The transition of modern diagnostic frameworks: A critical evaluation of the RDoC and network based models against traditional classification systems for predictive diagnosis.

**Premise**

The formation of the Research Domain Criteria Project (RDoC) in 2008 has resulted in a plethora of quantitative research, facilitating the modern classification of mental disorders, without the need for descriptive phenomenology. The strategic initiative, proposed by the National Institute of Mental Health (NIMH), provides a combination of grant funding and research contracts to facilitate the construction of a comprehensive platform for future research in the literature. This platform comprises of both neurological and behavioural evidence, providing an alternative diagnostic criteria for various psychological disorders. However, despite proven accuracy, the framework has yet to penetrate clinical psychiatric practice and the renowned DSM (Diagnostic Statistical manual of Mental Disorders) and ICD (International Classification of diseases) classification systems, holding professional judgement and experience at the centre of clinical diagnosis.

Modern RDoC endorsed research incorporates neurological biomarkers and behavioural patterns to facilitate the traditional classification factors. These quantitative criteria are capable of deriving more than just immediate psychiatric diagnosis with implementation of the systems extending towards neurodegenerative and progressive diseases alike. The variety of modern diagnostic criteria available is beginning to inform complex network models capable of describing the common behaviours and symptoms shared between mental disorders. Moreover, the further distinction of pre-clinical and prodromal symptoms enables an essentially predictive diagnosis of individuals at increased risk of forming these disorders. This pre-emptive modelling is the focal point of this essay, as modern research incorporating big data and time series forecasting has allowed for the pre-onset biological and behavioural deviations responsible for the development of progressive disorders such as: psychosis and Alzheimer’s disease (AD) to be accurately predicted.

The traditional judgemental, qualitative forecasting present in the DSM and ICD diagnostic manual demonstrates a large contrast in the information provided towards classification and predictive power, in comparison quantitative biomarkers. However, the core benefit of these judgemental systems is that they are grounded in experience. This basis results in relevant environmental and behavioural factors, otherwise overlooked in modern RDoC models due to the lack of extensive measurement techniques, omitting important qualitative pre-onset factors that do not align with the solely quantifiable diagnostic criteria. Instead, by incorporating both frameworks into a dynamic and comprehensive classification system, composite forecasting models have the potential to facilitate early
diagnosis of progressive disorders and diseases alike, as well as providing a foundation for future treatment methods and interventions for high-risk individuals.

In this essay I will evaluate traditional classification systems, alongside modern quantitative diagnostic criteria through their application to both neurodegenerative diseases (AD), as well as psychological disorders (Psychosis). The focal argument simultaneously centres about the system’s quantitative versus qualitative methods in regards to forecasting and the efficiency of identifying individuals at increased risk of developing mental disorders. Before finally, highlighting the importance of professional judgement when constructing new comprehensive models for an alternative perspective on early diagnosis, whilst examining potential avenues for preventative treatment methods in the future.

**Traditional Methods**

**Background**

Traditional classification frameworks such as the DSM and ICD manuals feature a series of diagnostic criteria, formed based upon consensus between multiple expert psychiatrists. Whilst the central contribution is derived from scientific evidence, revisions to the fundamental diagnostic structure are heavily reliant on previous professional experience and qualitative understanding of those in the field itself (dsm5.org, systems.hscic.gov.uk). The traditional system has been criticised however, as the recent revisions: DSM-V and ICD-10, fail to incorporate modern neurological and biological evidence, especially in regards to the classification of mental disorders (Belluck & Carey, 2013). Through the use of structured clinical interviews and certain standardised cognitive tests, professional psychiatrists examine individuals based upon a range of pseudo-quantitative diagnostic criteria. These criteria represent qualitative ideas, organised in the form of a systematic quota for clinical diagnosis.

Over the past 60 years the DSM and ICD diagnostic systems have been applied to variety of emergent psychological and neurodevelopmental disorders alike. This diverse application resulted in the systems becoming the international standards for psychological diagnosis in many clinical practices. However in the years that followed, research began to challenge both the reliability and validity of the diagnostic methods, in particular the DSM-III based upon increasing evidence of common false positive diagnoses (Williams et al., 1992). Despite this, supporters argue the qualitative nature of the clinical interviews forgoes the excess constraints of facilitate reliability, to allow for more diverse information to be gathered. Recent criticism remains centred upon this principle, particularly when extending the application of these manuals as predictive tools; we see the propensity for minuscule test-retest variability to fundamentally determine the difference between normality and clinical distinctions (Zausner et al., 2011).
Similar modern evidence targets the diagnostic criteria themselves, elaborating that the background symptoms of clinical disorders are formed through a network of contributory factors. The DSM and ICD representations are becoming increasingly detracted from the true nature of these disorders by building upon previously defined, by rarely recently endorsed attribution biases (Tversky & Kahneman, 1974). This is demonstrated in a recent review of the overlap between common psychiatric diagnoses utilising DSM-5 criteria (Regier et al., 2013). Attribution bias may also impact the interpretation of the clinical interview itself, as psychiatrists regularly rely upon previous experiences to inform diagnosis. This raises further issues of cultural difference in qualitative diagnosis and diagnostic inequality (Widiger & Sankis, 2000).

**PSYCHOSIS**

The application of traditional classification mechanisms for the early diagnosis of psychosis remains fundamentally ingrained into the minds of many clinical and academic professionals alike. The advantages of the qualitative diagnostic criteria remain imbedded in the freedom the clinical interview and subsequent analysis evoke. Some researches describe the system at an evaluation of consciousness, able to describe symptoms that modern biological techniques may find impossible to quantify (Cuthbert, 2014). This argument remains the central foundation of the widely adopted clinical interviews today. However in regards to psychosis, in which feelings of depersonalisation, anxiety and thought pressure alter momentary consciousness. Modern clinical interviews consistently face the challenge of thought insertion, as well as the danger of inducing delusional elaboration. Recent evidence suggests patients regularly feel detached from their own experiences due to questioning techniques and are unable to articulate themselves correctly (Sass et al., 2013).

A precursor to the clinical diagnosis of early psychosis centres upon the widely renowned Comprehensive assessment at-risk of mental states (CAARMS) interview. This method modifies the traditional DSM criteria to construct a predictive test for individuals at ultra-high risk of developing psychotic disorders (Yung et al., 2005). The recent evidence associated with the reliability of CAARMS interviews seems to form a double-edged sword, with finding demonstrating 10% of UHR cases resulting in psychosis and a further 40% provided early treatment to combat the onset of the disorder after a six month period (Miyakoshi et al., 2009). Critics argue of the efficiency of the interview, as 50%
of the sample remains falsely labelled as UHR, this pre-emptive diagnosis may pose a huge negative impact for individuals in vulnerable positions. However, the label may alternatively provide a supportive and pseudo-intervention to inspire those at risk to change their lifestyle. Additionally, the sheer predictive power demonstrated here has never before been achieved in any forecasting methods (economic, weather) over the course of 12 months (Makridakis, 2000).

Similar evidence for the predictive value of traditional methods may be garnered through the success of the Prevention through Risk Identification, Management, and Education (PRIME) system for schizophrenia capable of identifying early prodromal symptoms and providing engaging treatment paradigm to counter the further development of the disorder (Miller et al., 2003). Although, the predictive forecasting value here is across a much shorter scale this evidence emphasises the capabilities of early diagnosis and treatment. Finally, recent evidence is beginning to suggest that the discovery of sub-threshold psychotic experiences in general population samples, provides effective a predictive measure, increasing the likelihood of developing psychosis three-fold (Kaymaz et al., 2012).

**Alzheimer’s Disease**

Alzheimer’s disease is a life changing neurodegenerative disorder and the most common form of dementia. The disease can result in devastating consequences for sufferers themselves, alongside wide reaching effects on the economy and health services. Modern forecasting techniques have predicted that the disease will affect 1 in 85 people globally by the year 2050 (Brookmeyer et al., 2007). Primarily associated a progressive deterioration in cognitive function, the formation of Alzheimer’s normally presents itself after the age of 65, however pre-dementia and prodromal symptoms may become apparent much earlier. Previous classification systems incorporate traditional clinical classification techniques in combination with tests of cognitive functioning to diagnose individuals experiencing early stage development of the disorder (Dubois et al., 2007).

Although the application of the DSM and ICD systems is common practice for psychological disorders, the manuals contain criteria to classify neurodegenerative disorders, such as: Alzheimer's disease. These criteria are still widely accepted throughout clinical practice, with a plethora of evidence demonstrating both validity and inter-rater reliability of the DSM-IV criteria for the diagnosis of Alzheimer’s disease (Hogervorst et al., 2003). Despite this previous success, maintaining the use of a qualitative clinical classification for a neurological disorder seems inefficient. The differences in cognitive function and behaviours selected as criteria only reflecting the neural discrepancies responsible for the development of AD. These neurological foundations become increasingly important in regards to predictive diagnosis methods, although the diagnostic criteria persist due to the previous associated legal and medical related frameworks in place to facilitate dementia diagnosis.
(Cuthbert, 2014). Further evidence of the application of the DSM in a predictive sense demonstrates the capacity for the narrow criteria to omit potential individuals at risk of developing AD, as 94 patients were disregarded not meeting criteria or exhibiting substantial memory loss, only to be later diagnosed with Alzheimer’s in future neurological trials (Tierney et al., 1996). This demonstrates that traditional classification techniques, cannot reliably extend towards predictive diagnosis, instead a fundamental understanding of the physiological precursors, responsible for the visible signs and symptoms, may be required to infer individual risk when predicting the developmental trajectories of various disorders.

**RDoC Approach**

**Background**

The RDoC approach to diagnostic research addresses the previous faults and criticisms of the traditional methods. Modern research instead centres upon quantitative data over clinical consensus when forming predictive diagnostic systems, suggesting that the psychological and neurological disorders cannot be classified via qualitative distinction. The approach provides an alternative premise, suggesting disorders result from deviation from the norm without distinction, in a non-linear continuous scale (Cuthbert, 2014). Although, this premise seemingly removed the definitive clinical ‘classification’ itself, diagnosis is replaced with a spectrum of disorders and functional impairments, each contributing towards an individual unbiased clinical assessment. This comprehensive framework allows for criteria to develop over time to account for future risk and disease progression (Kotchen et al., 2011).

The success of the approach has not arrived without criticism, in contrast to traditional methods, as RDoC research has been labelled as reductionist and an oversimplification of once rich qualitative symptoms to narrow neural discrepancies (Parnas, 2014). During the RDoC process, traditional behavioural symptoms are translated to neurological biomarkers through previous understanding of the association cortical functions responsible (Bechtel et al., 2007). The true translation of traditional symptoms is rare however, as many RDoC experience operate reverse distinction-driven paradigms, which compare neural processing in patient groups against healthy, control groups. This method for criteria selection may be positive, as research is less reliant upon previous knowledge and expertise, but results in information further removed from the potential application in a clinical setting. The proposed removal of behavioural symptoms could lead to an increasing share of the population without knowledge of clearly defined clinical diagnosis. Short of preforming yearly compulsory fMRI and MEG scans, which is highly impractical and expensive. Without these qualitative diagnostic criteria common disorders will become near impossible to define for a normal concerned individual or family member shy of a £250,000 fMRI scanner.
**PSYCHOSIS**

The clinical application of the RDoC framework centres upon the idea that symptoms are multi-faceted clinical constructs comprising of various measurable biological and environmental contributors. Therefore, the approach has received intense backing in the area of newly classified neuropsychiatric disorders, in particular the development of schizophrenia and depression. This paradigm shift towards precision medicine aims to eliminate the various preconceptions and potentially damaging biases (composite symptoms), producing a data driven, highly comprehensive diagnostic system (Perez, 2014). In regards to psychosis the wider application of RDoC has resulted in numerous positive implications for early and prodromal diagnosis. Evidence utilising auditory mismatch negativity (MMN) an automatic neural response to conflicting auditory stimuli, demonstrates the efficacy of biomarker-based classification for schizophrenia. Sufferers display a significant reduction in MMN amplitude consistent across severe, as well as early stages of the disorder (Oknina et al., 2005). Auditory MMN measurements can occur without the need for consciousness in patients, reducing the propensity for subject bias, alongside the immediate environment upon clinical analysis (Naatahen et al., 1995).

Similar supporting evidence suggests that the combination of MMR measurements with the At-Risk mental states criteria (ARMS) can produce accurate predictions of clinical onset for individuals at risk of developing psychosis (Perez et al., 2013). This evidence even extending into forecasting the time lag before onset based upon previous MMR amplitude fluctuations of time, facilitating individual risk-analysis and potential treatment methods for the interval pre-onset of psychosis (Glover et al., 2012). These mechanisms have been incorporated to facilitate early treatments and drug development as a result of the knowledge derived from RDoC imaging studies and the translation of symptoms to neurological precursors (Wong et al., 2010). Recent evidence of this treatment involves targeted cognitive training (TCT), a method designed to improve auditory information processing, implemented as a result of MMR based evidence and research (Fisher et al., 2009). These methods have been shown to produce significant increases in auditory function, global cognition, as well as quality of life in many patients with early onset or prodromal psychotic symptoms. This application demonstrates the capability of predictive diagnosis and neurological biomarkers, to drive both reliable classification and pre-emptive treatments for patients at risk of developing neuropsychiatric disorders.

**ALZHEIMER’S DISEASE**

The current state of traditional diagnosis for Alzheimer’s disease remains effective in sensitivity but low in specificity, resulting in an average 36-month delay between symptom onset and diagnosis
With the importance and potential advantages of early diagnosis growing, a vast amount of research has begun to centre upon the otherwise unknown neural connectivity and precursory biomarkers associated with Alzheimer’s disease in order to define the disease in terms of the observable symptoms in a quantifiable manor. Recent research has subsequently produced multiple specific neurological biomarkers, the primary incorporating changes in the structural atrophy of the hippocampus as negative trends related closely to the early onset and resultant development of AD (Hampel et al., 2011). This method has been adapted for clinical diagnosis and remains an extremely effective technique for measuring the impact of early interventions and cognitive training treatments. However, the application cannot expand into predictive diagnosis as hippocampal deterioration rarely occurs pre-onset, as major changes mark the manifestation of AD itself.

Conversely evidence for applicable predictive biomarkers centres upon the build up of amyloid beta plaques in the brain, these plaques become active years before the initial presentation of symptoms and cognitive dysfunction. As a result Positron emission tomography (PET) analysis can be utilised to measure early changes parietal and temporal lobe activation, which reduces based upon the quantity of Amyloid beta plaques disrupting cortical connectivity (Habeck et al., 2012). Critics however, state that amyloid beta plaques occur normally through aging, and that evaluating AD based upon a factor with heightened background activation in the majority of controls may result in diluted classification thresholds. The rapid formation of amyloid plaques in AD may instead be utilised in a form of predictive time scale analysis. Multiple measurements overtime may demonstrate a subtle, linear increase in plaques representative of healthy controls, whilst distinguishing sharp, non-linear increases and assigning risk during early onset Alzheimer’s disease.

Furthermore, increasing evidence garnered through resting state functional magnetic resonance imaging (RS-fMRI) has highlighted the default mode network (DMN), a network of functional connections activated during periods of rest and reduced when performing actions or task-based paradigms. Systematic variations in the background fluctuations and functional connectivity of the DMN are capable of quantifying the pre-onset and prodromal symptoms of AD, with 97% accuracy (Chhatalwal et al., 2013). These processes differ fundamentally from other RDoC proposed biomarkers as the regional focus upon particular cortical areas is overlooked, with significance derived from the power and efficiency of the connections between these regions.

**Network based Approach Background**

The network-based approach, formed over recent years has shadowed the rising application of RS-fMRI. The approach focuses on the benefits of globally direction network based analysis to not
only determine pre-clinical biomarkers, but to convey physiological symptoms via a network of deployed biomarkers and prior knowledge ordered based upon functional relevance and connectivity with the associated dysfunction (Erler & Linding, 2010). This analytical and diagnostic technique aims to overcome the previously addressed difficulties associated with the lack of specific spatial and temporal positioning in many modern neuropsychiatric disorders (Bateman et al., 2012).

The development graph-based post-acquisition analysis for RS-fMRI has served to further the understanding of global functional organization in the brain. The comprehensive nature of the post-acquisition method allows for the discrimination of precursory biomarkers for various disease and disorders, with recent research targeting even complex disorders such as cancer and diabetes (Ahn et al., 2006). In regards towards clinical application itself however, evidence suggests an increasingly complex process in neurodegenerative diseases such as: Alzheimer’s and frontotemporal dementia. Recent research has demonstrated the efficiency of the network-based approach in distinguishing asymptomatic and symptomatic stages of AD, through a compensatory increase in functional connectivity before onset (Wu et al., 2011). This increase serves as a compensatory mechanism to early plaque formation in the DMN, and thus has been utilised to predict the period of onset for individuals at risk of developing dementia. The forecasting paradigm mirrors those of discount factor forecasting in economics to effectively determine the timescale and propensity for AD.

The network-based approach is merited for its non-reductionist neurological, comprehensive and collaborative efforts, evoking significant impact for new clinical pre-onset classification in a variety of mental and neurological disorders. The approach does not come without certain failings however, as previously claimed solely quantitative analysis methods, remain reliant on professional decision making in regards to biomarker identification and classification. Although these relationships between functional connective and associated symptoms are widely influenced by previous literature, certain clinical symptoms such as hallucinations and delusions in schizophrenia remain largely unexplored at a connective level, reliant upon subjective professional decisions to examine or omit spontaneous signals.

INCORPORATION OF NATURAL PSYCHOLOGY

During the process of compiling and evaluating various biomarkers for clinical effectiveness, a similar dependence on decision-making arises. Particularly in the case of predictive diagnoses; I suggest the formation of a comprehensive clinical system, with classification facilitated by network driven biomarker evidence, may provide a considerable increase in accuracy and inter-rater reliability, while retaining the rich qualitative information provided by structured clinical interviews. Through the application of structured clinical judgement and the seven-column technique, healthcare providers such as the NHS maybe able to construct a constantly evolving classification system, incorporating in-depth
information for the efficiency of network and biological biomarkers alike (Clarke et al., 2004). The technique be utilised in clinical practice with results contributing to the selectively of the system and application of differing diagnostic techniques dependent upon individual circumstances and presenting symptoms. This method will provide unbiased systems based approach to predictive clinical diagnosis, capable of selecting the most suitable precursory biomarkers for predictive diagnosis [Table 1]. The system will differ from consensus driven DSM and ICD manuals in which revisions typically occur once every twenty years. By providing a platform that adapts to previous successes or failures without omitting or excluding information that may be difficult to format (qualitative, subjective patterns), the future for predictive diagnosis will grow parallel with the system itself, facilitating various opportunities for pre-emptive and preventative clinical treatments.

**Future Potential for Pre-Onset Treatment**

The recent expanse of ‘big data’ and technological progression over the past decade has enable researchers to implement vastly comprehensive systems, developed sharing similar principles to the naturalistic system stated above. For example, the Global Alzheimer’s association interactive network (GAAIN) comprising of various biological, neurological and genetic information gathered over the course of AD in over 800 individual sufferers, has been utilised to construct individual risk factors for Alzheimer’s disease (Gomez-Ramirez & Wu, 2014). This system subsequently enables those at risk to pursue novel pre-onset treatments such as learning a new language or musical instrument, in addition to potential preventative treatments utilising anti-depressants or anti-inflammatory medications (Hashioka et al., 2009). Although these treatments are novel in nature and possess very little supportive literature, simply the act of early diagnosis of risk gives patients a chance to alter the potential outcome of the disease. Many modern pre-onset treatment methods for remain untested the majority of sufferers are not able to be diagnosed pre-emptively, however this is understandable as inaccurate diagnostic systems may produce spurious false positive results, but in regards to ‘risk’ individuals are not actually classified.
Predictive findings in network-based paradigms may additionally benefit from the integration of forecasting techniques such as: time series analysis of networks, to determine connectivity patterns leading towards psychosis or neurodegenerative disorders. Future research may focus upon the functional connectivity before primary onset of psychosis, patterns of diminishing activation or compensatory increases may provide further insights into the timescale and potential for development of disorders to determine an effective window for treatment. The ability to measure the pre-onset symptom both systematically and objectively (qualitative and quantitatively) across multiple periods of time, facilitates the potential to construct routines for improvement such as TCT, whilst progressively measuring the impact they have upon underlying function dysfunctions on a network level.

CONCLUSION

Despite the inherent disadvantages associated with both traditional and biomarker driven approaches to pre-onset clinical diagnosis, the collaboration of the two contrasting paradigm in the form of network based classification system omits many disadvantages whilst retaining the positive aspects of each. In the world of clinical diagnostic forecasting, or any forecasting for that matter, the more valuable knowledge from which you may derive understanding the more accurate future predictions will become. Therefore utilising naturalistic psychological techniques such as structured judgement can effectively quantify otherwise objective information, producing valuable information which may be considered alongside neurological biomarkers to facilitate diagnosis.

A plethora of recent research is starting to incorporate network based paradigm to derive underlying global processes in a variety of complex disorders and diseases, including: cancer and diabetes. The effective management of this influx of information may facilitate a new paradigm shift towards biomarker based risk assessments in a variety of clinical settings. However, the miss management and irresponsible use of this information has the potential to facilitate global excessive distinction from normality and false positive diagnoses of individuals that may not be at risk at all. Thus, it is paramount to bolster the vulnerable objective stages of the network driven approach through standardised and structured judgement, so the predictive capacity for good (early diagnosis and treatments) are not soured by an inconsistent foundation in the literature.

REFERENCES


9. dsm5.org, systems.hscic.gov.uk


