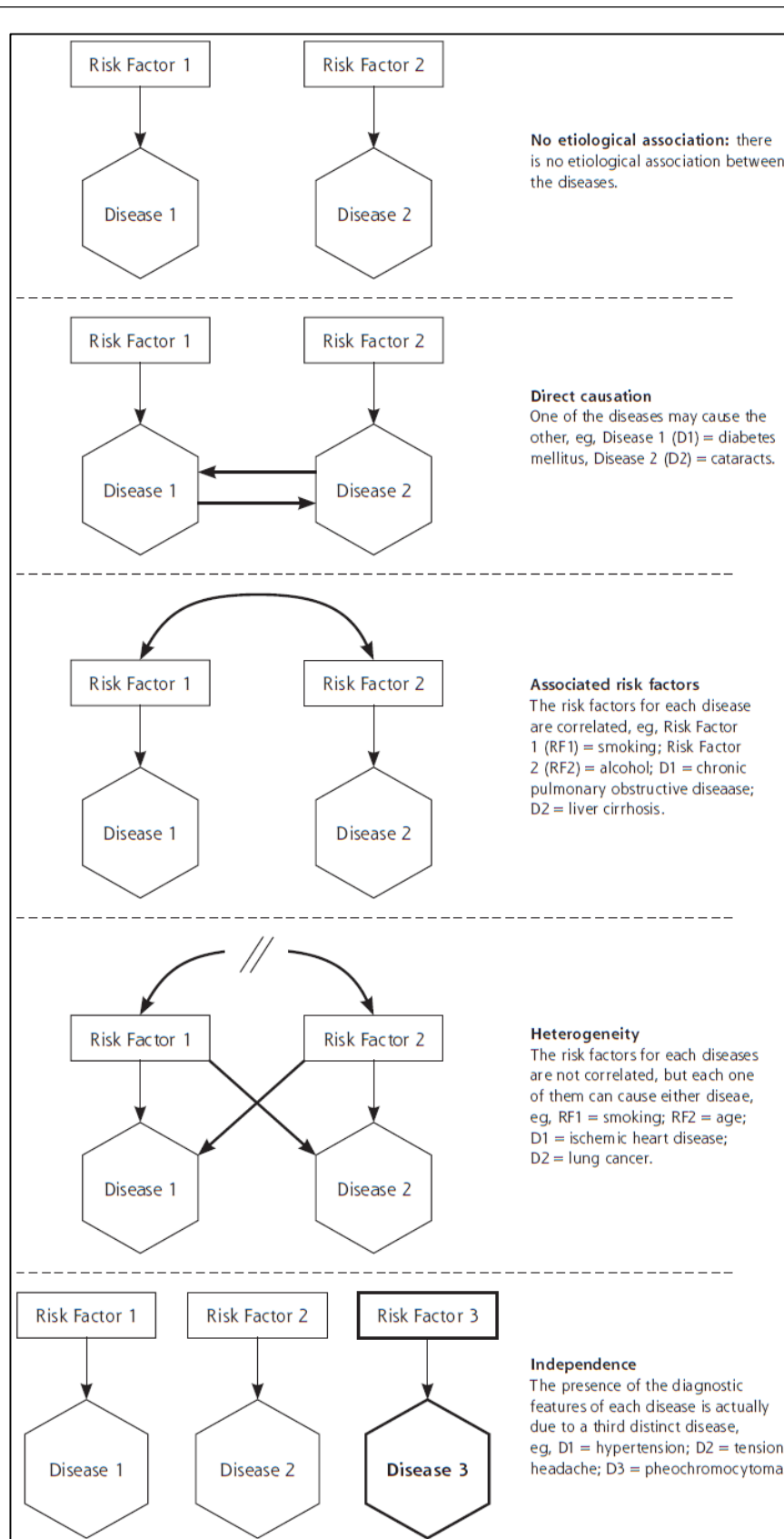
Figure 1. Etiological models of comorbid diseases. From Valderas et al.

(2009, p. 361).

In *direct causation*, one of the diseases may directly cause the other, such as diabetes mellitus leading to cataracts. This bears resemblance to a primary-secondary distinction or pathogenic comorbidity (Kaplan & Feinstein, 1974). The *associated risk factors model* instead refers to a relationship between two diseases via the correlation between their respective risk factors. This is similar to Kaplan and Feinstein's prognostic model. For example the association between the risk factors of smoking and alcohol use links co-occurrence of pulmonary obstructive disease and liver cirrhosis. In this case pulmonary obstructive disease has been mechanistically caused by smoking, and liver cirrhosis mechanistically caused by alcohol use, but the comorbidity of the two diseases is explained by the correlative relationship between the risk factors rather than each other. In contrast the *heterogeneity model* associates the contribution of multiple risk factors to each comorbid disease. Here both ischemic heart disease and lung cancer are mechanistically caused by both age and smoking risk factors, but the risk factors themselves are not correlated. Finally, in the *independence model*, or distinct disease model, the signs and symptoms of each comorbid disease are actually caused by a third disease. This relates generally to Kaplan and Feinstein's concept of diagnostic comorbidity, where the challenge relates primarily to correctly utilising signs, symptoms and course to discern the correct mechanistic cause. An example includes hypertension and headaches actually being due to a distinct third disease such as pheochromocytoma (a neuroendocrine tumour of the adrenal glands). As such the independence model does not refer to comorbidity at all, but rather the potential for misdiagnosis.

As with many models, these are simplified presentations of complex clinical presentations. Their simplification allows a focus on some questions while ignoring others in order to further our knowledge and practice (Keller, 2002). The models are not mutually exclusive and more complex configurations may be built that incorporate multiple diseases,

risk factors and protective factors (Valderas et al, 2009). Moreover, it is easy to see how they might be extended upwards to include broader environmental and social factors that impact on disease risk. Thus they continue to hold value across epidemiological and public health contexts.

Nonetheless, the clinical value of these etiological models of comorbidity remains very much in explicating the types of relationships that exist between correlative risk factors (disease correlates), causal mechanisms (mechanistic disease processes) and their observable outcomes (signs and symptoms). Moreover, the risk factors mentioned are quite proximal to the disease and its biological processes such as smoking, alcohol consumption and age. The presumed relevance of these models to clinical care is that they may clarify complex presentations, identify causal processes and provide a rationale to target subsequent medical or behavioural interventions (such as to stop smoking). Although there is capacity to include social and environmental factors further up a specified pathway to comorbidity, the concept of comorbidity itself remains grounded in the disease concept. Diseases may share causal mechanisms (direct causation), share proximal risk factors (heterogeneity) or co-occur frequently due to a relationship between risk factors. Thus in these models, while it may be recognised that higher level interactions influence comorbidity's occurrence, and in turn, that comorbidity has ramifications beyond its biological machinations, within the context of the contemporary medical model, concepts and explanations of comorbidity remain disease-bound.

Yet this relatively narrow concept of comorbidity as disease-bound poorly equates with awareness within the medical profession of the effects of broader social factors such as family functioning or spirituality to name a few (Mueller, Plevak, & Rummans, 2001; Schor et al., 2003). It appears a gap may exist between the perhaps implicit concepts and models that clinicians utilise to understand and explain mental disorder, and the explicit theoretical

models that exist in the literature. This again highlights a need for integration, this time of broader explanatory levels with biological models of mental disorder.

Status Quo – DSM-5

Despite comorbidity's central place in the psychiatric and psychological literature, its conceptualisation according to DSM-5 nosology remains somewhat opaque. While changes to its meta-structure have encouraged less absolutist perspectives, its concept of mental disorder remains very vulnerable to essentialist biases and reification. Thus the DSM-5 creates conceptual uncertainty, especially with regards to comorbidity.

Following DSM-III and DSM-III-R, Lilienfeld et al. (1994) argued that the reification of comorbidity was prevalent and problematic, especially due to its foundation in disease entities. He called for tighter terminology in the form of *co-occurrence* and *co-variation* to prevent assumptions of disorders as taxons. Spitzer (1994), instead viewed the term *comorbidity* as appropriate, denying implications of disease constructs and imploring its usefulness in reference to psychiatric disorders. Similarly, First et al. (1990) reiterated that the nosology was solely descriptive and thus comorbidity was merely an empirical event that should also be viewed as descriptive. A continued spotlight on comorbidity since that time has highlighted it as an issue that both informs and questions how psychiatric disorders are conceptualised and validated (Phillips et al., 2012a, 2012b).

The recent DSM-5 represents a marked improvement on its predecessors as regards learnings from the phenomena of comorbidity. This has led to recognition that "the boundaries between disorders are more porous than originally perceived" (APA, 2013, p.6), and that symptoms assigned to single disorders may occur in other disorders. Furthermore, diagnosis using (in part) a dimensional framework for personality disorders is offered to reduce comorbidity and increase the validity of this diagnostic group.

DSM-5 also acknowledges the heterogeneity of disorder presentation and the multifactorial nature of aetiology: "The historical aspiration of achieving diagnostic homogeneity by progressive subtyping within disorder categories is no longer sensible; like most common human ills, mental disorders are heterogeneous at many levels, ranging from genetic risk factors to symptoms" (APA, 2013, p.12).

The adoption of a meta-structure by which to group DSM-5 disorders was informed by multiple biological and psychological validators, including high comorbidity. The super-structure, or clustering of these chapters was based upon internalising and externalising factors. This organisational structure signals that comorbid diagnoses may be somewhat expected within chapters or across sequential chapters. Each of these steps move the DSM nosology away from a position that promotes mental disorders as natural kinds or essences and towards a conceptualisation that accepts fuzzy boundaries and comorbidity as part of the landscape of mental disorder.

However, the DSM-5 remains a system characterised by polythetic descriptive criteria and diagnostic categories. Although changes have taken place to some criteria, the conceptualisation of disorders and diagnostic process is largely unchanged from the DSM-IV-TR due to a lack of scientific evidence and theory to support alternative definitions. While there is clearly an attempt to incorporate lessons from the comorbidity literature to improve validity and encourage more flexible conceptualisations of mental disorder, for all practical purposes, diagnosis of mental disorder is akin to that described in DSM-III half a century ago. DSM-5 thus retains its prioritisation of empirical reliability over theoretical validity.

The concept of mental disorder endorsed by the DSM-5 is also questionable. While it contextualises mental disorder within its socio-cultural setting, its basis lies in Wakefield's harmful dysfunction (HD) analysis. Here mental disorder is conceptualised in two stages, as a mental function gone astray, that brings harm and distress to an individual (Wakefield, 1992).

Dysfunction is first objectively identified as "the failure of a mental mechanism to perform a

natural function for which it was designed by evolution" and then its harm is evaluated

according to prevailing social norms (p.373). Both stages are necessary in order to qualify for

status as mental disorder. Under this concept, comorbidity becomes *more than one natural*

dysfunction. Both Murphy (2006) and Zachar (2014) provide excellent critiques of the HD

analysis.

Identification of dysfunction rests on an ability to objectively identify natural

function. According to Wakefield (1992), a natural function can be understood as an ability or

capacity, such as a threat detection system, that via the process of natural selection has

allowed adaptation to environmental pressures to enable survival. Both Murphy and Zachar

cited the absolute paucity of existing factual evidence for the existence of natural functions,

as sufficient reason to discredit the HD analysis. While maintaining its foundation in

evolutionary explanation, Wakefield did subsequently reframe his concept of natural function

to refer to the effect of a mechanism that contributes to an explanation of the said

mechanism's "existence, structure or activity" (Wakefield, 2007, p. 152). Simply stated, a

natural function is a mechanism's reason for being. Rather than evidence or theories of

evolutionary development, this concept of natural function looks to objective evidence of a

mechanism's effects, existence, structures or activities as supportive of adaptive functioning

in the here and now.

Murphy (2006) argued that evidence does not support the notion that psychological

functions link to functionally distinguishable components of the brain, thereby, limited

evidence exists in favour of identifying natural functions via neuro-anatomical analysis. In

addition, he explained that dysfunction can be brought about both through a faulty

mechanism that receives adequate information (for example a reading disorder in the context

of educational support), and by a normal mechanism operating with deviant input (illiteracy

due to lack of educational opportunity). Wakefield (2007) argued that the former is a disorder

where the latter is not, however, the distinction becomes less clear in other examples where

the dysfunction may be adaptive in some environments but not in others. For example, a

tendency to dissociate due to a history of sexual abuse is a case where an arguably adaptive

function becomes maladaptive due to causes embedded in personal history. In such instances

however, the HD analysis does not assist in understanding whether the dysfunction is due to a

faulty dissociation capacity, an inability to accurately detect threat, a dysregulated emotion

response mechanism, or to a particular set of beliefs, perceptions and interpretations of the

self or world. Potentially all processes may play a role. Even when freed from its

evolutionary explanatory basis, the HD analysis cannot objectively identify dysfunction in a

reliable manner and therefore, cannot be used to answer the question "what is a mental

disorder?"

       While the HD analysis is in many ways an elegant attempt at defining a very slippery

concept, in promoting this conceptualisation, the DSM-5 may have encouraged a form of

psychological essentialism amongst its users. If mental disorder is understood as a

"dysfunction in the biological, psychological or developmental processes underlying mental

functioning" (APA, 2013, p. 20), it is easy to assume that it is the underlying dysfunctional

process that requires intervention. In this light, disorders take on essential qualities, as it is the

dysfunctional mechanism or mechanisms that denote a disorder with its identity. Placing

social norms at a separate evaluative stage emphasises that the cause is dysfunctional rather

than the outcome.

       In summary the DSM-5 gives mixed messages. While its organisational meta-

structure signals a need to think flexibly about the boundaries between disorders, its

categorical approach and definition of mental disorder based in the HD analysis endorses

more rigid and less integrative conceptualisations. As concepts of comorbidity are couched in

concepts of mental disorder, such ill-defined territory creates difficulties for understanding

comorbidity. Given the DSM's descriptive, atheoretical status, comorbidity can be construed

simply as an empirical phenomena of signs and symptoms that spread across diagnostic

boundaries. To some extent this is the approach encouraged in the description of comorbidity

that follows each diagnosis' criteria set. However, the meta-organisational structure, together

with acknowledgement that mental disorders are heterogeneous, indicates that comorbidity

may be more expected in some instances than others. It is hard to differentiate therefore,

whether comorbidity should be conceived of as separate disorders that co-occur due to shared

risk or causal factors, or in fact, whether comorbidity does not actually exist but instead

occupies a space on a spectrum or dimension that adjoins different disorders.

These conceptual inconsistencies within the DSM may lead clinicians to return to

their own beliefs and conceptualisations of mental disorder in order to reason about causative

processes. One of the strengths of an atheoretical approach is that it leaves room for multiple

explanatory perspectives. However, in the absence of relevant research or clinical guidelines

regarding treatment efficacy for comorbid or multimorbid presentations these

conceptualisations and causative inferences may serve as the primary basis for treatment

planning. Furthermore, concepts of the nature and cause of mental disorder, influenced by

both training and experience (Piotrowski, 2007), may easily fall prey to reification via an

essentialist bias, or alternatively, become unnecessarily complicated and lack clarity. While

conceptualisations of comorbidity remain inconsistent and the treatment efficacy research

remains unclear, it is hard to know which level or levels of explanation should be targeted,

which treatment option is more effective, and how the largest long-term and short-term gains

to well-being might be made in return for cost to the individual, insurer or state.

Comorbidity, therefore, highlights both strengths and inadequacies of DSM-5's

descriptive and atheoretical classificatory stance. In leaving room for construal of cause at

different levels, it paints a watercolour landscape upon which the subjective perspective of the clinician is applied to interpret how different causative factors might integrate together. Moreover, given the dominance of DSM categories in shaping research samples, this subjective interpretation is then reapplied to decide which factors should be prioritised for treatment.

Summary

As argued in Chapter One, the problem of comorbidity in current psychiatric diagnosis lays down a specific ethical challenge: to improve outcomes for those who experience comorbid psychiatric disorders. This thesis focuses on coherent concepts and explanations of comorbidity as a strategy to meet this goal: so that the individual experiencing mental disorder may be assisted in making sense of their experience; for the development of effective treatments and interventions; and to aid clinicians in carrying out the roles of assessment, communication and application of treatment with the client. Diagnosis, through the scientific practice of nosology, plays an integral role in meeting these objectives by providing a link from research to clinic and vice versa. Thus nosology is central to attempts to meet the stated ethical challenge we currently face.

Four concepts of comorbidity have been outlined in this chapter: comorbidity at the population and individual levels alongside comorbidity as described and understood in physical and mental health domains, specifically the DSM-5. Whichever perspective is considered, the meaning of the term derives from the meaning inherent in concepts of wellness, disease and disorder. Concepts of psychiatric comorbidity are thus dependent upon concepts of mental disorder.

Bearing in mind that concepts of mental disorder and comorbidity may not be explicitly expressed, clarification via nosology seems an important objective. The lack of clarity regarding psychiatric comorbidity in particular springs jointly from the multiple

perspectives influencing concepts of mental disorder, and the lack of consensus regarding how to integrate varying but often complementary conceptualisations that exist across different theoretical levels.

Chapter Four - Common Cause Models of Mental Disorder

High comorbidity at the disorder or population level continues to challenge the validity of psychiatric nosology. Bogenschutz and Nurnberg (2000) remarked that a number of methodological flaws may lead to spurious comorbidity. In some instances, an apparent association between diagnoses may reflect a nosological artefact. Examples cited included comorbidity due to phenotypic heterogeneity (where different phenotypic characteristics are expressions of the same underlying disease), and comorbidity due to the creation of artificial categorical boundaries where dimensional methods may serve better for conceptualising mental disorder. Spurious comorbidity serves little or no explanatory power, having been brought about artificially as a result of a flawed nosology. Valid comorbidity instead would hold explanatory significance and signal either distinct but shared etiological factors in co-occurring disorders (either at the direct causal or slightly removed risk factor level), or the influence of one disorder in the development of another.

In response, many have voiced a desire for classification based upon either (or in some cases both) a dimensional or etiological basis, rather than the descriptive framework utilised by the DSM (Aragona, 2009b; Hyman, 2010; Morris & Cuthbert, 2012). Others instead have championed dimensional methods as a way to understand the current relationships observed between DSM diagnoses via unifying latent causes (Clark, 2005; Krueger & Markon, 2006; Vaidyanathan, Patrick, & Iacono, 2011). The following chapters echo a dialogue between Massimiliano Aragona (2009a, 2009b) and Peter Zachar (2009) based on the significance of comorbidity to concepts and models of mental disorder.

Aragona (2009a) argued that the 'hypercomorbidity" observed in psychiatric diagnosis is a nosological artefact, an anomaly indicative of a Khunian crisis that "challenges the credibility of the system itself" (p. 30). Here, comorbidity heralds the call for a paradigm shift in classification practices. Zachar (2009), instead, challenged the notion that psychiatric

comorbidity will disappear with changes to nosology and argued that "the phenomena

covered by the term 'comorbidity' are real, expectable features of the psychiatric domain,"

although comorbidity may be "lowered and provided a better, evidence-based conceptual

framework" (p.13). In this instance comorbidity is characterised as an inevitable consequence

of attempts to classify mental disorder, due to the interconnected nature of the brain and the

nature of human functioning within the external environment.

Comorbidity Existence Conditions

Prior to considering this dialogue, a workable concept of comorbidity needs to be

articulated that will suffice across the range of perspectives for which it will be utilised. For

this purpose, comorbidity is considered to exist if:

a) A discriminable set of causal processes are, reliably associated with a set or cluster
   of symptoms; and

b) The symptoms are generally accepted as harmful, distressing or impairing; and

c) More than one causal process or causal processes co-occur;

d) At any one time;

e) At a rate within the population that is higher than might be expected by chance.

Criteria 'a' and 'b' essentially form the criteria for mental disorder. Similar to the HD

analysis it has both a causal and evaluative component. However, the causal component is not

nested in the concept of objectively identifiable dysfunction, instead the effect of the causal

processes (cluster of symptoms) is evaluated as dysfunctional (relative to social norms). Thus

it is the resultant effect that is deemed dysfunctional, rather than the causal process. It may be

useful to extend the concept of symptom sets to a concept of syndromes that entails shared

symptoms, signs, course, and treatment response (Kendler 2012).

The above existence conditions are by no means a comprehensive definition of

comorbidity or mental disorder, but instead, provide some grounding and constraints from

which to utilise the concept of comorbidity in the following analysis. Their emphasis lies not in a conceptual analysis of what differentiates disorder from normal functioning but instead, what properties characterise comorbidity. They also focus on causal mechanisms.

A useful concept to employ when considering mental disorder as a set of causal processes is the "mechanistic property cluster" (Kendler et al., 2011). Members of a cluster, in this case instances of a disorder, occupy a similar region in a multi-dimensional matrix space due to their similar causal mechanisms and properties. The causal dimensions may represent different features or symptoms of mental disorder, as well as causes across multiple levels. Note that this concept denotes symptoms with potential causal influence. While clusters may not have essential qualities, where all members share the same features with each other, they nonetheless exhibit relatively stable causal patterns and relationships that result in their position within the multi-dimensional matroid space. Causal relationships may be probabilistic as well as deterministic under this concept.
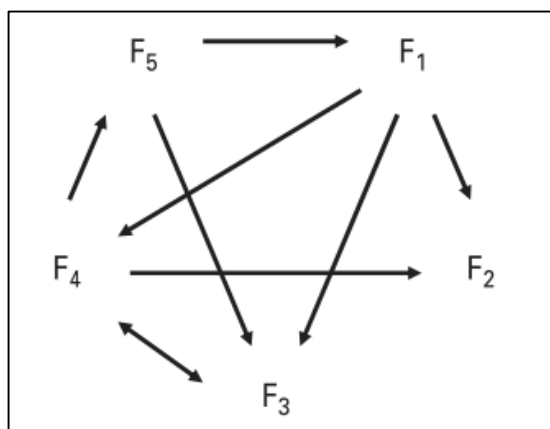

Figure 2. "One possibility for a property cluster kind in which individual clinical features (labelled F_1 to F_5) are causally inter-related to one another." From Kendler et al. (2011, p. 1147)

As argued in Chapter One, causal explanations often form the foundation upon which scientific concepts are shaped. With regards to comorbidity, a higher standard of explanation is required: an explanation of comorbidity must be coherent and integrative.

Causal mechanisms or explanations must be reliably associated with symptom clusters. This means that causal effects may be either mechanistically demonstrated, or more likely, risk factors or constructs are reliably associated with an effect via statistical modelling. The main concern for separating comorbidity from general heterogeneity is that causal processes are discriminable. That is, although they may be interactive with other causal processes or networks, they are not so interactive as to make them indistinguishable from other systems or any superordinate systems within which they operate. If the processes at work that result in symptom sets are not discriminable, then mental disorder is inherently heterogeneous. In this way comorbidity offers an opportunity to test whether mental disorders are so inherently heterogeneous that they cannot be classified except on the basis of pragmatic goals.

Additionally this concept of comorbidity insists that discernible causal processes must co-occur at the same time. Despite the concept of mental disorder being given an explanatory basis, we may still expect some disorders to co-occur at higher rates than others. However, we may hope that a nosology, with its theoretical and empirical underpinning, may be able to provide coherent explanation of this sort of comorbidity, which in this instance is identical to Lilienfeld et al.'s (1994) co-variation. We would not however expect such coherent explanation of all co-occurrence; this would result in explanatory models representative of the idiosyncratic individual. This again would indicate heterogeneity.

With this in mind it may be useful to consider a continuum. At one end is a concept of mental disorders as causal pathways or networks with discrete and homogeneous properties that lead to clear and distinct syndromes. This is consistent with the 'hard' medical

model (Kendler, 2012). At the other end is a concept of mental disorder as fully reflexive, where causes, networks and effects are so integrated with each other that causal pathways and symptom clusters become impossible to discriminate from one another. It is a possibility that some mental disorders exist in different zones along this continuum.

The concept of comorbidity therefore tests two premises: 1) that disorders are discriminable enough so as not to be completely heterogeneous; 2) that disorders are not completely invariant in their co-occurrence. This second supposition enables coherent, integrative explanations and concepts of comorbidity to exist beyond individualised, idiosyncratic disorder combinations. It also distinguishes comorbidity from simply a more severe or more complex manifestation of a single disorder.

As discussed in Chapter One, Kendler (2012) outlined seven criteria that indicate a good explanation: strength, causal confidence, generalizability, specificity, manipulability, proximity and generativity. In the following analysis these criteria, in addition with the need for coherent explanation are applied across a range of models of mental disorder. As discussed, coherence, in the context of explaining comorbidity, may require a certain level of integration between causal hypotheses.

Two common cause models are considered: models based in latent causal constructs and pathogenetic models of mental disorder. Dimensional models also offer an alternative approach to current classificatory practices, however, given limited space and the explicit focus on testing an etiological classification strategy, they are excluded from the following discussion.

Latent Causal Models of Mental Disorder

Several models of mental disorder based on latent constructs explicitly posit an underlying common cause. These models analyse current patterns of comorbidity as a means to understand the nature and structure of mental disorder. Alternatively this can be viewed as

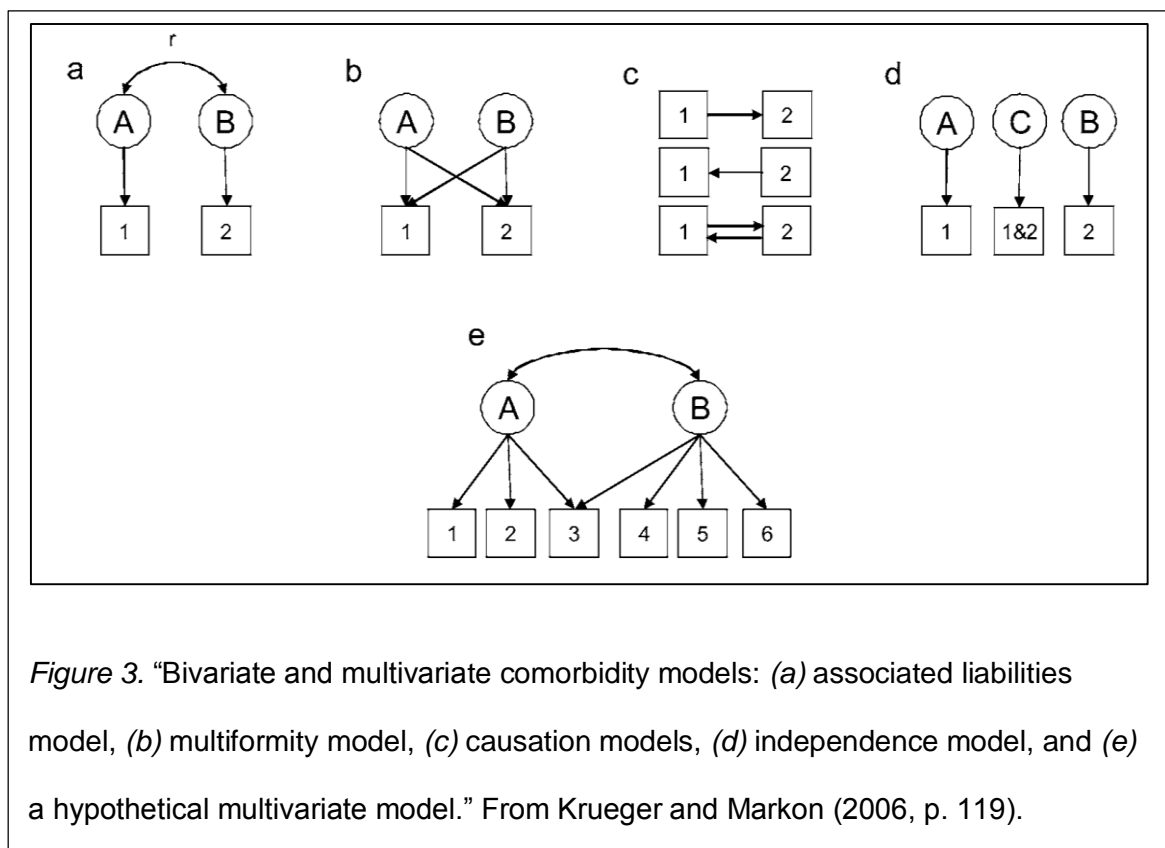an attempt to explain current comorbidity as due to hypothetical latent causal constructs. Three such models include Clark's model of comorbid personality and psychopathology as based in temperament (2005), Krueger and Markon's liability spectrum model of comorbidity (2006), and Vaidyanathan, Patrick and Iocono's person-centred characterisation of comorbidity (2011).

Clark's (2005) model attends to the relationship between personality and psychopathology, often demonstrated as comorbidity at the diagnostic level, or more generally, as sub-threshold personality characteristics that co-occur alongside mental disorder diagnoses. It explicitly posits a shared underlying cause in the form of temperament. Temperament is understood to have a genetic basis that shapes the development of personality structure through interaction with the environment over time. Three temperament dimensions of negative affectivity, positive affectivity and disinhibition, are posited in this way to causally underlie a hierarchical personality trait structure. Those traits and subtraits associated with the same temperament dimension are expected to be more closely related than those from different dimensions. It is the interplay between disinhibition and negative affectivity that appears particularly relevant to the development of psychopathology.

Clark suggested that personality and psychopathology are linked via these underlying temperament risk factors and their subsequent interactions with life experiences, especially adverse life events. The theory posits latent constructs, in the form of three temperament dimensions, as causal factors that interact with environmental factors to bring about the observed phenomena – personality and psychopathology. Thus the hypothesis is both etiological and developmental.

A similar model of comorbidity was proposed by Krueger and Markon (2006) in a meta-analysis of a "liability spectrum model of comorbidity". Here comorbidity was also explained via underlying liabilities that manifest differentially. Their work was an extension

of the bivariate etiological models of comorbidity described in Chapter Three, proposed by

Neale and Kendler (1995). Krueger and Markon's meta-analysis tested the fit of data from

five large, population based studies (utilising DSM defined categorical diagnoses), to various

multivariate structural equation models. It demonstrated that multivariate comorbidity models

converged on a hierarchical model with two superordinate constructs labelled internalising

and externalising liabilities.

Figure 3. "Bivariate and multivariate comorbidity models: *(a)* associated liabilities

model, *(b)* multiformity model, *(c)* causation models, *(d)* independence model, and *(e)*

a hypothetical multivariate model." From Krueger and Markon (2006, p. 119).

Evidence points to these liabilities existing as continua, which is how constructs are

conceptualised in Krueger and Markon's (2006), Neale and Kendler's (1995), and Clark's

(2005) models. The externalising construct indicates a liability towards substance use

disorder, antisocial personality disorder and conduct disorder. The internalising construct

indicates a liability towards mood and anxiety disorders, which can further be divided into a

distress sub-construct that encompasses depression, dysthymia and generalised anxiety

disorder, and a fear sub-construct consisting of panic disorder/agoraphobia, social phobia and

specific phobias. The superordinate internalising and externalising constructs are highly

correlated with each other, as are the subordinate distress and fear constructs. It was upon this

basis that the DSM-5 chapter order was reshuffled to give some explanatory value to the high

comorbidity observed within internalising and externalising disorders.

However, the comorbidity frequently observed between internalising and

externalising disorders such as depression and substance use disorder, challenges this

hierarchical structure. Vaidyanathan et al. (2011), building on Krueger and Markon's (2006)

work, utilised a class analysis method to characterise patterns of lifetime comorbidity

observed at the individual level. This study's aim was to investigate what patterns of

comorbid disorders are seen in individuals rather than what disorders commonly co-occur,

and in doing so, it sought clarification of the observed correlation between internalising and

externalising dimensions.

Utilising NCS and NCS-R data, the study converged with previous evidence,

identifying a fear class of individuals (experiencing comorbid phobias and panic disorder), a

distress class (depression, dysthymia and GAD), and an externalising class (conduct disorder

and substance abuse), as well as a class of individuals exhibiting few disorders (low

incidence of mental disorder). It also pointed to two main sources for the overlap between

internalising and externalising factors: a *multimorbid* class of individuals and a group of

disorders occurring across all classes (including the few-disorders class) at higher rates than

predicted by chance.

The multimorbid class included individuals with high levels of both internalising and

externalising disorders, as well as bipolar 1 disorder. This multimorbid class bears

resemblance to Zachar's vulnerable population. Individuals within this group demonstrated

the highest rates of overall comorbidity as well as the greatest overall severity of

psychopathology. The cross-class group of disorders included depression, social phobia and

PTSD, leading the authors to suggest that these disorders may reflect more general ways in which people within the larger population manifest distress in reaction to adverse life experiences such as loss, stress or trauma. Thus people with existing diatheses in internalising, externalising or multimorbid domains, may be more vulnerable to psychological distress in general, manifesting as increased prevalence of these three disorders across classes.

This study therefore also makes specific etiological claims regarding: 1) underlying vulnerabilities as exemplified in the broad internalising and externalising dimensions leading to manifestation of mental disorder; 2) a multimorbid class of individuals demonstrating liability to severe psychological distress and high comorbidity; 3) heightened psychological distress in those with such vulnerabilities via mechanisms normative in the general population.

In summary, models of mental disorder built on latent constructs conceptualise mental disorder as caused by an underlying vulnerability in combination with other factors such as life events. Such vulnerability is understood as a continuous dimension upon which an individual may measure. Such models utilise the common cause assumption implicit in factor analysis, where observable measures are thought to cohere due to an underlying latent cause or set of latent causes (Borsboom & Cramer, 2013; Zachar, 2000, 2014).

Clark (2005) was explicit in conceptualising negative affectivity, positive affectivity and disinhibition as temperament constructs founded in genetic cause. This inference relies on abductive reasoning to identify causal processes that might explain why observable variables cluster in this way. Thus it is a placeholder or what Haig (2014) identifies as a theory generation device to direct empirical and theoretical investigation, in this case towards genetic and environmental mechanisms.

Vaidyanathan et al. (2011) were also explicit in relating vulnerability constructs to underlying genetic cause. They extended their explanation to posit specific disorder manifestation via interactions between underlying vulnerability with life events, potentially mediated by general and normative psychological processes, as demonstrated by the cross-class disorders. They made no a priori assumptions regarding the respective effect size of genes, life events or general psychological processes in the aetiology of mental disorder. Similarly their model acts as a theory generation device.

Krueger and Markon's model (2006) also implied an underlying structure to mental disorder. However this model rested on the assumptions of the statistical analysis as means of justifying the taxonomy. Their analysis tested the fit of various structural models of mental disorder to data from multiple studies. This method equates with hypothesis testing rather than theory generation (Haig, 2014). As a result they argued that the manifestations of specific DSM mental disorders are for all purposes valid if conceived of as existing within a hierarchical structure and cohering due to these internalising and externalising vulnerabilities. The basis for their model, and their reconceptualisation of psychopathology in line with superordinate and subordinate liability constructs, was their analysis of comorbidity data.

However, like Vaidyanathan et al. (2011), their analysis was built upon data generated by diagnostic interview. Therefore while the model has much to say about the hierarchical structure of mental disorder as assessed by DSM diagnoses, it can say little about the underlying nature of mental disorder away from these predefined taxons. This is because the validity of their model rested upon the validity of the data as representative of the features of mental disorder. Of course such challenges are not unique to these methods, but are particularly important to consider in analyses that are so empirically driven.

Kline (1998) warned of the danger of going beyond the data in this way when he stated that "factors are not necessarily determinants… Factors depend entirely on the variables in the analysis"(p.68).

In summary, the concept of mental disorder that follows from these latent causal models is that manifestation of specific mental disorder is caused by a liability, most probably of genetic cause, in concert with environmental and potentially normative psychological mechanisms. This concept is etiologically driven. It is also in line with the biopsychosocial model of mental disorder. Comorbidity's conceptualisation is simpler. It results from the shared (genetic) liability that underlies two comorbid disorders. In those instances where comorbidity is unexpected, such as between an internalising disorder and externalising disorder, it is explained as either due to a genetic liability in concert with manifestation of psychopathology via normative psychological processes, or heightened overall vulnerability to severe psychopathology. In regard to the multimorbid group, comorbidity becomes difficult to separate from severity.

The nosological implication of these models of comorbidity is that diagnoses should be considered as existing within overarching liability continua. Thus the model does not reduce the incidence of comorbidity, but instead seeks to explain it. Hence, organising DSM-5 chapters around these internalising and externalising liabilities has served to provide the existing nosology with improved conceptual and explanatory coherence.

How does the model respond to the challenges of comorbidity? It does offer a somewhat coherent concept of comorbidity via latent genetic risk. With reference to the aforementioned explanatory criteria (Kendler, 2012), this speaks to the explanatory strength, generalizability, and the likely causal role of latent genetic risk in bringing about comorbid presentations. This model also offers a pluralist explanation of comorbidity in drawing on several levels of analysis (genetic risk, life events, psychological processes). Inclusion of

environmental and psychological processes has the potential to increase its explanatory specificity and proximity, helping to answer why two disorders may manifest together at this time.

However its concepts, explanation and integration remain very broad. Although latent constructs may assist in coherent explanation of comorbidity under the current classificatory system, they are unlikely on their own to answer the knowledge and ethical challenges that comorbidity generates. This becomes especially obvious when considering the multimorbid group. Does increased genetic vulnerability to multimorbidity in concert with normative psychological processes cause greater severity overall, or does liability in combination with different life events cause manifestation of multiple separate disorders? The model is unclear in this regard as the causal interactions are not its focus. As Berenbaum claimed, "there is a wide variety of reasons why signs and symptoms may covary other than their all being manifestations of independent latent disorders" (2013, p. 895).

Therefore the liability constructs, environmental effects and psychological mechanisms posited, act as placeholders and theory generation devices (Haig, 2014) for yet to be developed explanations about why comorbidity between DSM-5 diagnoses occurs and how particular comorbid presentations come into being. Kendler (2012) indicated that as a statistical concept, latent genetic risk offers little guidance for treatment development or application. With regards to comorbidity, latent causal models offer no details of the interactions and processes between causes and hence offer limited integrative explanation. They act as a potential guide, relying on other methods to flesh out the causal processes. "Ultimately, research that incorporates findings from multiple perspectives of interrelations among differing mental disorders is likely to contribute most to understanding, remediation, and prevention, of disorders of this type" (Vaidyanathan et al., 2011, p. 8).

Pathogenetic Models of Mental Disorder

A structure differentiating pathogenetic from pathophysiological processes (discussed in the next chapter), is borrowed from Oulis (2010). He identified pathogenetic processes as establishing a set of primary and distal genetic risk factors that may increase vulnerability to development of mental disorder. Pathophysiological processes however are broadly construed, encompassing more proximal processes, including the person's interactions with systems in the immediate environment, that lead to the emergent clinical presentation via physiological dysfunction.

The pathogenetic model of mental disorder centres its causal hypothesis at the genetic and molecular levels of analysis. Multiple twin studies have indicated that genetic factors contribute towards aetiology of many mental disorders such as schizophrenia, depression and anxiety disorders (Hettema, Neale, & Kendler, 2001; Sullivan, Kendler, & Neale, 2003; Sullivan, Neale, & Kendler, 2000). In particular the heritability of liability to schizophrenia is estimated to be very high, at between 73% and 90% (Sullivan et al., 2003), making it a priority to find the gene or group of genes responsible for this severe disorder. However, evidence suggests that genes associated with schizophrenia are also associated with bipolar disorder. Similar genotypes may therefore underlie different phenotypic presentations, indicating that elucidation of pathophysiological mechanisms will further challenge the validity of current classification (Craddock, O'Donovan, & Owen, 2006).

Taking this a step further, a recent article authored by the Cross-Disorder Group of the Psychiatric Genomics Consortium (2013) detailed a 'mega-analysis' of genomes sourced from 33,332 individuals who met criteria for one of five disorders: schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder or attention-deficit hyperactivity disorder (ADHD). Also included was a genome-wide analysis of 27,888 control

cases. This study identified single nucleotide polymorphisms (SNP's) at four loci[4]. Here

significance indicates that the genetic 'signal' of these SNP's exceeded a designated

threshold[5].

Specifically, the aggregate risk scores generated from occurrence of these four

polymorphisms indicated cross-disorder effects for the three adult-onset disorders included in

the study, major depressive disorder, bipolar disorder and schizophrenia. Nominal effects

were also observed for the two childhood onset disorders included in the study. The authors

interpreted these findings as indicative of pleiotropic genetic effects. Pleiotropic effects are

already documented in autoimmune and metabolic diseases, where (in its simplest form)

variance at one gene may lead to many different phenotypic presentations, presentations that

currently cross diagnostic boundaries. This concept is akin to that of phenotypic

heterogeneity described earlier (Bogenschutz & Nurnberg, 2000). In addition, given two of

the SNP's identified were involved in calcium-channel signalling, the authors suggested that

this biological mechanism may be a key contributor to pathogenesis of a number of mental

disorders, indicating it as a potential target for treatment. They stated that their findings were

"relevant to the goal of moving beyond descriptive syndromes in psychiatry and towards a

nosology informed by disease cause" (Cross-Disorder Group of the Psychiatric Genomics

Consortium, 2013, p.17).

This statement strongly expresses a concept of mental disorder as a disease process,

with explanatory priority given to the genetic level of analysis and its immediate

physiological consequences via protein expression, molecular signalling and cellular

mechanisms. Unlike Mendelian genetic disorders such as Huntington's disease and cystic

---

[4] This included two SNP's in regions on chromosomes three and ten (the former region
encompassing more than 30 genes), and two SNP's involved in calcium-channel signalling,
that showed a significant association across all five mental disorders considered.
[5] $p < 5 \times 10^{-8}$

fibrosis, it is likely that multiple genetic factors are involved in the pathogenesis of mental disorders. A classification system based in this model would need to utilise an aggregative genetic risk profile or similar to identify the constellation of underlying genetic causes.

This model has much in common with latent genetic risk models such as Clark's (2005) temperament construct. However, a genetic risk profile, although also a statistically generated device is directly linked to specific biological casual factors. It is grounded in biological mechanistic explanation. In quantifying the risk associated with specific alleles, it acts as the statistical reverse of a latent genetic construct. Instead of abductively inferring underlying explanation of observable features, a genetic risk profile seeks to predict the effect size of specific genetic causal factors. This is a deductive enterprise. Diagnosis based on a genetic profile would therefore be based in an inductive application of research that identified a certain phenotype was probably caused by a specific array of alleles. This concept matches well with the concept of an endophenotype:

> An *intermediate phenotype* (often referred to as an endophenotype) is a quantitative biological trait that is reliable and reasonably heritable…. If a candidate intermediate phenotype is to provide meaningful information about a disorder, it should be associated with variant alleles that distinguish patients and their unaffected siblings from healthy controls on quantitative measures. The most useful intermediate phenotype candidates will also be functionally associated with aspects of the core clinical deficits of the disorder. (Preston & Weinberger, 2005, p. 166)

Different disorders would therefore be conceptualised based upon the endophenotype associated with their phenotypic symptom clusters. While some alleles may be associated with a general risk to mental disorder due to their generic mechanistic effects (such as posited for calcium channel signalling), others may heighten risk for specific phenotypic presentations.

Alternatively, interactions between genetic effects at the molecular and cellular levels may be found to result in specific phenotypic effects. As a result, advances in biomarkers at the molecular or cellular level of analysis could be utilised to complement a genetically driven concept of mental disorder. A concept of mental disorder grounded in genetics therefore, may not wholly operate at the genetic level, instead it may span presence of particular alleles and the identification of direct downstream molecular consequences.

Referring back to the comorbidity existence conditions stated earlier, comorbidity may be conceptualised as more than one endophenotype as observed in the analysis of an individual's genome. The concept may also include presence of more than one set or system of molecular and cellular processes resulting from the genome's configuration. Classification in this instance is a statistical construct, such as an endophenotype, that confers risk via biological mechanistic explanation. It may also include presence of molecular markers that indicate that more than one set of biological causal processes is at play. Current comorbidity would certainly be considered an artefact due to the incorrect parsing of disorders based on phenotypic presentation, especially given that evidence of pleiotropic effects already points to this being the case.

How would a concept of mental disorder as pathogenetic perform in relation to comorbidity's knowledge challenges? It remains uncertain whether the incidence of comorbid diagnosis would be significantly reduced through classification based on endophenotypes and molecular markers. It also remains uncertain whether an etiological foundation in genetics would provide comorbid diagnosis with an integrative coherent explanation for either the client or clinician, or for the development of treatments and interventions. This is because while twin studies demonstrate that heritability of mental disorders is relatively high, indicating robustness across different background conditions, genetic analyses for most mental disorders show small effect sizes. Even aggregate genetic risk profiles continue to

prove insufficient for diagnostic or predictive purposes (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). While genetic endophenotypes are likely have a considerable causal role, other physiological, or environmental factors also play a significant role in the aetiology of mental disorder. In addition, genetic antecedents also show low proximity to mental disorder (Kendler, 2012).

A number of concerns regarding the causal role of endophenotypes have also been voiced (Kendler & Neale, 2010). Models based on endophenotypes need to distinguish between a mediational (causal) and risk indicator (correlational) models. The concept presented here relies upon a mediational model, where the endophenotype is either mechanistically or statistically (via structural equation modelling) shown to causally effect the resultant phenotype. Mediational models also need to demonstrate strong reliability. A founding in genetics does not excuse models of high measurement error between participants or within participants across time. Additionally, consideration of partial mediation models is necessary, especially given evidence of environmental effects in aetiology of mental disorder. Endophenotypes may also actually reflect environmental effects such as *in utero* infections, birth complications, or maternal substance use (Kendler & Neale, 2010). The low strength and above methodological concerns challenge this model's explanatory coherence. However, pathogenetic models of mental disorder indirectly offer relatively high manipulability via development of pharmaceutical treatments (Kendler, 2012).

Finally, coherent explanation of comorbidity rests on an ability to integrate explanations of separate mental disorders in order to explain the singular comorbid presentation as observed in an individual or group. This would largely depend on the model's ability to mechanistically explain interactions between endophenotypes, their physiological consequences and observed phenotypic effects. Given evidence of the role that environmental factors plays in shaping phenotypic display, it is unlikely that a genetic model of mental

disorder would explain a sufficient amount of the variance observed to function alone as a
coherent explanation of comorbidity.

Figure 4. "**(a)** A liability-index model for endophenotypes (EPs). Genetic variance V_G
influences both an EP and a psychiatric disorder (PD). These observed variables also
have residual variation, RVE and RVP, due to other sources. **(b)** A mediational model for
EPs. Genetic variance causes variation in the EP, which in turn causes variation in PD.
EP and PD have residual variance components RVEP and RVPD, respectively." From
Kendler and Neale (2010, p. 791)

There are also potential ethical issues associated with this model, which
conceptualises mental disorder as inherent to the person. Mental disorder largely becomes an
issue of protein expression as coded for by dysfunctional genes. Given that genes themselves

are not easily manipulable, disorder remains resident within the individual's genome essentially from birth until death. Thus, functional change would probably be achieved by changing molecular processes via (most likely) lifelong pharmaceutical treatment, or potentially in some cases, early intervention. This may be somewhat applicable for certain cases of schizophrenia, bipolar disorder and autism, but the notion is contrary to the demonstrated efficacy of psychological treatments such as cognitive behavioural therapy for anxiety and depressive disorder.

Using a concept of comorbidity as posited in the existence conditions, two models of mental disorder have been analysed in this chapter. While latent causal models act as theory generation devices, suggesting avenues for future research, they fail to meet the desired explanatory standards due to their empirical reliance and lack of causal explication. Alternatively, pathogenetic models may in future offer strong causal explanation and manipulability, yet alone, are likely to fail to account for the variant features of mental disorder brought about through interaction with environmental factors. In the following chapter, pathophysiological models of mental disorder are considered in light of comorbidity's explanatory and ethical challenges, alongside two epistemological strategies: emergent simplification and integrative pluralism.

Chapter Five - Emergent Simplification Versus Integrative Pluralism

Mental Disorder as Pathophysiological Dysfunction

Although a causal account of mental disorder (and arguably many physical disorders) as the consequence of multi-factorial, multi-level, systems interactions is likely more accurate (Kendler, 2012), once explanations and models of mental disorder encompass environmental effects they become significantly more complicated. Simplification strategies may be used to make explanations and manipulations more tractable, understandable and manageable. Alternatively, simplification may be based upon an assumption that a particular level of analysis is either more usefully exploited or more causally central in any consequential manifestation of mental disorder.

Oulis (2010) described pathophysiological mechanisms as being central to understanding, classifying and treating mental disorder. Although mechanisms are integrated in complex systems across many levels, from biological to psychological to social, "the final effects of all types of psychopathological mechanisms are necessarily mediated by individuals' minding brains through their impact on them." He continued to say that "brain systems carrying out mental functions are the central or ultimate referents of psychopathological explanations, though not necessarily the more weighty ones"(Oulis, 2010, p.30.). In this view, another reason to focus on the level of psychophysiological dysfunction is that it is likely to be proximal to any consequential distress. Although distal factors, such as past trauma, may in many circumstances have a stronger causal role than any underlying genetic liability, the pathophysiological level arguably targets variables that are more amenable to treatment. Based on this assumption, analysis and explanation at this level may therefore be more informative for treatment development and application.

This approach is consistent with what Kendler (2012) and Schaffner (2008) refer to as *emergent simplification*, where we might hope that a number of etiological pathways

converge through a single bottleneck prior to manifesting as mental disorders. Thus the focal level of explanation and classification, physiological dysfunction, would be supported by multiple etiological explanations behind that bottleneck.

The Research Domain Criteria (RDoC) provides an excellent example of such an approach. In response to the many aforementioned theoretical and evidential questions overshadowing psychiatric diagnosis, the National Institute of Mental Health (NIMH) embarked on a new scheme in order to address its strategic goal to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behaviour and neurobiological measures" (NIMH, 2014). This places RDoC as a framework with which to structure and integrate research, rather than as a clinical diagnostic enterprise. It is via the RDoC framework that NIMH now funds much research into mental functioning and disorder. However in the same way as the Research Diagnostic Criteria (RDC; Spitzer, Endicott & Robbins, 1975) of the 1970's did, it does have explicit classificatory ambitions that also align with other NIMH strategic objectives aimed at improving nosological explanatory strength and treatment outcomes. In fact, the RDoC has been framed by its chief contributors as an extension of a long-term project to improve psychiatric reliability and validity begun by the RDC in the 1970's (Insel et al., 2010). We may therefore safely consider it a placeholder framework that will prove very influential in the formation of future psychiatric and psychological nosology.

In simple terms the RDoC is a matrix to guide research, with each row representing a functional domain and each column representing a method, termed a "unit of analysis", for measuring that domain. The five domains include: negative valence systems; positive valence systems; cognitive systems; systems for social processes; and arousal/regulatory systems.

DOMAINS/CONSTRUCTS	UNITS OF ANALYSIS							
	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation/attachment								
Social communication								
Perception/understanding of self								
Perception/understanding of others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

Figure 5. Research Domain Criteria matrix. From Cuthbert (2014, p. 30)

These domains, and the constructs and sub-constructs within them are dimensional and behaviourally described. They can also be considered an endophenotype or intermediate phenotype. The *negative valence systems* domain for example, includes systems involved in responses to aversive experiences, and is comprised of constructs responsible for acute threat, potential harm, sustained threat, frustrative non-reward and loss. Functioning within this domain may be characterised by either an excessively low or excessively high response to threat, loss or non-reward. Thus functioning can be quantified as a profile of responses across these several constructs, at any point along the constructs' continua, from low to high. In choosing to define the domains in this way, they retain a broad and flexible form, quite unlike the narrow categorical criteria of the DSM. However, in choosing to define the domains using observable behavioural properties, it does appear the framework is seeking to offer an

aggregative explanatory connection between its underlying mechanisms, processes and systems (as explicated by methods across various levels of analysis) and observable, functional behaviour.

It is important to remember that these domains are constructs themselves, posited to hold together due to the underlying properties and relationships within neural systems. Like the DSM diagnostic criteria, these constructs have been defined by groups of experts with reference to the evidence, rather than coming directly from specific empirical investigation. In fact, analyses that have uncovered patterns amongst multiple mental disorders, such as the internalising and externalising factors mentioned prior (Krueger & Markon, 2006; Vaidyanathan et al., 2011) have contributed towards the structure of these constructs. Despite decisions being based in evidence, and open to iterative revision in light of new evidence, it is important to remember that human choice is influencing the shape of this project.

Although RDoC's proponents warrant that all levels of analysis affect the biology and psychology of mental disorder, the framework's focal unit of analysis is that of brain circuits. This level was chosen based on several assumptions: that mental disorders are brain disorders, best characterised as dysfunctional neural circuits; that these circuits can be identified using tools from neuroscience such as functional magnetic resonance imaging; and that genetics and neuroscience research will eventually enable the use of biomarkers to "augment" use of clinical signs and symptoms in diagnostic practice (Insel et al., 2010; Morris & Cuthbert, 2012). In short, the RDoC project directs funding to research that will assist in identifying pathophysiological mechanisms. Such research searches for tangible links between brain circuit constructs and their functional consequences, likely via behavioural constructs. In improving the understanding of how brain relates to behaviour, the RDoC project seeks to guide a search for various treatment strategies, including molecular therapies, neuroplasticity paradigms, and psychosocial treatments (Cuthbert & Insel, 2010).

The choice to centre explication, if not explanation, at the level of neural circuits aligns the RDoC approach with that of emergent simplification (Kendler, 2012; Schaffner, 2008), where multiple etiological pathways flow through a bottleneck prior to their ultimate presentation as observable mental disorder. It also bears resemblance to Oulis' hypothesis regarding the process of psychogenesis as the manifestation of (in many cases) complex, integrative, multi-level causal processes via pathophysiological mechanisms (2010). Thus while it remains pluralistic and open to explanation at many levels, it also assumes that mental disorder necessarily operates via neural circuits. The hope appears to be that targeting this level of analysis will bring the greatest gains, both in terms of explanatory value and treatment efficacy.

The RDoC matrix specifies cells, molecules and genes as units of analysis that respectively descend in stepwise fashion from the bottleneck of neural circuits, and inversely, physiology, behaviour, self-reports, and methodological paradigms as progressively ascending from neural circuits. For example, within the construct of acute threat/fear, neural circuits of interest include parts of the amygdala, prefrontal cortex and autonomic nervous system, to name a few. Cells such as neurons and glia; molecules such as dopamine, glutamate and cortisol; and the genes which code for these molecules are included within this construct in the units of analysis that follow down from the level of neural circuits. Travelling up from the neural circuits leads to consideration of physiological responses such as fear potentiated startle, skin conductance and heart rate; behaviour such as freezing, response time and avoidance; self-reports such as the BAI (Beck Anxiety Inventory) and STAI (State-Trait Anxiety Inventory); to paradigms such as fear conditioning and viewing aversive pictures or films, located at the upper edge of the matrix. In this way the construct of acute threat is characterised by an accumulation of theory and evidence across these different methods, methods which span biological and psychological fields of interest.

In summary, the RDoC matrix, although pluralistic in its attribution of cause, conceptualises mental disorder as necessarily flowing through the level of neural circuits towards consequential observable manifestation. Thus, while leaving room for higher and lower levels of explanation, its concept of mental disorder is nested within the physiological level of analysis.

Although the RDoC project is currently a nascent research engine, it has explicit goals to improve classification (Insel et al., 2010). If neural circuits become the primary level at which mental disorder is conceptualised, and they are open to identification via biomarkers and neuroimaging, then this would imbue classification with the potential to objectively identify a dysfunctional mechanism. Under this scheme, the concept of mental disorder aligns with the current Harmful Dysfunction analysis.

Hypothetically, mental disorder may be classified at the level of a higher level domain, such as the negative valence system, or at the level of a construct or sub-construct, such as the acute threat construct. Functioning may be deemed pathological based on severity at either end of the dimension (for example an overactive or underactive acute threat neural circuit). Alternatively or additionally, functioning may be deemed pathological based upon correlates and causal inferences linking circuit measures to functional impairment via self-report data and clinical observation.

An interpretation that emphasises pathophysiological processes would conceptualise comorbidity as the resultant effect of two or more dysfunctional neural circuits. Again, these circuits may reside within the same general domain or may indicate dysfunctional processes across domains (high acute threat comorbid with low approach motivation). Irrespective, current comorbidity is viewed as more than a methodological artefact, it is viewed as indicative of a need for a paradigm shift in classification specifically, and research approaches more generally.

The success of this model in offering coherent and integrative concepts and explanations of comorbidity depends on whether rich and variant etiological pathways are shown to causally travel through the level of neural circuits. If this process of emergent simplification is reliably demonstrated then the concept of mental disorder and comorbidity nested in neural circuits may offer high value across Kendler's (2012) multiple explanatory criteria (strength, causal role, generalizability, specificity, manipulability and proximity.)

The issue remains that the level at which mental disorder is best conceptualised should not be decided a priori, but instead should be decided upon the basis of empirical evidence (Lilienfeld, 2014) and theoretical considerations. While RDoC certainly offers the potential for integrative concepts and explanation of mental disorder and comorbidity, in choosing to focus concepts of disorder at the neural circuit, its founders are taking a gamble on the neural circuit's causal role. Its strong focus on biological levels of analysis has led to claims that risks of reification are high (Berenbaum, 2013), and that the scheme is flawed due to its reductive assumptions (McLaren, 2011).

The RDoC's founders argue against claims of reification and reductionism by referring to the inclusion of levels of analysis such as behaviour and self-report in the matrix.

Importantly, all of these levels are seen as affecting both the biology and psychology of mental illness. With the RDoC approach, independent variables for classification might be specified from any of these levels of analysis, with dependent variables chosen from one or more other columns. (Insel et al., 2010, p. 749).

However, the role of levels of analysis such as self-report and behaviour, seems to largely focus on a duty to provide a methodological link to the functional effects of neural circuits and their biological mechanisms. The causal roles of cognitions, affect and behaviour do not appear to be given the same explanatory significance as neural circuits and their biological underpinnings. Instead cognitions, affect and behaviour are deemed important as

manifest indicators of the functional impact that pathophysiological mechanisms and their etiological antecedents cause.

Even if they are given equal explanatory status, it may be difficult for this model to clarify what role feedback processes from higher levels of analysis may have in bringing about dysfunction as conceptualised at the neural circuit level. Dynamical methods would need to be used to characterise whether causal interactions between circuits and higher-level processes are bi-directional. Although this is a possibility, it is certainly not the concept of mental disorder emphasised by this model. This also speaks to the model's medical focus on aetiology rather than the concept of maintenance of dysfunction that is prominent in psychological theory and treatment approaches.

Given the current uncertainty regarding the etiological bottleneck role of neural circuits, it is difficult to assess this model's explanatory coherence and integration with regards to comorbidity. "Structural and functional magnetic resonance imaging studies have suggested a range of central nervous system abnormalities that correlate with mental disorder but the specificity and strength of these associations, as well as their causal status, remain uncertain" (Kendler, 2012, p.16). Of course the hypothesis that RDoC is following is that the reason that specificity and strength of neural correlates is poor, is due to the current incorrect parsing of mental disorder on a phenotypic, descriptive basis. At this stage the evidence is inconclusive.

While Lilienfeld (2014) asserted that "RDoC is a calculated gamble that appears to be worth the risk" (p.1), he also stressed the need to learn from previous research experience. The RDC of the 1970's led to a paradigm classificatory shift via the DSM-III, a shift that resulted in the reification of mental disorder categories. A significant risk associated with this model of mental disorder, especially given the fallibility of biological explanation to essentialist biases, is that neural circuits will become reified as the cause of disorder. This

seems to fly in the face of promising biologically based models of human functioning and

agency, such as dynamic systems theory and emergent materialism (Christenson & Hooker,

2000).

Comorbidity: Artefact or Inherent?

The latent construct, pathogenetic and pathophysiological models discussed thus far,

are in line with Aragona's (2009) call for a paradigm shift in classificatory practices due to

currently observed hypercomorbidity. They each conceptualise comorbidity as an artefact of

current classificatory and diagnostic methodology, instead seeking to explain mental disorder

based on underlying causal processes. However, as demonstrated neither latent construct or

pathogenetic models of mental disorder are likely to meet the demands for coherent and

integrative explanation required by comorbidity. Coherent and integrative explanation may be

possible at the neural circuit level, however this is dependent upon neural circuits acting as a

causal bottleneck for the development and maintenance of mental disorder. What are the

alternatives if we are unwilling to take such an a priori gamble?

"High rates of comorbidity in psychiatry will not simply disappear once scientists

develop a better nosological paradigm" (Zachar, 2009, p.14). In contrast to Aragona (2009a),

Zachar characterised comorbidity as an inevitable consequence of attempts to classify mental

disorder. He argued that "the phenomena covered by the term 'comorbidity' are real,

expectable features of the psychiatric domain" (p.14). Pointing to the interconnected nature of

the human brain, its entwined structural and functional architecture, and humans' dynamic

and integrative nature of functioning with the external environment, he surmised it unlikely

that classification based in aetiology will tidy away the problem of comorbidity. Instead, he

supported a nosological goal to lower comorbidity and provide an improved framework for

its conceptualisation based in research and evidence. Zachar's stance is not anti-realist, but

pragmatic. In fact perhaps because of his realist perception of human functioning as

inherently complex, he argued for a nosology commensurate with pragmatic goals rather than

based in essentialist aspirations towards natural kinds (Kendler et al., 2011; Zachar, 2000,

2014).

In response to these assertions, let us consider comorbidity as typified by members of

a vulnerable population (Zachar 2009) or multimorbid class (Vaidyanathan et al., 2011).

Individuals in this group experience more severe and more complex manifestation of

psychopathology. Arguably, it is this group to which our explanatory models and treatment

evidence should be attuned. It is highly likely that behind such presentations lies a complex

confluence of causal factors and pathways. Seeking to understand mental disorder or

comorbidity in all its detail may result in an explanation that lacks clarity or manipulability.

Perhaps a level of generalisation and idealisation is necessary. Alternatively, strategies to

simplify causal pathways at one level, for example neural circuits, may fail to capture

important casual contributors, weaken explanatory depth and coherence, and lead to

essentialist assumptions and reification. Furthermore, idealisation of models of mental

disorders that greatly emphasise differential diagnosis over descriptive psychopathology may

result in decreased applicability of models to complex clinical presentations, as observed in

the comorbid client.

It is a possibility that multimorbidity may be relatively etiologically simple, resulting

from causes at primarily one broad level of explanation. A genomic configuration as indicated

by an endophenotype may designate clear risk to psychotic processes. Neural circuit analysis

may indicate dysfunctional neurodevelopment across several domains of functioning. These

genetic and physiological factors may establish a developmental course in adolescence that

leads to a wide constellation of disabling symptoms - substance use, anxiety, depression, a

breakdown in interpersonal relationships and continued psychosis - even within the context of

a highly supportive environment. Inversely, a developmental pathway beginning with low

genetic and neurodevelopmental liability to mental disorder may be thrown off an adaptive

course as a result of environmental factors such as exposure to trauma and sexual abuse in

early adulthood, resulting in a similar constellation of symptoms - substance use, anxiety,

depression, a breakdown in interpersonal relationships and psychosis.

Both scenarios, while causally divergent are relatively simple, with cause located

primarily at either the biological or environmental level. However if effective treatment or

intervention is required, broad explanation is likely to be insufficient. Analysis across

multiple levels is needed to understand how micro, molar and macro levels of functioning

each influence the other. Some levels are likely to have a more central and stronger causal or

maintaining role than others.

These examples clearly demonstrate two key implications: 1) No one level of

explanation is fundamental (Murphy, 2006); 2) Even within individuals with similar

presentations, causal pathways are likely to vary, and the respective impact of causes at

different levels is therefore also likely to vary. Neither of these points is unique to comorbid

presentations, it is a result of the multifactorial nature of mental disorder. However,

comorbidity serves to remind us of the likely interactive and variant nature of etiological and

maintenance processes in mental disorder. Given it is the comorbid population which

experiences the greatest severity and distress it follows from the implications above that: 1)

Denoting any level of analysis with explanatory weight a priori to evidence is unjustified and

potentially harmful; 2) We must embrace concepts and methods that are able to help us

understand the integrative and variant causal nature of psychopathology; 3) substantive

theory is indispensable when addressing the issue of comorbidity, alongside responsivity to

relevant data.

Integrative Pluralism

"Neither its complications nor its chaotic dynamics should scare away the curious, nor drive them to replace clear-eyed investigation of the nuanced beauty of complexity with the austere, clean lines of the simple and timeless" (Mitchell, 2009, p.11).

Sandra Mitchell (2008, 2009) championed the adoption of integrative pluralism as an epistemological theory to bring us closer to understanding complex scientific challenges: "Pluralism in causes, pluralism in ontological levels, and pluralism in integrations will characterise the scientific explanation of complex system behaviour" (2009, p. 110). Integrative pluralism embraces the use of multiple causal factors, across many levels of analysis, to form models that combine in multiple ways to shape explanations of complex causal systems. The difference between this approach and one based in emergent simplification is obvious. Emergent simplification may embrace pluralism in cause and ontological level, but its hopes are vested in avoiding messy integrative explanation by demonstration of a causal level through which all etiological processes, travel such as the neural circuit.

The characteristics of mechanisms common to biological systems indicate that emergent simplification strategy is unlikely to be successful (Mitchell, 2009). Take for example the issue of feedback mechanisms. Feedback mechanisms are observed across molecular, behavioural and social levels in a range of biological species, often acting as both an upward and downward causative force. While effecting changes in lower level causal systems, a feedback mechanism may also bring about self-organisation, homeostasis or chaos in higher level behaviour. Similarly, even within the level of the cell, the effect of change in one variable (e.g. knockout or mutation of a gene) may be altered by compensatory strategies internal to the cell, such as redundancy (a mechanism that utilises 'spare copies' of genes to ensure a biological process will continue) and degeneracy (compensatory intracellular

mechanisms). A network capable of reorganising itself, suggests properties of non-modularity, non-aggregation and non-linear dynamics (Mitchell, 2009).

Acceptance of these mechanisms and characteristics as important in biological causal systems has implications for our methods, concepts, models and explanations. Each needs to adapt to the different levels of contingency and stability that may be present within causal networks or systems. How then do we best understand or represent such complex causality?

One potential tool, network analytic methods, is discussed later. However, while technology may offer some assistance, Mitchell (2009) also turned to pragmatism for guidance, suggesting that our representations need to be attuned to both the limits of our cognitive abilities and our purposes. Firstly, irrespective of their specificity, if models are theoretically sound and based in evidence, we may interpret them as accurate ways to map relationships and capture the topography of cause and effect in mental disorder. Secondly, the decision to adopt models and concepts at either a fine-grain or coarse-grain needs to be based on our goals and objectives. Any generalisation or idealisation should take place with this in mind. For example, a classification system may utilise a categorical cut-off despite demonstration of an underlying dimensional structure, as such a cut-off may assist in allocating resources to those most in need.

Finally, resultant models and concepts should be interpreted with awareness that such strategies may have been employed at least partly in order to help us make sense of inherent complexity. Although it may be the goal of scientific realism to represent nature in correspondence with the "truth", Mitchell's pragmatism highlights the extraordinary complexity of the world. An implication of this complexity is that a fully explicated understanding of interactions within and between complex systems, even solely within the realm of mental disorder, may be beyond our cognitive capacity and research methodology.

In response we should attune our enquiries to the goals that matter the most, while at the same time remaining aware of our cognitive and methodological shortcomings.

Reductive, material models of mental disorder often work by explication of mechanistic processes across biological levels (circuit to cell to molecule to gene). However, models of beliefs, emotions and behaviours may not integrate easily with these mechanistic processes. Murphy (2006) argued that a process of decomposition (of behaviour, emotion or cognition into its structural or functional parts) and localisation (at the neural circuit level) while desirable, may not be possible for all human functioning. For example, we are unlikely to find the difference at a material (neural) level between a specific intent for murder and a specific intent for self-defence (Campbell, 2008). Nor would it be especially useful to understand how some thoughts or actions manifest materially when their meaning is relationally, rather than physically bound (Baker, 1999; Campbell, 2008). In this way, by cashing-in on already integrated systems and processes, self-report measures that capture information at the level of belief and desire, may work as better predictors of behaviour than quantification or characterisation of neural processes (Lilienfeld, 2014).

Denoting cause and effect is often a form of inter-level explanation in itself. Mechanistic explanation, for example describes the variant effect of genes at the molecular and cellular level. Decomposition and localisation is another integrative strategy, for example, describing abilities such as speech (behaviour), as capacities of Wernicke or Broca's areas of the brain (anatomy). Additionally decomposition and localisation can describe functional rather than structural components. In these instances localisation tends towards characterisation as networks rather than anatomical components (Bechtel, 2012; Pessoa, 2013). Network models are especially useful for understanding emergent phenomena, where methods that sum or aggregate component parts may provide an inadequate characterisation of the resulting phenomena (Schaffner, 2008). Network explanatory models are often applied

to the brain or cognition. Yet another recent application is a causal symptom network model (Borsboom & Cramer, 2013), where symptoms themselves are modelled as forming causal structures. Changes in sleep (physiology) may cause changes in mood (affect) and concentration (cognition) for example. All of these integrative methods include quantification of cause and effect and the ability to track change in relation to time. The inclusion of a dynamic dimension or component appears particularly important in developing integrative models given the influence of feedback processes on causal systems across time. Thus longitudinal research across short and longer time-spans seems imperative.

Mitchell argued that multiple integrative models, utilising multiple methods, may be required to understand mental disorder (2008). The examples above illustrate the availability of such methods. Utilising several methods is also consistent with a robust approach that combines reduction and reconstruction (Barabási, 2011; Pennington, 2014). With such tools at our disposal, the challenge therefore, lies in how best to combine these different inter-level explanations into a cohesive integrative model or theory of mental disorders.

Explaining and integrating cause across multiple levels leads to significant complexity. The granularity of these models and concepts should therefore be reflective of our objectives (Mitchell, 2008). These might differ according to purpose between primary health clinicians, specialists, researchers and public health specialists (Valderas et al., 2009). While the biopsychosocial model may be a useful heuristic it is likely too generic. As argued, a clear goal is the development and application of successful classification and treatment for those who experience the most severe psychopathology, the multimorbid population. This requires coherent and integrative concepts and explanations of specific mental disorders and their comorbid variants. Exactly what level of detail or scope is required can only be decided through iterative investigation. However, one thing is certain, a wide range of research methods will need to be employed in order to understand how detailed a useful representation

needs to be. Moreover, such methods need to be capable of capturing complex emergent properties and non-aggregative, non-modular and dynamic relationships.

Woodward (2008) argued that, while one level of explanation may be chosen over another on an empirical basis, such that it better accounts for an effect, sometimes it may be necessary to choose or define variables at a broader level in order to see an effect. Similarly, models that are too detailed may lack clarity. This is what Mitchell (2009) referred to in emphasising that our models should reflect our cognitive capacities. This pragmatic realisation, that the complexity of mental disorder may be beyond our cognitive limitations, suggests that advances in modelling technology will play a crucial role in assisting classification and diagnosis into the future.

Thus integrative pluralism forms an epistemological framework for thinking about concepts and models of mental disorder. It accepts multiple explanatory levels and multiple ways of combining theories across these levels, to develop a more comprehensive understanding of the world. At the same time it recognises the need for conceptual and explanatory coherence. While remaining open to realist assumptions that our causal representations correspond accurately with the nature of the world, it eschews essentialism. Instead it is guided by pragmatism: pragmatism to guide decisions regarding what explanations are best fit for purpose; and pragmatism in realising that our abilities to discover and represent the world as it "truly" is, although perhaps incrementally improving, will likely remain limited.

With the framework offered by Mitchell's integrative pluralism in mind, two models of mental disorder are analysed in the following chapter. The RDoC project, this time engendered with a pluralist perspective, is reconceptualised and discussed, followed by network models of mental disorder. Again, each is considered in relation to comorbidity's

specific challenges and demands. A brief concluding chapter then summarises the main

findings of this thesis.

Chapter Six - Integrative Models of Mental Disorder

A Continuum of Causal Structures

In contrast to Feinstein's (1970) concept of comorbidity as co-occurring independent disease processes, Zachar stated that "comorbidity in psychiatry is a broader concept, referring to a variety of conditions that overlap in multiple ways" (2009, p.14).

Let us return to the idea of a continuum of causal characterisations, from homogeneity to heterogeneity. While the continuum acts as a contrastive tool, sharpening the differences between concepts of mental disorder, it also enables a less absolutist conceptualisation, enabling identification of similarities and points of divergence. A similar approach was used by Zachar and Kendler in their analysis of different models of mental disorder (2007).

This continuum is not one of types of causal factors or symptoms (which is often what is meant when mental disorder is described as heterogeneous); the continuum instead characterises types of causal interactions, processes, mechanisms and interactions that take place in the development and maintenance of a mental disorder. Borrowing Kendler et al.'s (2011) concept, it is a continuum of homogeneous to heterogeneous mechanistic property clusters. At one end is a concept of mental disorders generated by discrete, homogeneous causal networks that lead to clear and distinct syndromes. At the other end, a concept of mental disorder as fully reflexive, where causes, networks and effects are so highly integrated with each other that it becomes difficult to identify distinct causal pathways and symptom clusters. While Aragona's conceptualisation of mental disorder is more towards the homogeneous, Zachar's exists more towards the heterogeneous end of the continuum.

Homogeneous causal pathways arguably have the following features: a (relatively) small number of causal factors that demonstrate reasonable effect size; a (more) discrete or linear causal chain; a causal system that is (more) distinct from other systems; less variance in causal process as a result of higher level feedback mechanisms; a quasi step-function or

threshold effect that separates mental disorder from normality or other mental disorders more clearly; a causal sequence that is less affected by changes in background conditions; a causal structure that is relatively stable across time.

Alternatively, heterogeneous causal pathways are likely to possess the following features: many relatively weak causal factors; a complex causal chain that is difficult to disentangle from its effect or from other causal systems; a causal chain that is highly nested within superordinate causal systems; high variance in response to feedback effects or changes in background conditions; no step-change or threshold functions, only small quantitative changes; high redundancy and degeneracy; a causal structure that changes quickly across time.

The concept of comorbidity is dependent upon where mental disorder is demonstrated to reside along this continuum. If the causal characteristics of mental disorders are mostly heterogeneous then comorbidity dissolves into increasingly complex causal clusters. As Zachar suggested above, it may be possible that different disorders inhabit different zones on the continuum. In this case, the nature of comorbidity will differ depending upon which disorders are thought to co-occur at any one time. While both concepts of mental disorder leave room for multifactorial cause at any explanatory level, the nature of the causal pathways may differ significantly. That is, the way causal factors interact to form a sufficient explanation for an observed effect may differ.

Research Domain Criteria Reconceptualised

The explanatory potential of the RDoC project resides in its attempt to systematically structure explanation and evidence across multiple levels, using numerous methods, spanning biological and psychological fields of interest. The RDoC initiative is a social project aiming to generate theory and evidence about the nature of human mental functioning. Despite its

risks and shortcomings, it is clear that the intention is to create an inclusive and provisional framework to guide coordinated enquiry.

However, as discussed, one of the risks associated with the RDoC's current strategy is its a priori emphasis on biological explanation and conceptualisation of mental disorder as brain disease. Five of the RDoC's seven chosen levels of analysis are biological. In addition, exclusion of higher level explanatory phenomena, such as beliefs and desires (not to mention interpersonal functioning) demote the use of self-report measures to a role of linking neural circuitry to its proposed functional output (Berenbaum, 2013; Lilienfeld, 2014). The ultimate risk, given its role as a central funding source for research, is that due to the dominance of a biological evidence base, biological explanations will come to further dominate concepts of mental disorder at the cost of investigations into the role of causes at other levels. The risks of this are especially high given the financial incentives for development of pharmaceutical treatments. Given the history of reification of psychiatric diagnoses and evidence of one of the mechanisms by which it happens, psychological essentialism, reification of these biological models would certainly follow.

Pluralism instead denotes multiple explanatory levels with causal relevance. While cause and effect across levels of explanation may interact, they also need not be fully integrative or reductive in order to be valid. Explanations at different levels may exist at that level as characterised by their typical causal processes and interactions. A non-reductive account recognises that higher level entities and processes, such as thought or spirituality, need not be realised or localised in the material of the brain in order to bestow these levels with explanatory significance. Although we may form partially reductive accounts by integrating explanations across levels to clarify causal pathways, in doing so, reduction does not replace the higher levels of explanation; instead it clarifies the lower levels (Murphy, 2008).

Thus an alternative interpretation of the RDoC framework may denote it with greater explanatory potential than currently exists through its strategy of emergent simplification. This is reliant upon several conceptual and methodological alterations. Firstly, a truly pluralist approach would grant higher ontological levels with an explanatory status equal to lower biological levels. In addition, all explanations would be held to similar empirical standards in demonstrating scope and stability of effect. For example the measurement error or predictive accuracy required from functional magnetic resonance imaging data, would be comparable to that required of self-report or behavioural measures (Lilienfeld, 2014).

A more systematic approach to integrative explanation across levels and disciplines would also certainly be beneficial. The RDoC project has the potential to provide a methodological and conceptual framework for linking explanations of cause and effect across different levels of analysis. In doing so it may become obvious that some mental phenomena can be explained in a fairly linear fashion across levels. It is also likely that causal sequences in other mental phenomena are more heterogeneous, with risk factors at either lower or higher levels mapping less succinctly onto constructs, and feedback effects complicating the direction of causation.

If concepts of mental disorder are based in an understanding of aetiology and maintenance processes, the extent to which a causal sequence can be reliably determined to result in a set of phenomena becomes central to the conceptualisation of any disorder. This will invariably involve iterative attempts to increase the reliability of ways to identify causal structures. Hence, there seems little room in the future for absolutist or reified interpretations of diagnoses. At this stage the RDoC may assist in bringing together a model that x causal processes or risk factors across y levels cohere well enough to be considered part of a causal system that together is reliably associated with z effects on functioning. The mapping of explanations across levels may not be exact, but if it is attuned to our goals and cognitive

abilities, it may be good enough to provide guidance for treatment and understanding of mental disorder.

A concept of mental disorder using this framework would be characterised by multiple causes and multiple types of interactions within a relational model that held together well enough for the purposes of diagnosis, treatment development and application. In order to provide a useful classification function, a causal model would need to explain enough variance in effects, and be independent (enough) from other causal systems so to be differentiated from other disorders or normality. Different mental disorders or groups of disorders might differ according to their most influential causal features. As suggested previously, different mental disorders would likely exist in different zones between homogeneous and heterogeneous causal structures. The types of models are therefore likely to differ: while some may explicate mechanistic processes sequentially across different explanatory levels, some may instead comprise a probabilistic network of factors including symptoms, past life events and biological markers.

Under this conceptual scheme, comorbidity would be indicated by the presence of data (for example signs, symptoms, objective observations, self-report and historical information) that was best accounted for by more than one causal model. In addition, if the RDoC project is successful in offering coherent explanation of the casual processes underlying mental disorder then it should bring us closer to offering explanations of how and why different mental disorders regularly co-occur.

This pluralistic approach also offers the greatest opportunity for models to be built that adequately meet the desired explanatory criteria (Kendler, 2012). This speaks to the generativity of the RDoC project situated within an integrative pluralist epistemological framework. While few variables at any level are likely to demonstrate strong effect on their own, a comprehensive causal model that includes multiple factors is likely to explain a larger

portion of the observed variance. Similarly strong causal confidence may not be demonstrated at all levels, but other criteria such as predictive validity of the overall model may suffice or prove more useful than high causal confidence at one level of explanation. Generalizability may vary across mental disorders depending on the nature of each disorder's causal structure. In fact, perhaps it is this aspect to which models will need to be most acutely attuned. For example, although shared genetic or developmental factors may play an important early causal role, different environmental conditions or biological factors may designate divergent causal pathways. Thus, the generalizability of overall causal models may become less important than the need to create models that reliably match etiological pathways. This may be especially important for individuals who experience comorbid conditions.

Specificity of any model however relates more to the notion of pathways or systems being discriminable enough to be considered separate. In some cases models may be more causally homogeneous and specificity relatively high. If, however, it is accepted that some disorders are causally heterogeneous, variables that endow manipulability may be prioritised for the purpose of treatment and assessment. Proximal variables involved in maintenance processes may be highlighted for similar reasons. Specificity, manipulability and proximity each directly relate to the ethical goal of delivering better treatments for the comorbid population and individuals of which it is composed.

A Tool for Characterising Complexity and Integration

Borsboom and Cramer (2013) propose an integrative network model of mental disorder rooted not in underlying causes such as a disorder construct, but rather in the causal relations existing between symptoms. Network models contain two principle conceptual components: nodes and edges. In causal symptom networks, symptoms act as the nodes (usually represented by circles) and edges are the lines that connect them. Edges can

represent different relationships such as correlations, odds ratios or neuronal connectivity. Using a matrix, the distance and strength of connections between nodes can be calculated and then visually represented. Techniques have been used to: characterise mental disorder based in analysis of the definitions of DSM-IV diagnoses (Borsboom, Cramer, Schmittmann, Epskamp, & Waldorp, 2011); model onset and termination of depression using analysis of auto recorded emotions (van de Leemput et al., 2014); explain the often seen positive correlations that occur between cognitive tasks in intelligence testing as a result of reciprocal causation rather than an underlying g factor (Van Der Maas et al., 2006); explain patterns of comorbidity seen between MDD and GAD via bridge symptoms (Cramer, Waldorp, van der Maas, & Borsboom, 2010); and explore the relationships between autism and OCD (Ruzzano, Borsboom, & Geurts, 2014).

Borsboom & Cramer (2013) state that: "Using network analysis techniques, such systems can be represented, analysed and studied in their full complexity…. It provides a middle ground in which disorders exist as systems, rather than as entities" (p.93). The network theoretical framework provides a method for building general models of disorders at a population level. For example, many individuals' symptom networks could be compared to create more generalised or idealised models. Network analysis also holds potential as a clinical tool to analyse the symptom networks of individuals presenting for treatment. Coupled with technology such as smartphone apps that enable the collection of time-series data, clinicians may in future have the opportunity to visualise and characterise clients' individual symptom networks. As such, new methods of assessment may develop. Borsboom and Cramer (2013) claim that network analysis techniques can be used to identify which symptoms are most influential in a network. Thus, assessment utilising these methods may offer guidance for prioritising treatment of certain symptoms, while also allowing client and clinician to track changes in the network over time. Such highly personalised analysis offers

an opportunity to bridge the methodological individual-population gap that has proved especially challenging for the effective treatment of comorbid disorders.

Within these models, symptoms play an integral causal role in the aetiology of what may be termed a disorder. In fact, it is the concept of disorder which undergoes significant transformation. No longer characterised by common underlying causes, as posited by latent constructs, pathogenetic or pathophysiological models, instead, a mental disorder is best thought of as a nested causal system. In a symptom network model, "the relation between symptoms and disorder becomes one of mereology (a part-whole relation)…" (Borsboom & Cramer, 2013, p.96). It is the network itself, which becomes the disorder. This somewhat turns the construct of disorder on its head.
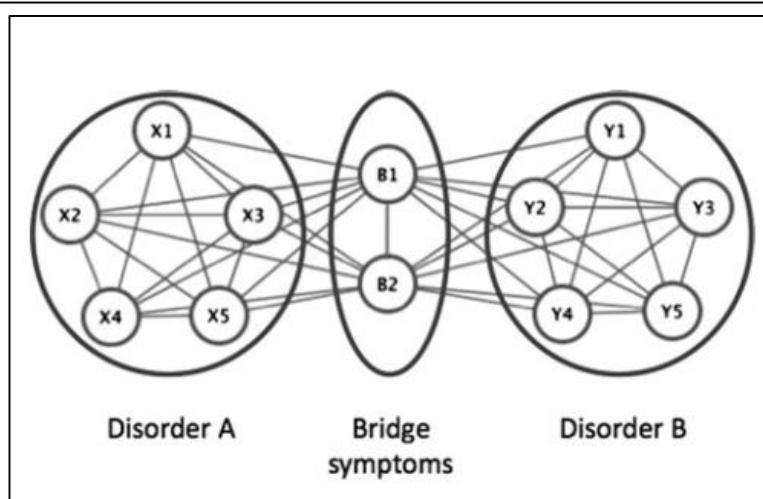

Figure 6. "Comorbidity under a network approach. Disorder A consists of bidirectionally related symptoms $X_1 - X_5$, and disorder B consists of symptoms $Y_1 - Y_5$. Symptoms B_1 and B_2 are *bridge symptoms* that overlap between disorders A and B. In this model, comorbidity arises as a result of direct relations between the bridge symptoms of two disorders." From Cramer et al. (2010, p. 140)

Although disorders are likely to have fuzzy rather than clear boundaries, they may still be adequately defined on the basis of the properties of the network. It is possible that

symptoms will display differential connections to one another, and in doing so form symptom

clusters or communities that share dense connections within the community and fewer

connections to symptoms outside the community. Indeed, analysis of DSM-IV diagnostic

definitions revealed this phenomenon, known as *small world architecture*, demonstrating

high clustering (short distance between nodes or symptoms) within disorders (Borsboom et

al., 2011). Similarly, an analysis of NCS-R data (Cramer et al., 2010) suggested that a

plausible approach to classification using these methods might be choosing to categorise on

the basis of, for example, the three most central symptoms in an MDD cluster. However, in

both studies, some communities were also shown to have a high degree of overlap with other

communities, leading to implications regarding the nature of comorbidity.

The phenomena of comorbidity currently observed in relation to DSM diagnoses, is

therefore thought to arise due to the causal relationship between symptoms that bridge

disorders or communities. The empirical network of MDD and GAD, elucidated in the study

by Cramer et al., (2010), revealed that comorbidity was more likely caused by a

unidirectional causal relationship from the MDD to GAD symptoms, potentially via core

psychological symptoms such as depressed mood and loss of interest. Moreover, symptom

clusters that indicated presence of both disorders, were more strongly connected in those who

presented with at least one set of overlapping symptoms. For example, MDD and GAD

diagnoses share symptoms relating to sleep, fatigue, restlessness and concentration. This

relationship was not accounted for by the diagnoses sharing these symptoms, rather, the

clusters of each disorder were much more highly interconnected in individuals who presented

with these symptoms. The authors, therefore, suggested that it was indeed the causal

relationships between symptoms that lead to comorbidity in this instance.

However, symptom communities may be so intertwined that there remains no factual

basis upon which to segregate disorders. Given this eventuality, disorders may be classified

solely on the basis of practical consequences (Schmittmann et al., 2013). Whether symptom communities or disorders are reliably discriminable from one another, away from the structure of DSM diagnoses, remains to be seen. Additionally, it will be interesting to discover whether variance in networks between individuals is contained enough to denote disorders with typical features.

At this point it is important to recognise the limitations of this method and its related concept of mental disorder. Like other psychometric methods, the resultant model is conceptually dependent upon the data from which it is formed. Thus, its validity rests upon the decisions made along the way to include or exclude particular symptoms or types of data. Similarly, its reliability is dependent upon its ability to adequately measure the data. Nonetheless, proponents of these types of models make a strong argument for their theoretical strength as a characterisation of the observable features of mental disorder, especially in comparison to the theoretical assumptions needed to endorse concepts bound in latent constructs (Borsboom & Cramer, 2013; Schmittmann et al., 2013; Van Der Maas et al., 2006).

Such methods do offer potential for characterising complex systems, are widely used across other disciplines for similar purposes, and are especially pertinent in relation to the "data explosion" witnessed over the last few years (Barabási, 2011). Already there is evidence that mental disorders show characteristics typical of complex networks such as critical slowing down or tipping points (van de Leemput et al., 2014), small world architecture, and hubs and communities (Borsboom et al., 2011; Cramer et al., 2010). These methods also respond to Mitchell's (2009) demands for characterisation of bi-directional, non-aggregative and dynamic relationships.

Network analysis techniques are an intriguing tool with obvious potential. However, it remains likely that multiple levels of explanation will be required to understand mental

disorders (Kendler, 2012). For example, characterisation of mental disorder solely at the symptom or descriptive level (even if denoted with causality) does not explain patterns of heritability observed in many disorders. While network analysis potentially offers ways of identifying which symptoms to target in treatment, by itself it offers little guidance regarding how to change or prevent symptoms. As with latent constructs, there is a need to draw on other methods to develop resilient theories.

However, a network approach appears to be a flexible tool that can be utilised across different levels of analysis. Borsboom and Cramer (2013) use a metaphor of Russian dolls to describe the concept of networks nested within networks across explanatory levels. Symptom networks may therefore be nested within higher level social networks. Symptoms, themselves nodes in a network of mental disorder, may be described by a network of interactions at lower levels. Sleep problems for example "are complexly structured, with feedback cycles between hormones, external cues, and behaviours that give rise to the circadian rhythm" (Borsboom & Cramer, 2013, p.104).

Thus it appears that the explication of mental disorders as complex and integrative causal networks or "mechanistic property clusters" (Kendler et al., 2011), is a possibility in the foreseeable future. Combining methods used in the RDoC project with network analysis techniques will likely foster conceptual and explanatory coherence and integration. A flexible, multidisciplinary, multi-method approach seems essential to such a pursuit.

Conclusion

It has been argued that the adoption of a classification system grounded in causal theories and models is probably our best strategy for improving outcomes for those who experience mental disorder. This thesis has specifically addressed the pursuit of etiological classification in light of the phenomenon of comorbidity.

Psychiatric comorbidity makes a clear ethical demand: to improve outcomes for those who experience multiple mental disorders. Improving outcomes for the comorbid population is an important ethical goal because it is these individuals who carry the highest disability and distress resulting from psychiatric disorder. Knowledge objectives spring directly from this ethical goal – coherent, integrative explanation of mental disorder – for the purpose of helping clients make sense of their experiences, to develop effective treatments, and to aid clinicians in communication, assessment and treatment. However, another reason to listen to the demands of comorbidity has become clear throughout the course of this thesis. The phenomenon of comorbidity likely reflects the complexity of mental disorder. Thus, comorbidity sets the standard to which our explanatory theories should strive to accommodate and our concepts seek to address.

Acceptance of this complexity does not mean rejection of a realist strategy. It simply means more flexibility is required in our concepts, theories and methods of investigation. Allen Frances refers to a "humble realism" (Phillips et al., 2012a). In reference to the issues discussed in this thesis, this is a realism accompanied by awareness of the massive causal complexity that is likely involved in describing and explaining mental disorder. Hence, it is sensitive to the limitations of our cognitive capacities and methodologies to map the world as it "truly" is. With such awareness, humble realism may form a fruitful partnership with pragmatism as a way to sharpen our focus of inquiry to meet our goals.

Acceptance of complexity also provides a form of protection against reification. History is likely to repeat itself if the current RDoC strategy to prioritise neural circuits is maintained. Just as reification of DSM diagnoses took place despite explicit statements regarding their atheoretical and descriptive status, so conceptualising mental disorder as brain disorder at this level, even with multiple disclaimers that cause at other levels plays an important role, will certainly lead to reification of disorder constructs under the RDoC project. There is an acute need to remain aware of inherent biases for psychological essentialism in this context. Moreover, its emphasis of biological mechanisms will result in a significantly larger evidence base in support of biological theories than alternative causal explanations. We should therefore eschew such simplification strategies at this time, in favour of the potential benefits brought by richer explanations.

Several strategies may assist in representing complex causal processes. A continuum depicting variance in causal structure from homogeneous to heterogeneous provides a useful heuristic. Network models also offer potential for analysing and visualising interactions between causes, as well as representing integration across different explanatory levels. Integrative pluralism is an epistemological framework that not only entertains causes at many levels, but is also open to different kinds of integration between causes. Despite this, it may ultimately be preferable to choose one level of analysis at which to conceptualise single or multiple mental disorders. If so, this choice can be made with open eyes that such a simplification strategy reflects a particular purpose.

The phenomenon of psychiatric comorbidity, therefore, not only drives us to advance explanation, concepts, and classification of mental disorder for the purpose of improving client and patient outcomes, but also provides methodological and epistemological guidance in order to address such a challenge.

References

Alonso, J., Buron, A., Bruffaerts, R., He, Y., Posada-Villa, J., Lepine, J. P., . . . Tachimori, H.

(2008). Association of perceived stigma and mood and anxiety disorders: results from

the World Mental Health Surveys. *Acta Psychiatrica Scandinavica, 118*(4), 305-314.

American Psychiatric Association. (1952). *Diagnostic and statistical manual: Mental

disorders*. Washington, D.C.: American Psychiatric Association, Mental Hospital

Service.

American Psychiatric Association. (1968). *Diagnostic and statistical manual of mental

disorders: Second edition (DSM-II)*. Washington, DC: American Psychiatric

Association.

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental

Disorders: Third Edition (DSM-III)*. Washington, DC: American Psychiatric

Association.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental

Disorders: Third Edition – Revised (DSM-III-R)*. Washington, DC: American

Psychiatric Association.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental

Disorders: Fourth Edition (DSM-IV)*. Washington, DC: American Psychiatric

Association.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental

Disorders: Fifth Edition (DSM-5)*. Washington, DC: American Psychiatric

Association.

Andrews, G., Slade, T., & Issakidis, C. (2002). Deconstructing current comorbidity: data

from the Australian National Survey of Mental Health and Well-being. *The British

Journal of Psychiatry, 181*(4), 306-314.

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 40*(1), 57-87. doi: 10.1017/s0021963098003448

Aragona, M. (2009a). About and beyond comorbidity: Does the crisis of the DSM bring on a radical rethinking of descriptive psychopathology? *Philosophy, Psychiatry, & Psychology, 16*(1), 29-33. doi: http://dx.doi.org/10.1353/ppp.0.0214

Aragona, M. (2009b). The role of comorbidity in the crisis of the current psychiatric classification system. *Philosophy, Psychiatry, & Psychology, 16*(1), 1-11. doi: 10.1353/ppp.0.0211

Baker, L. R. (1999). What is this thing called 'commonsense psychology'? *Philosophical Explorations, 2*(1), 3-19.

Barabási, A.L. (2011). The network takeover. *Nature Physics, 8*(1), 14-16.

Barlow, D. H., DiNardo, P. A., Vermilyea, B. B., Vermilyea, J., & Blanchard, E. B. (1986). Co-morbidity and depression among the anxiety disorders: issues in diagnosis and classification. *The Journal of nervous and mental disease, 174*(2), 63-72.

Bechtel, W. (2012). Referring to localized cognitive operations in parts of dynamically active brains. In A. Raftopoulos & P. Machamer (Eds.), *Perception, realism and the problem of reference* (pp. 262-284). Cambridge, UK: Cambridge University Press.

Berenbaum, H. (2013). Classification and psychopathology research. *Journal of Abnormal Psychology, 122*(3), 894.

Berkson, J. (1946). Limitations of the application of fourfold table analysis to hospital data. *Biometrics Bulletin*, *2,* 47-53.

Bogenschutz, M. P., & Nurnberg, H. G. (2000). Theoretical and methodological issues in psychiatric comorbidity. *Harvard Review of Psychiatry, 8*(1), 18-24. doi: 10.1093/hrp/8.1.18

Borsboom, D., & Cramer, A. O. (2013). Network analysis: an integrative approach to the

structure of psychopathology. *Annual review of clinical psychology, 9*, 91-121.

Borsboom, D., Cramer, A. O. J., Schmittmann, V. D., Epskamp, S., & Waldorp, L. J. (2011).

The small world of psychopathology. *PLoS ONE, 6*(11). doi:

http://dx.doi.org/10.1371/journal.pone.0027407

Boyd, J. H., Burke, J. D., Gruenberg, E., Holzer, C. E., Rae, D. S., George, L. K., . . . Nestadt,

G. (1984). Exclusion criteria of DSM-III: a study of co-occurrence of hierarchy-free

syndromes. *Archives of General Psychiatry, 41*(10), 983-989.

Brown, T. A., & Barlow, D. H. (1992). Comorbidity among anxiety disorders: Implications

for treatment and DSM-IV. *Journal of Consulting and Clinical Psychology, 60*(6),

835.

Brown, T. A., Campbell, L. A., Lehman, C. L., Grisham, J. R., & Mancill, R. B. (2001).

Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a

large clinical sample. *Journal of Abnormal Psychology, 110*(4), 585.

Bruce, S. E., Yonkers, K. A., Otto, M. W., Eisen, J. L., Weisberg, R. B., Pagano, M., . . .

Keller, M. B. (2005). Influence of psychiatric comorbidity on recovery and recurrence

in generalized anxiety disorder, social phobia, and panic disorder: A 12-year

prospective study. *American Journal of Psychiatry, 162*(6), 1179-1187. doi:

10.1176/appi.ajp.162.6.1179

Campbell, J. (2008). Comment: Psychological Causation without Physical Causation. In K. S.

Kendler & J. Parnas (Eds.), *Philosophical Issues in Psychiatry: Explanation,*

Phenomenology, and Nosology (pp. 184-215). Baltimore, Maryland: The John

Hopkins University Press.

Christensen, W. D. & Hooker, C. A. (2000). An interactivist-constructivist approach: to intelligence: Self-directive anticipative learning. *Philosophical Psychology, 13,* 50-45 doi: 10.1080/09515080050002717

Clark, L. A. (2005). Temperament as a Unifying Basis for Personality and Psychopathology. *Journal of Abnormal Psychology, 114*(4), 505-521. doi: http://dx.doi.org/10.1037/0021-843X.114.4.505

Clegg, J. W. (2012). Teaching about mental health and illness through the history of the DSM. *History of Psychology, 15*(4), 364-370. doi: http://dx.doi.org/10.1037/a0027249

Coppen, A., Shaw, D., & Farrell, J. (1963). Potentiation of the antidepressive effect of a monoamine-oxidase inhibitor by tryptophan. *The Lancet, 281*(7272), 79-81. doi:10.1016/S0140-6736(63)91084-5

Craddock, N., O'Donovan, M. C., & Owen, M. J. (2006). Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophrenia Bulletin, 32*(1), 9-16.

Cramer, A. O., Waldorp, L. J., van der Maas, H. L., & Borsboom, D. (2010). Comorbidity: A network perspective. *Behavioral and Brain Sciences, 33*(2-3), 137-150.

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet, 381*(9875), 1371.

Cuthbert, B. N. (2014). The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry*, *13*(1), 28-35.

Cuthbert, B. N., & Insel, T. R. (2010). Toward new approaches to psychotic disorders: The NIMH Research Domain Criteria project. *Schizophrenia Bulletin, 36*(6), 1061-1062.

Dennis, N. L., Larkin, M., & Derbyshire, S. W. (2013). 'A giant mess': Making sense of

complexity in the accounts of people with fibromyalgia. *British journal of health

psychology, 18*(4), 763-781.

Feighner, J. P., Robins, E., Guze, S. B., Woodruff, R. A., Winokur, G., & Munoz, R. (1972).

Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry,

26*(1), 57-63.

Feinstein, A. (1970). The pre-therapeutic classification of co-morbidity in chronic disease.

Journal of Chronic Diseases, 23(7), 455-468. doi: 10.1016/0021-9681(70)90054-8

Fenton, W. S., Blyler, C. R., & Heinssen, R. K. (1997). Determinants of medication

compliance in schizophrenia: Empirical and clinical findings. *Schizophrenia Bulletin,

23*(4), 637-651.

First, M. B. (2012). The development of DSM-III from a historical/conceptual perspective. In

K. S. Kendler & J. Parnas (Eds.), *Philosophical issues in psychiatry II: Nosology* (pp.

127-140). Oxford, UK: Oxford University Press.

First, M. B., Spitzer, R. L., & Williams, J. B. (1990). Exclusionary principles and the

comorbidity of psychiatric diagnoses: A historical review and implications for the

future. In C. R. Cloninger & J. D. Maser (Eds.), *Comorbidity of mood and anxiety

disorders* (pp. 83-112). Washington, DC: American Psychiatric Press, Inc.

Frances, A., Widiger, T. A., & Fyer, M. R. (1990). The influence of classification methods on

comorbidity. In C. R. Cloninger & J. D. Maser (Eds.), *Comorbidity of mood and

anxiety disorders* (pp. 41-60). Washington, DC: American Psychiatric Press.

Gadermann, A. M., Alonso, J., Vilagut, G., Zaslavsky, A. M., & Kessler, R. C. (2012).

Comorbidity and disease burden in the National Comorbidity Survey Replication

(NCS-R). *Depression and Anxiety, 29*(9), 797-806. doi:

http://dx.doi.org/10.1002/da.21924

Gannon, W. J. (1984). The formulated fix: The role reification in the diagnostic process.

    Psychology: A Journal of Human Behavior, 21(3-4), 43-48.

Gelman, S. A. (2004). Psychological essentialism in children. *Trends in Cognitive Sciences,*

    8(9), 404-409.

Green, B. L., Krupnick, J. L., & Chung, J. (2006). Impact of PTSD comorbidity on one-year

    outcomes in a depression trial. *Journal of clinical psychology, 62*(7), 815-835. doi:

    10.1002/jclp.20279

Guze, S. B. (1982). Comments on Blashfield's article. *Schizophrenia Bulletin, 8*(1), 6-7.

Haig, B. D. (2014). Investigating the psychological world: Scientific method in the

    behavioural sciences. Cambridge, MA: MIT Press.

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A review and meta-analysis of the

    genetic epidemiology of anxiety disorders. *American Journal of Psychiatry, 158*(10),

    1568-1578.

Hughes, L. D., McMurdo, M. E., & Guthrie, B. (2013). Guidelines for people not for

    diseases: The challenges of applying UK clinical guidelines to people with

    multimorbidity. *Age and ageing, 42*(1), 62-69.

Hyman, S. E. (2010). The diagnosis of mental disorders: The problem of reification. *Annual*

    review of clinical psychology, 6, 155-179. doi:

    http://dx.doi.org/10.1146/annurev.clinpsy.3.022806.091532

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010).

    Research domain criteria (RDoC): Toward a new classification framework for

    research on mental disorders. *American Journal of Psychiatry, 167*(7), 748-751.

Jablensky, A. (1991). Diagnostic criteria in psychiatry: A straitjacket or a prop? *European*

    Psychiatry, 6(6), 323-329.

Jacobs, D. H. P., & Cohen, D. P. (2012). The End of Neo-Kraepelinism. *Ethical Human Psychology and Psychiatry, 14*(2), 87-90.

Jensen, P. S. (2003). Comorbidity and child psychopathology: Recommendations for the next decade. *Journal of abnormal child psychology, 31*(3), 293-300.

Kaplan, B. J., Dewey, D. M., Crawford, S. G., & Wilson, B. N. (2001). The term comorbidity is of questionable value in reference to developmental disorders data and theory. *Journal of Learning Disabilities, 34*(6), 555-565.

Kaplan, M. H., & Feinstein, A. R. (1974). The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *Journal of Chronic Diseases, 27*, 387-404.

Keller, E. F. (2002). *Making sense of life: explaining biological development with models, metaphors, and machines*. Cambridge, MA: Harvard University Press.

Kendall, P. C., & Clarkin, J. F. (1992). Introduction to special section: Comorbidity and treatment implications. *Journal of Consulting and Clinical Psychology, 60*(6), 833.

Kendell, R. E., Cooper, J. E., Gourlay, A. J., Copeland, J. R. M., Sharpe, L., & Gurland, B. J. (1971). Diagnostic criteria of American and British psychiatrists. *Archives of General Psychiatry*, *25*(2), 123-130.

Kendell, R., & Jablensky, A. (2003). Distinguishing between the validity and utility of psychiatric diagnoses. *The American Journal of Psychiatry, 160*(1), 4-12.

Kendler, K., & Neale, M. (2010). Endophenotype: a conceptual analysis. *Molecular psychiatry, 15*(8), 789-797.

Kendler, K. S. (1996). Major depression and generalised anxiety disorder : Same genes, (partly) different environments - Revisited. *British Journal of Psychiatry, 168*(30), 68-75.

Kendler, K. S. (2012). Levels of explanation in psychiatric and substance use disorders: Implications for the development of an etiologically based nosology. *Molecular psychiatry, 17*(1), 11-21. doi: 10.1038/mp.2011.70

Kendler, K. S., & Gardner, C. O. (2011). A longitudinal etiologic model for symptoms of anxiety and depression in women. *Psychological Medicine, 41*(10), 2035-2045. doi: 10.1017/S0033291711000225

Kendler, K. S., Zachar, P., & Craver, C. (2011). What kinds of things are psychiatric disorders? *Psychological Medicine, 41*(6), 1143-1150. doi: http://dx.doi.org/10.1017/S0033291710001844

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., . . . Wang, P. S. (2003). The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA: Journal of the American Medical Association, 289*(23), 3095-3105. doi: http://dx.doi.org/10.1001/jama.289.23.3095

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 62*(6), 617-627. doi: http://dx.doi.org/10.1001/archpsyc.62.6.617

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., . . . Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the national comorbidity study. *Archives of General Psychiatry, 51*(1), 8-19. doi: http://dx.doi.org/10.1001/archpsyc.1994.03950010008002

Kessler, R. C., & Price, R. H. (1993). Primary prevention of secondary disorders: A proposal and agenda. *American Journal of Community Psychology, 21*(5), 607-633.

Klerman, G. L. (1990). Approaches to the phenomena of comorbidity. In C. R. Cloninger & J.

    D. Maser (Eds.), *Comorbidity of mood and anxiety disorders* (pp. 13-40). Washington,

    DC: American Psychiatric Press Inc.

Kline, P. (1998). Factor analysis and psychometric measurement. In *The new psychometrics:*

    Science, psychology, and measurement (pp. 51-69). London: Routledge.

Krueger, R. F. (2008). Psychometric perspectives on comorbidity. In J. E. Helzer & J. J.

    Hudziak (Eds.), *Defining psychopathology in the 21st century: DSM-V and beyond*

    (pp. 41-54).Washington, DC: American Psychiatric Publishing Inc.

Krueger, R. F., & Markon, K. E. (2006). Reinterpreting comorbidity: A model-based

    approach to understanding and classifying psychopathology. *Annual review of clinical*

    psychology, 2, 111.

Lee, S. J., Crowther, E., Keating, C., & Kulkarni, J. (2013). What is needed to deliver

    collaborative care to address comorbidity more effectively for adults with a severe

    mental illness? *Australian and New Zealand Journal of Psychiatry, 47*(4), 333-346.

    doi: 10.1177/0004867412463975

Lilienfeld, S. O. (2014). The research domain criteria (RDoC): An analysis of methodological

    and conceptual challenges. *Behaviour Research and Therapy*. doi:

    http://dx.doi.org/10.1016/j.brat.2014.07.019

Lilienfeld, S. O., Waldman, I. D., & Israel, A. C. (1994). A critical examination of the use of

    the term and concept of comorbidity in psychopathology research. *Clinical*

    Psychology: Science and Practice, 1(1), 71-83.

Maj, M. (2005a). The aftermath of the concept of 'psychiatric comorbidity'. *Psychotherapy*

    and Psychosomatics, 74(2), 67.

Maj, M. (2005b). 'Psychiatric comorbidity': An artefact of current diagnostic systems? *The British Journal of Psychiatry, 186*(3), 182-184. doi: http://dx.doi.org/10.1192/bjp.186.3.182

McLaren, N. (2011). Cells, circuits, and syndromes: a critical commentary on the NIMH Research Domain Criteria project. *Ethical Human Psychology and Psychiatry, 13*(3), 229-236.

Meehl, P. E. (2001). Comorbidity and taxometrics. *Clinical Psychology-Science and Practice, 8*(4), 507-519. doi: 10.1093/clipsy/8.4.507

Meyer, C., Rumpf, H. J., Hapke, U., & John, U. (2004). Impact of psychiatric disorders in the general population: Satisfaction with life and the influence of comorbidity and disorder duration. *Social psychiatry and psychiatric epidemiology, 39*(6), 435-441.

Mezzich, J. E., Ahn, D. W., Fabrega, H., & Pilkonis, P. A. (1990). Patterns of psyhiatric comorbidity in a large population presenting for care. In C. R. Cloninger & J. D. Maser (Eds.), *Comorbidity of mood and anxiety disorders* (pp. 189-204). Washington, DC: Amerian Psychiatric Press.

Ministry of Health. (2014). Health Targets. Retreived from http://www.health.govt.nz/new-zealand-health-system/health-targets

Mitchell, S. D. (2008). Explaining Complex Behaviour. In K. S. Kendler & J. Parnas (Eds.), *Philosophical issues in psychiatry: Explanation, phenomenology, and nosology* (pp. 19-37). Baltimore, Maryland: The Johns Hopkins University Press.

Mitchell, S. D. (2009). *Unsimple truths: Science, complexity, and policy*. Chicago, IL: University of Chicago Press.

Mojtabai, R., & Olfson, M. (2010). National trends in psychotropic medication polypharmacy in office-based psychiatry. *Archives of General Psychiatry, 67*(1), 26-36.

Morris, S. E., & Cuthbert, B. N. (2012). Research Domain Criteria: Cognitive systems, neural

circuits, and dimensions of behavior. *Dialogues Clin Neurosci, 14*(1), 29-37.

Mueller, P. S., Plevak, D. J., & Rummans, T. A. (2001). Religious involvement, spirituality,

and medicine: Implications for clinical practice. *Mayo Clinic Proceedings, 76*(12),

1225-1235.

Murphy, D. (2006). *Psychiatry in the scientific image*. Cambridge, MA: MIT Press.

Murphy, D. L. (2008). Levels of Explanation in Psychiatry. In K. S. kendler & J. Parnas

(Eds.), *Philosophical issues in psychiatry: Explanation, phenomenology, and

nosology* (pp. 99-124). Baltimore, Maryland: The Johns Hopkins University Press.

National Institute for Health and Clinical Excellence. (2009). Depression in adults: The

treatment and management of depression in adults, CG90. Manchester, UK: NICE.

Retreived from http://www. nice.org.uk/guidance/cg90

National Institute of Mental Health (NIMH). (2014). Research Domain Criteria. Retrieved

from http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml

Neale, M. C., & Kendler, K. S. (1995). Models of comorbidity for multifactorial disorders.

American journal of human genetics, 57(4), 935.

NIMH. (2014). Strategic Objective 1. Retrieved from http://www.nimh.nih.gov/research-

priorities/strategic-objectives/strategic-objective-1.shtml

Olatunji, B. O., Cisler, J. M., & Tolin, D. F. (2010). A meta-analysis of the influence of

comorbidity on treatment outcome in the anxiety disorders. *Clinical Psychology

Review, 30*(6), 642-654. doi: 10.1016/j.cpr.2010.04.008

Oulis, P. (2010). Nature and main kinds of psychopathological mechanisms. *Dialogues in

Philosophy, Mental and Neuro Sciences 3(2)*: 27-34.

Pennington, B. F. (2014). Scientific Explanation. In *Explaining Abnormal Behavior : A

Cognitive Neuroscience Perspective* (pp.3-8). New York, NY: Guilford Publications.

Pessoa, L. (2013). Network Perspective on Brain Function *The cognitive-emotional brain: from interactions to integration* (pp. 193-227). Cambridge, Massachusetts: The MIT Press.

Phelan, M., Stradins, L., & Morrison, S. (2001). Physical health of people with severe mental illness. *British Medical Journal, 322*(7284), 443-444.

Phillips, J., Frances, A., Cerullo, M. A., Chardavoyne, J., Decker, H. S., First, M. B., . . . Zachar, P. (2012a). The six most essential questions in psychiatric diagnosis: A pluralogue part 1: Conceptual and definitional issues in psychiatric diagnosis. *Philosophy, Ethics, and Humanities in Medicine, 7*.

Phillips, J., Frances, A., Cerullo, M. A., Chardavoyne, J., Decker, H. S., First, M. B., . . . Zachar, P. (2012b). The six most essential questions in psychiatric diagnosis: A pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philosophy, Ethics, and Humanities in Medicine, 7*.

Pincus, H. A. (2012). DSM-IV: Context, concepts and controversies. In K. S. Kendler & J. Parnas (Eds.), *Philosophical issues in psychiatry II: Nosology* (pp. 145-160). Oxford, UK: Oxford University Press.

Pincus, H. A., Tew Jr, J. D., & First, M. B. (2004). Psychiatric comorbidity: is more less? *World Psychiatry, 3*(1), 18.

Piotrowski, N. A. (2007). Comorbidity and psychological science: Does one size fit all? *Clinical Psychology-Science and Practice, 14*(1), 6-19. doi: 10.1111/j.1468-2850.2007.00057.x

Preisig, M., Merikangas, K., & Angst, J. (2001). Clinical significance and comorbidity of subthreshold depression and anxiety in the community. *Acta Psychiatrica Scandinavica, 104*(2), 96-103.

Preston, G. A., & Weinberger, D. R. (2005). Intermediate phenotypes in schizophrenia: A

selective review. *Dialogues in clinical neuroscience, 7*(2), 165.

Prince, M., Patel, V., Saxena, S., Maj, M., & et al. (2007). Global Mental Health 1: No health

without mental health. *The Lancet, 370*(9590), 859-877. doi:

10.1371/joumal.pmed.00304424

Regier, D. A., Burke, J. D., & Burke, K. C. (1990). Comorbidity of affective and anxiety

disorders in the NIMH epidemiologic catchment area program. In C. R. Cloninger &

J. D. Maser (Eds.), *Comorbidity of mood and anxiety disorders* (pp. 113-122).

Washington, DC: American Psychiatric Press.

Robins, E., & Guze, S. B. (1970). Establishment of diagnostic validity in psychiatric illness:

Its application to schizophrenia. *American Journal of Psychiatry, 126*(7), 983-987.

Rosenhan, D. L. (1973). On being sane in insane places. *Science, 179*(4070), 250-258. doi:

http://dx.doi.org/10.1126/science.179.4070.250

Ruzzano, L., Borsboom, D., & Geurts, H. M. (2014). Repetitive behaviors in autism and

obsessive–compulsive disorder: New perspectives from a network analysis. *Journal of

Autism and Developmental Disorders*. doi: http://dx.doi.org/10.1007/s10803-014-

2204-9

Sachs, G., Peters, A., Sylvia, L., & Grunze, H. (2014). Polypharmacy and bipolar disorder:

What's personality got to do with it? *The International Journal of

Neuropsychopharmacology, 17*(07), 1053-1061.

Schaffner, K. (2008). Etiological Models in Psychiatry: Reductive and Non-reductive

Approaches. In K. S. Kendler & J. Parnas (Eds.), *Philosophical issues in psychiatry:

Explanation, phenomenology, and nosology* (pp. 48-89). Baltimore, Maryland: The

Johns Hopkins University Press.

Schmittmann, V. D., Cramer, A. O. J., Waldorp, L. J., Epskamp, S., Kievit, R. A., &
    Borsboom, D. (2013). Deconstructing the construct: A network perspective on
    psychological phenomena. *New Ideas in Psychology, 31*(1), 43-53. doi:
    http://dx.doi.org/10.1016/j.newideapsych.2011.02.007

Schor, E. L., Billingsley, M. M., Golden, A. L., McMillan, J. A., Meloy, L. D., Pendarvis, B.
    C., . . . Milazzo, C. (2003). Report of the task force on the family. *Pediatrics, 111*(6),
    1541-1571.

Schulte, S. J., Meier, P. S., & Stirling, J. (2011). Dual diagnosis clients' treatment satisfaction:
    A systematic review. *BMC Psychiatry, 11*. doi: 10.1186/1471-244x-11-64

Shafran, R., Clark, D., Fairburn, C., Arntz, A., Barlow, D., Ehlers, A., . . . Ost, L. (2009).
    Mind the gap: Improving the dissemination of CBT. *Behaviour Research and
    Therapy, 47*(11), 902-909.

Slade, T., Johnston, A., Oakley Browne, M. A., Andrews, G., & Whiteford, H. (2009). 2007
    National Survey of Mental Health and Wellbeing: Methods and key findings.
    Australasian Psychiatry, 43(7), 594-605.

Sloman, S. (2005). What is a cause? In *Causal Models: How People Think about the World
    and Its Alternatives* (pp. 21-35). New York: Oxford University Press.

Spitzer, R. L. (1994). Psychiatric "Co-occurrence"? I'll Stick with "Comorbidlty". *Clinical
    Psychology: Science and Practice, 1*(1), 88-92.

Spitzer, R. L., Cohen, J., & Fleiss, J. L. (1967). Quantification of agreement in psychiatric
    diagnosis: A new approach. *Archives of General Psychiatry, 17*(1), 83-87. doi:
    http://dx.doi.org/10.1001/archpsyc.1967.01730250085012

Spitzer RL, Endicott J, Robins E. (1975). Research diagnostic criteria.
    Psychopharmacological Bulletin, 11, 22–25.

Spitzer, R. L., & Fleiss, J. L. (1974). A re-analysis of the reliability of psychiatric diagnosis. *The British Journal of Psychiatry, 125*, 341-347. Doi: http://dx.doi.org/10.1192/bjp.125.4.341

Spitzer, R. L., Forman, J. B., & Nee, J. (1979). DSM-III field trials: I. Initial interrater diagnostic reliability. *The American Journal of Psychiatry, 136*(6), 815-817.

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of General Psychiatry, 60*(12), 1187-1192.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry, 157*(10), 1552-1562.

Swendsen, J. D., & Merikangas, K. R. (2000). The comorbidity of depression and substance use disorders. *Clinical Psychology Review, 20*(2), 173-189.

Szasz, T. S. (1960). The myth of mental illness. *American Psychologist, 15*(2), 113-118. doi: http://dx.doi.org/10.1037/h0046535

Thagard, P. (1989). Explanatory coherence. *Behavioral and Brain Sciences, 12*(03), 435-467.

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., . . . Team, S. S. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *American Journal of Psychiatry, 163*(1), 28-40. doi: 10.1176/appi.ajp.163.1.28

Vaidyanathan, U., Patrick, C. J., & Iacono, W. G. (2011). Patterns of comorbidity among mental disorders: A person-centered approach. *Comprehensive Psychiatry, 52*(5), 527-535. doi: http://dx.doi.org/10.1016/j.comppsych.2010.10.006

Valderas, J. M., Starfield, B., Sibbald, B., Salisbury, C., & Roland, M. (2009). Defining
comorbidity: Implications for understanding health and health services. *The Annals of
Family Medicine, 7*(4), 357-363.

van de Leemput, I. A., Wichers, M., Cramer, A. O. J., Borsboom, D., Tuerlinckx, F., Kuppens,
P., . . . Scheffer, M. (2014). Critical slowing down as early warning for the onset and
termination of depression. *PNAS Proceedings of the National Academy of Sciences of
the United States of America, 111*(1), 87-92. doi:
http://dx.doi.org/10.1073/pnas.1312114110

van den Akker, M., Buntinx, F., & Knottnerus, J. A. (1996). Comorbidity or multimorbidity:
What's in a name? A review of literature. *European Journal of General Practice, 2*(2),
65-70.

Van Der Maas, H. L. J., Dolan, C. V., Grasman, R. P. P. P., Wicherts, J. M., Huizenga, H. M.,
& Raijmakers, M. E. J. (2006). A dynamical model of general intelligence: The
positive manifold of intelligence by mutualism. *Psychological Review, 113*(4), 842-
861. doi: http://dx.doi.org/10.1037/0033-295X.113.4.842

Wagner, T., Krampe, H., Stawicki, S., Reinhold, J., Jahn, H., Mahlke, K., . . . Ehrenreich, H.
(2004). Substantial decrease of psychiatric comorbidity in chronic alcoholics upon
integrated outpatient treatment: Results of a prospective study. *Journal of Psychiatric
Research, 38*(6), 619-635. doi: 10.1016/j.jpsychires.2004.04.007

Wakefield, J. C. (1992). The concept of mental disorder: On the boundary between biological
facts and social values. *The American Psychologist, 47*(3), 373-388. doi:
10.1037/0003-066X.47.3.373

Wakefield, J. C. (2007). The concept of mental disorder: Diagnostic implications of the
harmful dysfunction analysis. *World Psychiatry : Official Journal of the World
Psychiatric Association (WPA), 6*(3), 149-156.

Weinstock, L. M., Gaudiano, B. A., Epstein-Lubow, G., Tezanos, K., Celis-deHoyos, C. E., &
Miller, I. W. (2014). Medication burden in bipolar disorder: A chart review of patients
at psychiatric hospital admission. *Psychiatry Research, 216*(1), 24-30.

Widiger, T. A., & Shea, T. (1991). Differentiation of Axis I and Axis II disorders. *Journal of
Abnormal Psychology, 100*(3), 399-406. doi: http://dx.doi.org/10.1037/0021-
843X.100.3.399

Woodward, J. F. (2008). Cause and Explanation in Psychiatry: An Interventionist Perspective.
In K. S. Kendler & J. Parnas (Eds.), *Philosophical issues in psychiatry: Explanation,
phenomenology, and nosology* (pp. 132-183). Baltimore, Maryland: The Johns
Hopkins University Press.

World Health Organization. (1992). The ICD-10 classification of mental and behavioural
disorders: Clinical descriptions and diagnostic guidelines.

Zachar, P. (2000). Psychiatric disorders are not natural kinds. *Philosophy, Psychiatry, &
Psychology, 7*(3), 167-182.

Zachar, P. (2009). Psychiatric comorbidity: More than a Kuhnian anomaly. *Philosophy,
Psychiatry, & Psychology, 16*(1), 13-22. doi: http://dx.doi.org/10.1353/ppp.0.0212

Zachar, P. (2014). *A Metaphysics of Psychopathology*: MIT Press.

Zachar, P., & Kendler, K. S. (2007). Psychiatric disorders: A conceptual taxonomy. *The
American Journal of Psychiatry, 164*(4), 557-565. doi:
http://dx.doi.org/10.1176/appi.ajp.164.4.557

Zimmerman, M., & Mattia, J. I. (1999). Psychiatric diagnosis in clinical practice: Is
comorbidity being missed? *Comprehensive Psychiatry, 40*(3), 182-191.