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Delineating classical schizophrenia: Quantifying disorganization and the core deficit in classical schizophrenia and exploring their neural correlates

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Abstract

Despite the moderate efficacy of antipsychotic medication, many patients with psychotic illnesses continue to experience persisting symptoms and disability. The classical descriptions of schizophrenia by Kraepelin and Bleuler emphasize disorganization and impoverishment of mental activity together with impairment of cognition and role function. In this thesis, we examine the core classical features of disorganization, impoverishment, and cognitive dysfunction, along with impairment in role-function in psychotic illnesses. In addition, we examine the relationship between these classical features and reality distortion, the characteristic feature of florid episodes of psychosis.

Methods of quantifying disorganization and impoverishment using systematic review of three common symptom scales is presented in Chapter1, along with methods to quantify formal thought disorder (FTD) using speech and language manifestations. Cognition as a core feature is presented with supporting evidence in Chapter 2 along with rationale for neural investigation tools that we employed.

Chapter 3 presents confirmatory factor analysis (CFA) investigation of core features to identify a single latent variable of shared variance (classicality), termed putative core deficit, along with cluster analysis to try to seek the answer for dimensionality versus categorical nature of classicality. Chapter 4 presents maximum likelihood factor analysis (EFA) and cluster analysis in an independent sample with stable psychosis illness, but with advantage of availability of persistent measures of disorganization and impoverishment, in addition to current measures. Chapter 5 presents delineation of core deficit from a heterogenous multi-centre mix sample of recent onset and established schizophrenia. Chapter 6 presents neural correlates of classicality in the sample described in chapter 5. Relationship of core deficit with reality distortion and FTD is explored in all three independent samples, in addition to neural correlates.

Our results demonstrate that a single latent variable of core deficit is derived from each of the three independent samples, and we further demonstrate in two samples that core deficit predicts reality distortion as well as positive correlation with FTD measure. We argue for core deficit to be a valid and replicable marker of classicality which can be targeted with focussed interventions to potentially ameliorate the burden of psychosis and to improve outcome. Through our cluster analysis, we demonstrate that classicality data fits into dimensional nature rather than discrete categories. Our results provide evidence for post-movement beta rebound (PMBR), an electrophysiology neural marker, to be diminished in proportion to the severity of core deficit. Limitations include small sample size, cross-sectional nature of data and potential confounding effect from variables such as medication exposure. We recommend for future large-scale research and clinical efforts towards potential development of a new scale utilising severity of core deficit, along with trials of focussed psychopharmacology and neuromodulation interventions to ameliorate the severity of core deficit.

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Statement of Contributions

The research work presented in this thesis is a result of extensive collaborative work by large team of researchers led by Prof. Peter Liddle. Contributions specific to this thesis work are given below, but the list is not exhaustive:

Chapter 1: Systematic review of literature to derive disorganization and impoverishment scores was completed by me and Farhad Shokraneh and Prof. Peter Liddle. Following our series of meetings and detailed academic discussions about the lack of quantification methods for disorganization and impoverishment (psychomotor poverty), me and Prof. Liddle agreed to delineate the symptom items which can reflect the dimensions of disorganization and impoverishment from three commonly used symptom scales of PANSS, SSPI and CASH. I completed the initial literature search and extensive reading and analysis of the available literature towards such quantification of disorganization and impoverishment. I then approached Farhad Shokraneh who has expertise with systematic reviews including Cochrane reviews to help us identify any other missing literature. Farhad and I repeated the final systematic review leading to grouping of items from factor analysis results which is reported in this thesis. I took the lead in completing the literature review, analysing the results, discussing all the details in a series of supervision meetings with Prof. Liddle eventually leading to the grouping of items for disorganization and impoverishment from each of the three commonly used symptom scales. I had plans to submit the manuscript for publication, but by then the review from Shafer & Dazi was published and hence we did not go ahead with such plans.

Furthermore, I have trained myself under Prof.Liddle for the scoring of items on Thought Language Index(TLI) leading to quantification of thought disorder from speech manifestations. I have spent a considerable amount of research time towards retrieving TLI data from MISP and CONN studies along with storage and analysis. I have taken the lead along with Prof. Liddle in co-ordinating and training the registrars and MSc students who completed TLI

scoring and inter-rater reliability. TLI is the copyrighted material of Prof. Peter Liddle who has helped by sharing the relevant information from manual.

Chapter 2: I have taken the lead along with Prof. Liddle in the conceptualisation and utilisation of cognition as core of classicality. I have completed detailed systematic review of literature of cognitive impairment and its quantification in psychosis and schizophrenia along with review of symptom measures. This was a daunting task which required hundreds of hours of my research time and guided by Prof. Liddle's expertise and knowledge, I have been able to study the cognitive dysfunction as integral part of classicality along with disorganization and impoverishment. Furthermore, I have the joint lead with Prof. Liddle towards synthesising evidence till date to support Digit Symbol Substitution test (DSST) as the sensitive tool for quantification of cognitive dysfunction in psychosis spectrum disorders.

Furthermore, I completed with the structural neuroimaging analysis for SPRING study Nottingham participants (this is reported in Chapter 6) using Voxel Based Morphometry (VBM). I started as Clinical research fellow and the co-ordinating lead for Nottingham site for multi-centre study: SPRING (Study of Psychosis and the role of inflammation and GABA/Glutamate). I lead a team of clinical research nurses, registrars and the professionals from Peter Mansfield Imaging centre to complete the recruitment, data collection and analysis of clinical and neuroimaging data. I led the Nottingham site to complete the recruitment and in-fact we were able to over-recruit than the target of 20 participants per each arm of the study (Early phase, established phase and healthy controls). This task was a tremendous success for my determined efforts and diligence given the challenges of under-recruitment and slow progress of Nottingham site before I took up the co-ordinating role. Furthermore, I worked collaboratively with my colleagues from Peter Mansfield Centre to successfully complete the neuroimaging acquisition for structural and functioning measures (VBM, MRS, MEG). Further, I took the lead in storage, analysis and reporting of SPRING data. I continue to be part of

the core team of SPRING, and we are submitting our main manuscript for publication soon.

Chapter 3: PMBR analysis was completed by Lauren Gascoyne and team. PMBR results were available for our investigation. Sian Robson had published from overlapping subsample before. I led the team of speciality trainee doctors who scored PANSS, SSPI and CASH for disorganization and impoverishment. These doctors were Christina Kelly, Catherine Faruqi and Malkeet Gill. I was instrumental from conceptualisation to implementation of the study of items from three common scales to derive disorganization and impoverishment scores as alluded to before. I approached the specialty trainees who displayed research interest, helped and guided them complete the research ethics and governance training. I took the lead in getting them all trained towards the scoring of symptom scales of PANSS, SSPI and CASH and we achieved good inter-rate reliability. I completed the confirmatory factor analysis of the data reported in this chapter. I prepared the manuscript and we successfully published in Schizophrenia Bulletin with me as the leading author.

We are grateful to the original team including Prof. Peter Liddle, Elizabeth Liddle, Lena Palaniyappan and Jyothika Kumar who completed data acquisition from MISP study. I further took the lead in completing two-step cluster analysis from initial stages of finalising the appropriate method of cluster analysis to completing the statistical analysis on SPSS and reporting the results. Furthermore, the scores utilised in this chapter for disorganization and impoverishment from PANSS, CASH and SPSS symptom scales were derived by me, and team of speciality trainees as alluded to before. I led that team with co-ordination, training, inter-rater reliability and dissemination of results. Furthermore, I completed the statistical analysis in SPSS including group differences and correlation analysis.

Chapter 4: PMBR and Beta bursts values were computed by Paul Briley and the team led by Elizabeth Liddle and Peter Liddle. We are grateful to the original team including Lena Palaniyappan and Vijendra Balain who completed

the data acquisition and analysis including clinical variables. Current symptom scores, persistent symptom scores, other clinical variables and PMBR values were available to us for our investigation. Although, pre-recorded data and the symptom scores were available to us from before, I took the lead along with Prof. Liddle in the conceptualisation, design and conduct of this study analysis and reporting. I completed the maximum-likelihood factor analysis in SPSS for both persistent symptom measures and current symptom measures. I completed the two-step cluster analysis utilising persistent symptom measures and current symptom measures respectively. I co-ordinated the team of students and trainees who completed TLI scoring. Furthermore, statistical analysis tests were completed by me using SPSS.

Chapter 5 and Chapter 6: We are grateful to principal investigators Prof. Bill Deakin, Prof. Peter Liddle and Prof. Stephen Williams along with entire SPRING study team who completed the data collection. I led the Nottingham team in the successful recruitment of patients and controls (78 in total including 50 patients with schizophrenia) and with data acquisition, storage and analysis. I led the team of clinical research nurses, multi-disciplinary professionals including from faculty of Physics from Sir Peter Mansfield Imaging Centre (SPMIC) towards successful co-ordination of recruitment of eligible patients and healthy matched controls and completing screening including blood sample collection and MRI imaging data acquisition for MRS and MEG data. Furthermore, I led the co-ordinated collaborative work with multi-disciplinary colleagues from Manchester and Cardiff centre towards successful completion of the study including data acquisition, storage and analysis. Along with Prof. Peter Liddle, I took the lead in the supervision of clinical symptoms rating by all professionals involved in scoring clinical and cognitive symptoms such as PANSS, SSPI and TLI scores.

Dr. Elizabeth Liddle has taken the lead for main analysis, and we are grateful for providing us with relevant measures including site-adjusted MRS metabolite values. Lauren Gascoyne completed PMBR analysis and helped us with scores. I took the lead for VBM analysis of SPRING data from Nottingham site and jointly completed the analysis of VBM data with Dr. Sudheer Lankappa under the guidance of Prof. Peter Liddle.

I have completed all the factor analysis and cluster analysis presented in Chapters 3,4,5 and 6 along with other relevant analysis such as correlation and mean differences under the supervision of Prof. Peter Liddle and Dr. Elizabeth Liddle.

I was registered as a full-time PhD student for 6 months from February 2017 to August 2017 followed by being registered as part-time student from August 2017 until now. I do not have any conflicts of interests related to this work.

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1.1 Introduction:

1.1.1 History of schizophrenia research leading to core features

Accounts of illness resembling schizophrenia have been described in ancient Vedas, which are the backbone of Hinduism (Ashok et al., 2012) and Babylonian king Nebuchadnezzar probably suffered from schizophrenia-like psychosis (Cook, 2021). But the modern concept of schizophrenia evolved in 19th century from European psychiatrists who started describing the diseases of unknown causes. Morel described these cases as “démence précoce’ in France, whereas Clouston (Clouston, 1884; Morel, 1860) first used the phrase "adolescent insanity" in Scotland. Kahlbaum from Germany defined the catatonic syndrome (Kahlbaum, 1863) , and his pupil Hecker, identified Hebephrenia (Hecker, 1871). But Emil Kraepelin (1856–1926) was the one who suggested combining those disparate clinical presentations into a single nosological entity known as "dementia praecox" (Kraepelin, 1921). His choice of the title “dementia praecox” implied a persisting disruption of mental activity with onset in young adult life.

Furthermore, whilst appreciating the heterogeneity of the clinical disorders comprising “dementia praecox”, Kraepelin recognised that the “fundamental disorders“ which supported the concept of the disease entity were cognitive deficit (a “general decay of mental efficiency”) and avolition (“loss of mastery over volitional action”) (Kraepelin, 1921).

Disjointed and weakened volition were proposed by Kraepelin as the primary psychological processes of “dementia praecox”. Bleuler, Swiss Psychiatrist, proposed similar conception. He termed dementia praecox as "schizophrenia" because he believed that the fundamental process was "fragmentation of mind." He listed the essential symptoms that, in his opinion, were present in every case and in every phase of the disease. Among these, affective blunting and loosening of association were the primary core features 2. By looseness of associations, he implied the disruption of the threads that bind together the various aspects of thinking and he proposed that looseness of associations

was not only fundamental but primary, insofar as other symptoms arose from it (P. F. Liddle, 2019).

Such disruption of the thread which binds together the various aspects of mental activity is termed disorganization of mental activity, which manifests as both disorganization of speech (language) and disorganization of goal-directed activity (behaviour). Similarly, affective blunting described by Bleuler is prototypical of diminished mental activity, manifesting in reduced quantity and quality of speech, affect and physical activity. Such diminished mental activity is termed as psychomotor poverty or impoverishment of mental activity. Throughout this thesis work, terms of disorganization and impoverishment are used to describe these fundamental features, which can be seen in many neurological and neuropsychiatry conditions, but predominantly seen and well-studied in psychosis spectrum disorders.

Furthermore, cognitive dysfunction, as recognised by Kraepelin can be conceptualized as core feature of classical schizophrenia, along with disorganization and impoverishment of mental activity. Evidence towards disorganization, impoverishment and cognitive dysfunction being the core features of classical schizophrenia and their association with impaired role-function is given below:

1.1.2 Disorganization and Impoverishment as core features

Johnstone et al., (1978), following their investigation of alpha-flupenthixol, demonstrated that antipsychotics were more successful in treating delusions and hallucinations than in treating negative symptoms that reflect diminished level of mental activity (E. Johnstone et al., 1978). Concurrently, the development of X-ray computed tomography demonstrated that certain individuals suffering from schizophrenia possessed larger cerebral ventricles (E. C. Johnstone et al., 1976). This influenced Crow, who postulated two separate pathological processes for schizophrenia: structural brain damage producing negative symptoms and dopamine overactivity producing positive symptoms including delusions and hallucinations (Crow, 1980a).

However, Bleuler's concept of loosening of association, which was both fundamental and primary, did not fit into Crow's dichotomy. It is noteworthy that subtle formal thought disorder, manifest as vague and wandering speech was found to be poorly responsive to antipsychotic treatment (Spohn et al., 1986), but Crow considered the disordered form of thought as a positive symptom. In the subsequent years, this issue about loosening of association was addressed by investigations employing factor analysis of the symptoms of chronic schizophrenia (Arndt et al., 1991; Bilder et al., 1985; P. F. Liddle, 1987c). Three clinical syndromes were recognised from the segregation of so derived symptoms: reality distortion (delusions and hallucinations), disorganization (positive formal thought disorder, inappropriate affect, bizarre behaviour), and core negative features (blunted affect, poverty of speech, decreased spontaneous movement).

It is worth noting that the term negative symptoms encompassed items such as attentional impairment (Andreasen, 1989) which can reflect either disorganization or impoverishment (psychomotor poverty) of mental activity. Liddle (1987c) introduced the term psychomotor poverty to describe the core negative features that reflect diminished mental activity, taking into account the discrepancies from previous description of cluster of symptoms. Liddle introduced the term disorganization to describe the cluster of symptoms reflecting the disruption of mental activity akin to loosening of association. Furthermore, disorganization and psychomotor poverty were found to be associated with impaired role function by Liddle (1987c) and similar results were reported in the subsequent studies (Bowie et al., 2011).

It is important to appreciate that the range of symptoms included in the study and the makeup of the patient sample both influence the factor analysis's outcomes. A factor analysis of a large sample of early phase cases of psychosis, encompassing both affective and nonaffective psychoses, was reported by McGorry et al (1998). Four factors were reported, which included a "Bleulerian factor"; excitement; depression; and reality distortion (delusions, and hallucinations). The symptoms included in the Bleulerian

factor represented both disorganized and diminished mental activity. Though reality distortion is present in both affective and nonaffective psychoses, and depression and excitement are hallmarks of affective psychosis, it is possible that the Bleulerian symptoms are a reflection of a process unique to nonaffective psychoses such as schizophrenia. As the illness progresses, impoverishment of mental activity becomes more noticeable, and the difference between impoverishment and disorganization becomes more pronounced. In the early stages of the illness, mental impoverishment and disorganization symptoms load onto a single factor (P. F. Liddle, 2019).

With regards to non-clinical populations, it is noteworthy that three dimensions have been identified by meta-analysis and subsequent confirmatory factor analysis: disorganization, cognitive/perceptual, and interpersonal ("negative" features) (Wuthrich & Bates, 2006). These correspond reasonably well to the three symptom clusters from factor analysis in schizophrenia. Furthermore, Dominguez et al. discovered that disorganization and interpersonal deficits (negative symptoms) predict the development of overt psychosis and subsequent functional impairment in a 10-year follow-up study of adolescents (Dominguez et al., 2010). These results suggest that psychomotor poverty and/or disorganization are associated with predisposition to reality distortion typical of overt psychosis (P. F. Liddle, 2019), in addition to revealing interpersonal deficits and disorganization as risk factors for poor functional outcome.

Studies of individuals deemed to be at ultra-high risk (UHR) for psychosis also show a similar correlation between Bleulerian symptoms seen before to overt psychosis and poor long-term outcome. Ziermans et al. (Ziermans et al., 2014) found that disorganization symptoms, as measured by the Scale of Prodromal Symptoms, were highly predictive of a poor functional outcome in their 6-year follow-up study of 41 UHR adolescents.

In summary, impoverishment (psychomotor poverty) and/or disorganization not only predict later functional impairment in UHR patients and nonclinical persons with schizotypal symptoms, but they are also associated with poor

functional outcome in established illness (P. F. Liddle, 2019). Furthermore, Legge et al, in their genetic association study involving cross-sectional sample of 1220 individuals with schizophrenia, found evidence that higher levels of disorganized symptoms and lower levels of current cognitive ability were significantly associated with schizophrenia polygenic risk score, suggesting that these phenotypes are markers of increased genetic liability to schizophrenia (Legge et al., 2021). This finding is consistent with a twin study that found that the disorganized symptom dimension was a marker of genetic loading for psychotic disorders (Cardno et al., 2001)

1.1.3 Cognition as core feature

Both Kraepelin (1921) and Bleuler (1950) considered cognition as one of the core features of schizophrenia. Although cognition and clinical symptoms were previously considered different domains of schizophrenia, it was learnt later that it is important to consider the areas of shared variance, such as negative and disorganized symptoms. Liddle and colleagues found that, in cases of stable illness, each clinical syndrome was associated with specific cognitive impairment, particularly executive dysfunction (P. F. Liddle, 1987a). Cognitive impairment has been found to be a crucial determinant of functioning and outcome in schizophrenia by numerous studies (Green, 1996; Green et al., 2004; Green & Harvey, 2014). Cognitive deficits in schizophrenia have been found to be associated with disorganization and negative symptoms (Green et al., 2000; Kerns & Berenbaum, 2002). Cognitive deficits have been noticed in schizophrenia regardless of illness stage. Impairment in multiple cognitive domains are found to be associated with disorganization and negative symptoms (Green & Harvey, 2014; Greenwood et al., 2008; Subotnik et al., 2006). The concept that cognitive abnormalities are fundamental to schizophrenia and satisfy many requirements to be classified as significant "endophenotypes" is reinforced by genetic research as well (Braff et al., 2007a).

1.2 Clinical quantification of symptoms and cognitive dysfunction

1.2.1 Quantifying cognitive dysfunction in schizophrenia

Diverse cognitive impairment is reported in schizophrenia, but meta-analytic work has suggested that impairments in processing speed as indexed by performance on Digit Symbol Coding type tasks reflect one of the largest effects sizes for cognitive impairment in schizophrenia (Dickinson et al., 2007). Digit Symbol Substitution Test (DSST), which measures processing speed, working memory, associative memory, attention and executive function (Jaeger, 2018), has been found to be a sensitive tool for measuring schizophrenia specific cognitive impairment (Daderwal et al., 2022).

1.2.2 Quantifying disorganization and impoverishment

In the years following Crow's demonstration of the potential importance of negative symptoms, the most frequently used instruments for assessing the symptoms of schizophrenia were the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). Andreasen combined in the SANS and SAPS in the Comprehensive Assessment of Symptoms and History (CASH) which was designed to provide a comprehensive information base concerning the current and past signs and symptoms, premorbid functioning, cognitive functioning, sociodemographic status, treatment, and course of illness (Andreasen et al., 1992).

More recently, (Kay et al., 1987) introduced the Positive and Negative Syndrome Scale (PANNS). To date, the PANSS has become the most used scale for assessing psychotic symptoms through a semi-structured interview and has been translated into more than 40 different languages (Khan et al., 2013).

Despite the fact that neither CASH nor PANSS were designed with a view to assessing symptoms of Disorganization, factor analytic studies conducted using the SAPS, the SANS, and the PANSS have demonstrated the existence of

a disorganization dimension that has become the object of attention because it has been shown to be strongly reproducible across many studies (Peralta & Cuesta, 2001). However, some symptom items in the PANSS scale phenomena that might reflect either negative symptoms or disorganization. For example, the PANSS item, affective blunting, includes both blunted affect and inappropriate affect.

Meanwhile Liddle developed the 'Signs & Symptoms of Psychotic Illness (SSPI) scale' (P. F. Liddle, Ngan, Duffield, et al., 2002) with the aim of covering the common symptoms of psychotic illness in a jointly exhaustive but mutually exclusive manner. Factor analysis revealed five symptom dimensions: reality distortion, disorganization, psychomotor poverty, excitation and depression/anxiety. SSPI has been demonstrated to be a sensitive and reliable tool for quantifying the disorganization and impoverishment (Houenou et al., 2007)

Recent meta-analysis has confirmed five similar dimensions from PANSS scale (Shafer & Dazzi, 2019). However because several symptom items in PANSS are not mutually exclusive, there are some relatively minor differences in the character of the five PANSS dimensions compared with those identified using the SSPI.

Given the lack of established measure to quantify disorganization and impoverishment in schizophrenia, we set out derive a cluster of symptoms for each of these core features, by conducting a systematic literature review. The aim of this review was to arrive at a selection of items from each of the three commonly used symptom scales in schizophrenia (namely PANSS, SSPI, and CASH) that would define, respectively, disorganization and impoverishment.

This systematic review attempted to answer the question of which symptom items would come together as cluster/dimension from previous factor analysis studies for each of three scales (PANSS, SSPI and CASH) to help quantify the disorganization and impoverishment dimensions.

It is noteworthy that similar efforts of systematic review have been tried in the past (Peralta & Cuesta, 2001; PERALTA & CUESTA, 2007) along with individual symptom scales separately (Shafer & Dazzi, 2019). But systematic study of three commonly used scales in schizophrenia research to delineate the dimensions of disorganization and impoverishment hasn't been completed yet.

Methods

We searched Embase (via Ovid), MEDLINE (via PubMed), and PsycINFO (via Ovid) on 5 July 2019. We employed a search strategy designed to identify studies that used factor analyses to investigate the relationships between symptoms assessed using the three rating scales of interest. The search terms were refined by reviewing relevant reviews and examining controlled vocabularies from databases (MeSH, Emtree, and APA Thesaurus). An information specialist (FS) designed and tested the search strategies against the existing collection of papers from previous reviews. We ran an initial search (Table 1-1) in MEDLINE (PubMed) then we adapted it for the other databases.

Table 1-1: Medline search strategy

((Schizophrenia/Diagnosis[MH] OR Schizophrenia/Complications[MH] OR "Schizophrenia, Childhood/Diagnosis"[MH] OR (Schizophrenic Psychology[MH] AND Psychiatric Status Rating Scales[MH]) OR ("Psychiatric Status Rating Scales/Statistics and Numerical Data"[MH] AND Psychometrics[MH])) AND ("Factor Analysis, Statistical"[MH] OR Component Structure*[TI] OR Factor Model*[TI] OR Factor Structure*[TI] OR Factorial Structure*[TI] OR Symptom Dimension*[TI] OR Symptom Structure*[TI])) OR ((Psychotic Disorders/Diagnosis[MH] OR Schizophrenia/Diagnosis[MH] OR (Schizophrenia[MH] AND Syndrome[MH])) AND ("Factor Analysis, Statistical"[MH] OR "Models, Psychological"[MH] OR ((Cluster Analysis[MH] OR "Models, Psychological"[MH] OR "Models, Statistical"[MH] OR Principal Component Analysis[MH]) AND Psychiatric Status Rating Scales[MH]) OR Factor Analysis[TI] OR Formal Though*[TIAB] OR Principal Component Analys*[TIAB])) OR ((Psychotic Disorders/Diagnosis[MH] OR Schizophrenia, Disorganized/Diagnosis[MH] OR Schizophrenia[MH] OR Schizophrenia[TI]) AND ((Signs[TIAB] AND Symptoms[TIAB] AND Psychotic[TIAB] AND Illness[TIAB]) OR SSPI[TIAB] OR Psychomotor Poverty[TIAB]))

Abbreviations: [TI] = a word in the title; [TIAB] = a word in the title or abstract; [MH] = a Medical Subject Heading (MeSH) term ('exploded')

We augmented the search by examining the reference sections of selected papers.

Selection strategy

All the studies which reported the factor loadings from factor analysis of the items in each of the three scales were selected.

From the selected studies for each of the scales, the items reported in at least 20% of the published studies were included in deriving the composite measure for disorganization and impoverishment for each scale.

Inclusion criteria

All the studies which included the factor analysis leading to symptom dimensions from PANSS, SSPI, and CASH were included. Comprehensive

Assessment of Symptoms and History (CASH) includes items from the Scale for the assessment of positive symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). Studies reporting factor loadings derived from CASH or from SANS and SAPS (more than 20 in number) were selected. Numerous studies reporting factor loadings for the Positive and Negative Symptom Scale (PANSS) were found (more than 80 in number). In the case of the Signs and Symptoms of Psychotic Illness (SSPI) scale, there were fewer studies reporting factors analyses. Therefore, studies that reported scoring disorganization and impoverishment using a specified combination of relevant items were included (more than 10 in number)

Exclusion criteria

Factor analyses or symptom dimension studies using other scales such as BPRS, checklists such as the Operational Checklist for Psychotic Disorders (OPCRIT) were excluded. Studies using abbreviated forms of the scale were excluded. Studies using only the total scores of the scales were excluded if there was no evidence towards a grouping of symptom items towards factors/dimensions.

Results

The Prisma flow chart is shown in Figure 1-1. The final selection of studies included 94 studies of PANSS, 12 studies of SSPI and 28 studies of CASH (SANS & SAPS.

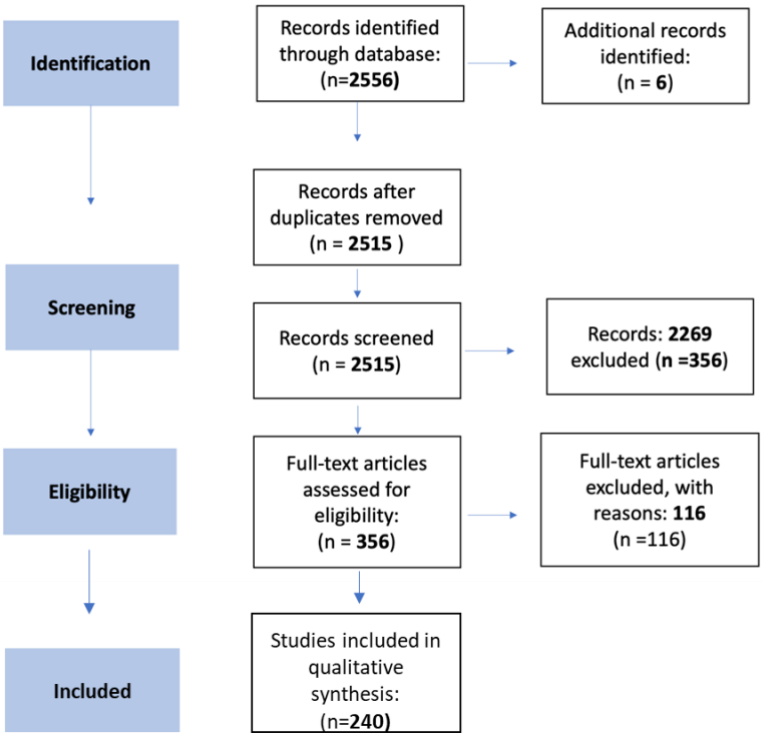

Figure 1-1: Prisma flow chart

From the selected studies for each of the scales, the items reported in at least 20% of the published studies were included in deriving the composite measure for disorganization and impoverishment for each scale. The derived composite measures of disorganization and impoverishment from each scale consisted of items as given in Table 1-2.

Table 1-2: Items constituting disorganisation and impoverishment factors from the three scales

PANSS	SSPI	CASH
	Disorganization	
P2 Conceptual disorganization	9. Attentional impairment	Bizarre behaviour global
N5 Difficulty in abstract thinking	10. Disorientation	Positive formal thought disorder global
N7 Stereotyped thinking	14. Inappropriate affect	Catatonic motor behaviour global
G5 Mannerism and posturing	17. Disordered form of thought	Inappropriate affect
G9 Unusual thought content	18. Peculiar behaviour /mannerisms	Attention global
G10 Disorientation		
G11 Poor attention		
G13 Disturbance of volition		
G15 Preoccupation		
	Impoverishment	
N1 Blunted affect	3. Anhedonia	Alogia global
N2 Emotional withdrawal	12. Underactivity	Affective flattening global
N3 Poor rapport	13. Flattened affect	
N4 Passive social withdrawal	16. Poverty of speech	
N6 Lack of spontaneity and flow		

Following our systematic review leading to deriving disorganization and impoverishment from symptom scales, we set out to derive disorganization and impoverishment from the speech and language manifestations in schizophrenia.

1.2.3 Deriving Disorganization and Impoverishment from the speech and language abnormalities in Schizophrenia

Background

Formal thought disorder has long been regarded as one of the cardinal symptoms of schizophrenia (Andreasen, 1986). The assessment of formal thought disorder (FTD) has been a challenge ever since Bleuler specified loosening of association as the core symptom of schizophrenia, being both primary and fundamental. Disorders of thought processes that are

characterized by a deficiency in organizing thought in a definite logical sequence for a certain goal are considered as FTD (Roche et al., 2015). The poverty of speech, poverty of content, the pressure of speech, distractible speech, tangentiality, derailment, incoherence, illogicality, clanging, neologisms, and word approximations were reported as more pathologic types of FTD (Andreasen, 1986).

FTD usually persists during the illness chronically in an attenuated form, yet it tends to deteriorate in acute episodes (Radanovic et al., 2013; Subotnik et al., 2006). Negative FTD, identified with the poverty of speech and poverty in the content of speech, tends to remain stable throughout schizophrenia (Andreasen and Grove, 1986). Positive FTD, determined by features like derailment, circumstantiality, tangentiality, blocking, and incoherence usually declines or disappears as the acute episode alleviates (Andreasen & Grove, 1986; Xu et al., 2014).

It is worth pointing out that many of the aspects of FTD described by Andreasen are observed in Bipolar Mood Disorder as well. The issue of identifying aspects of FTD that are characteristic of schizophrenia is challenging. In an investigation of FTD in patients with various different psychotic disorders, Andreasen and Grove (1986) found that patients with Bipolar Mood Disorder and patients with schizophrenia exhibited similar amount of positive formal thought disorders but differed in negative thought disorders, such as poverty of speech.

However, other investigators have proposed approaches to assessing FTD that do succeed in distinguishing FTD characteristic of Bipolar Disorder from that characteristic of Schizophrenia. In particular, in a comparison of mania with schizophrenia using the Thought Disorder index (TDI) developed by Johnstone and Holtzman (1979), Solovay et al (1987) found that the speech of manic patients tends to be extravagantly combinatory whereas the speech of patient with schizophrenia is more disorganized and includes peculiar words and phrases. Johnson and Holzman's TDI assesses abnormality of thought during completion of the Wechsler Adult Intelligence Scale and the Rorschach

test. The procedure employed by Johnson and Holzman is scarcely practical for routine clinical use because it takes a long time to administer, and the scoring is complex. In an attempt to develop a more practical scale sensitive to similar features to those identified by Solovay et al (1987) as characteristic of schizophrenia , Liddle developed the Thought and Language Index (TLI) (P. F. Liddle, Ngan, Caissie, et al., 2002). It is plausible that the phenomena elicited in the TLI might be characteristic of the disorganization of speech in classical schizophrenia.

Quantifying thought disorder: Thought Language Index (TLI)

The 'Thought Language Index (TLI)' is designed to measure formal thought disorder in speech samples elicited in standard conditions (P. F. Liddle, Ngan, Caissie, et al., 2002). A set of 8 unrelated representational pictures are presented one at a time, and the subject is instructed to describe each picture. Following a 1-minute period of free response, the examiner conducts a brief inquiry into the reasons for the subject's responses. In a brief version of the TLI, validated by Sommer et al (2010), the subject is required to respond to only three pictures.

In the three-picture version, the stimuli are:

- A farm scene depicting three iconic rural figures: a bare-chested farmer ploughing a field using a horse-drawn plough; a pregnant woman in rustic garb learning against a tree; and a neatly dressed young woman with a serious expression on her face in the foreground.
- A handsome man and woman. The man is looking away from the woman while the woman appears to be attempting to attract his attention.
- A dock-side picture in which a woman leans over the parapet of a bridge looking at the water below. In the background a well-built foreman is overseeing the unloading of a barge. Overhead the sun's rays emerge dramatically from behind back circular shape, apparently representing a solar eclipse.

The TLI is designed to emphasize relatively subtle disorders including peculiarity of words and sentence construction. For example, the category designated Peculiar Use of Words includes various sub-types of abnormality ranging in severity from unusual word usage through to neologisms. To calculate scores, the various sub-types are assigned weights ranging from 0.25 to 1.0, reflecting the relative severity of the disturbance of thinking. In general, responses of questionable deviance are weighted 0.25, while phenomena that are deviant are weighted 1.0.

Where possible, closely related types of thought disorders are combined into single categories in the TLI to facilitate statistical analysis of the scores. For example, in assessing loose connections between words and ideas, Andreasen distinguishes between derailment and tangentiality. Liddle (P. F. Liddle, 1987c) demonstrated that these aspects of FTD are strongly correlated in schizophrenic patients. Therefore, in the TLI, tangentiality, and derailment are combined in a single category designated “looseness”.

The categories of abnormality defined in the TLI are as follows:

Impoverishment of Thinking

- Poverty of Speech
- Weakening of Goal

Disorganization of Thinking

- Looseness
- Peculiar Word Usage
- Peculiar Sentence Construction
- Non-logical Reasoning (Peculiar Logic)
- Distractibility

Throughout this dissertation research work, PANSS derived disorganization and impoverishment have been mainly used, along with utilising SSPI measures (Chapter 3 and 4). TLI derived measures of FTD are used for comparison and contrast.

1.3 Summary

As described earlier in this chapter, disorganization and impoverishment, along with cognitive dysfunction are present in all stages of schizophrenia, from pre-morbid to chronic phase. They are poorly responsive to antipsychotic treatment. They are correlated with each other, and in-fact, disorganization and impoverishment are part of same Bleulerian factor in early phase of the illness. They are the main determinants of functioning and outcome. These features, taken together, seem to separate the affective psychosis from non-affective psychosis. Disorganization, impoverishment and cognitive dysfunction plausibly represent the manifestations of underlying core deficit, which was recognised in the classical descriptions of schizophrenia by Kraepelin and Bleuler. In light of this, Liddle proposed the term 'classical schizophrenia' which represents a near homogenous group of patients with tendency for persisting functional impairment, characterised by prominent core features of disorganization, impoverishment and cognitive dysfunction, in contrast to the heterogenous schizophrenia from DSM diagnosis.

Furthermore, Evidence till date and the clinical observations point to two kinds of presentations of individuals with stable schizophrenia. One, in which the patients continue to be articulate in their speech and some 'coherence' can still be found in their chain of thinking and behaviour. These group of patients have better chance of holding their jobs when they are not going through florid episodes of psychosis. These patients have better cognitive reserve and abilities. They might have achieved professional qualifications and skills than the second group of patients, who suffer from persisting impairment. This persisting impairment is found in the domains of functioning, cognition and academic abilities. They suffer from enhanced disorganization of mental activity and the impoverishment (psychomotor poverty), which can be identified from subtle signs and symptoms such as conceptual disorganization and poverty of speech. This second group of individuals with pronounced persisting cognitive impairment, role-function impairment, enhanced disorganization and impoverishment, is the group of

'classical schizophrenia' that Bleuler and Kraepelin believed in, 100 years ago. This group of individuals suffer from reduced pre-morbid intelligence, and it is noteworthy that all these features tend to be present in late childhood/early adulthood, before the onset of florid psychosis symptoms such as delusions and hallucinations. These impairments tend to persist through-out their life-course and the current intervention strategies do not treat/cure these features.

These cases of classical schizophrenia should be discernible from across the spectrum of psychotic disorders including Bipolar affective disorder (BPAD), schizo-affective disorder and schizophrenia.

Through the means of TLI, we have indicated that it is possible to quantify disorganization and impoverishment by using the analysis of speech samples in standard conditions. In subsequent chapters, we will also examine the degree to which TLI scores provide a useful measure of the severity of classicality of classical schizophrenia.

1.3.1 Thesis plan

Classicality is referred to as the extent to which the core features come together to account for the characteristics of classical schizophrenia as described by Kraepelin and Bleuler. We shall try to identify the shared variance of core features and try to derive a classical dimension reflective of the core features, if there is any. These investigations are reported in Chapter3, Chapter4 and Chapter5.

Chapter 2 will provide a more detailed discussion of cognitive impairment in schizophrenia, together with an outline of the measurements of brain structure and function that are likely to be relevant to understanding the mechanism of classical schizophrenia. Chapters 3 will report a study of the putative classical clinical features and relevant brain measurements in a sample of cases of psychotic illness, including both schizophrenia and bipolar mood disorder assessed in a stable phase of illness. Chapter 4 will report a

similar study of patients of psychotic illness in a stable phase of illness, but in this study, we also assessed severity of symptoms persisting throughout the course of the illness. Chapter 5 will present an examination of putative classical clinical features in a multi-centre study of schizophrenia (Study of Psychosis and the role of inflammation, Glutamate/GABA) (SPRING). Chapter 6 will present an investigation of the relationship between classical clinical features and measures of brain structure and function in the SPRING study.

Chapter 2: Cognition as core feature of classicality and proposed neural abnormalities of classicality in schizophrenia

Abstract

This chapter introduces cognition as core classical feature, along with introducing the neuroimaging techniques that are employed in our investigations of classicality in schizophrenia.

These include Voxel Based Morphometry (VBM) applied to T1 weighted MRI images to assess grey matter volume; EEG and Magnetoencephalography (MEG) to measure Post Movement Beta Rebound (PMBR); and MR Spectroscopy to quantify brain metabolites.

2.1 Introduction

2.1.1 Cognition as a core of classicality:

In addition to the brief overview in Chapter1 to support cognition as classical feature, we present here the evidence to support cognition as integral part of classicality.

Cognition has been studied as a central component in the clinical symptoms of schizophrenia since the first description. One of the main characteristics of schizophrenia is cognitive dysfunction, and previous research has demonstrated cognitive impairment affecting both daily functioning and the clinical outcome (Green & Harvey, 2014).

Both Kraepelin (1921) and Bleuler (1950) implied cognitive impairment as core feature of schizophrenia. Kraepelin attempted to classify schizophreniform illness utilising cognition as core feature, whilst Bleuler conceptualised that compound cluster such as attentional impairment would be associated with primary symptoms (anhedonia, ambivalence, autism, loosening of association) and further that accessory symptoms such as delusions and hallucinations develop from these fundamental symptoms.

In the mid-years of the twentieth century, researchers focussed on distinguishing cognitive performance observed in functional psychoses from cognitive impairments occurring in 'organic' brain diseases. The emphasis shifted to arbitrary, easily visible, positive and negative symptoms (Andreasen & Olsen, 1982; Crow, 1980b). The evidence for ventricular enlargement in schizophrenia revealed by X-ray Computed Tomography led to a re-appraisal of cognitive impairment in schizophrenia (E. C. Johnstone et al., 1978). Shared variance and overlapping of symptoms was observed among psychomotor poverty, disorganization and cognitive impairment (Bilder et al., 1985; P. F. Liddle, 1987b; Ventura et al., 2009).

Numerous studies have demonstrated that cognitive impairment is a key correlate and determinant of functioning in schizophrenia (Green, 1996;

Green et al., 2004). Moreover, antipsychotic medications do not substantially improve cognitive impairments(Keefe et al., 2007). Significant relationship between functional outcome and cognition has been consistently observed. It has been replicated and extended to include a broad spectrum of patient populations and stages of illness in multiple countries using a wide range of evaluations, including prodromal (Carrión et al., 2011). Research conducted in the previous few decades has shown that cognition and functioning are closely related. Cognitive impairments in schizophrenia are associated with disorganization, negative symptoms, and poor functional outcome (Green, 1996; Weinberger & Gallhofer, 1997)

Standardized neuropsychological tests have been utilized in previous research on schizophrenia to examine various cognitive aspects of the disorder. Research indicates that cognitive impairments are characteristic of schizophrenia at any stage of the disease; those who have recently experienced their first episode show a pattern of impairments on tasks involving learning, verbal fluency, executive functioning, and verbal memory, with information processing speed showing the greatest deficits (Addington & Addington, 1999; Kerns & Berenbaum, 2002). Additionally, previous research (Censits et al., 1997; Schuepbach et al., 2002) has demonstrated that when cognitive symptoms in schizophrenia improve, negative symptoms tend to diminish while positive symptoms do not.

Genetic studies in schizophrenia provide further evidence that cognitive impairments are unquestionably relevant to the illness and meet several important criteria for being classed as major "endophenotypes" (Braff et al., 2007b). They are quantifiable, stable, and exhibit an attenuated form among first degree relatives. Furthermore, they rank among the most heritable characteristics associated with illness, at least in families with a history of significant mental illness. Genetic research has further demonstrated that a variety of cognitive domains are heritable in families with one or more individuals with schizophrenia (Gur et al., 2007). Memory and attention are

examples of cognitive domains that seem to have a strong hereditary component.

Since Kraepelin's time, cognitive impairment has been closely studied to see if it changes depending on the stage of the disease, particularly to examine if deterioration in cognitive function is a sign of schizophrenia. The development of research on schizophrenia in the recent decades has made it possible for us to differentiate between the effects of interventions, the duration of the illness, and the phase of the illness on cognitive functioning, as well as to more precisely identify the risk states earlier (Cannon et al., 2016). It is now manifestly clear that the hallmark of cognitive impairment is not significantly different prior to the onset of diagnosable illness of schizophrenia. Furthermore, there is limited consistent evidence of cognitive decline apart from treatment resistance associated persisting impairments in established illness (Harvey et al., 2010).

Accumulating evidence indicates that cognitive function in schizophrenia may have a greater impact on quality of life and functioning, than other symptoms of the illness, such as delusions or hallucinations (Barch & Ceaser, 2012; Nuechterlein et al., 2011).

2.1.2 Cognitive impairment across psychosis spectrum

Disorders, such as schizoaffective disorder, major depression with psychosis, and bipolar disorder, are frequently referred to as "affective psychoses" because they involve difficulties with mood (depression or mania) in addition to symptoms like hallucinations or delusions. Schizophrenia is frequently referred to as a "non-affective psychosis." A crucial topic is whether affective psychoses' cognitive impairment is similar to or distinct from schizophrenia's in terms of its form and/or degree. This would support a fundamentally distinct function for cognition in emotional psychoses if the qualitative differences were different. However, if there are similarities in the pattern or profile of cognitive impairment, this finding would be in line with the theory that affective and nonaffective psychoses share some psychopathological

traits (Barch & Ceaser, 2012; Craddock et al., 2009). Empirical and meta-analytic studies have shown that the degree of cognitive impairment associated with schizophrenia is greater than that associated with bipolar disease and psychotic major depression (Depp et al., 2007; Hill et al., 2004; Krabbendam et al., 2005). The literature comparing schizophrenia and schizoaffective disorder presents mixed results. While some studies (Gooding & Tallent, 2002; T. E. Smith et al., 2002) found very similar levels of cognitive impairment in these two disorders, others (Heinrichs et al., 2008) found evidence of worse cognitive impairment in schizophrenia.

Despite evidence of a greater degree of cognitive impairment in schizophrenia compared to affective psychoses, the literature generally indicates that the profile of cognitive impairment is similar across affective psychoses and schizophrenia. Put another way, schizoaffective illnesses, bipolar disorder, psychotic major depression, and schizophrenia tend to exhibit cognitive impairment in similar domains but with a graduation in severity across disorder, with the greatest severity in schizophrenia (Depp et al., 2007; Reichenberg et al., 2009; M. J. Smith et al., 2009). Therefore, the research on cognitive dysfunction in psychosis implies that all psychoses—affective or non-affective—are associated with some level of cognitive impairment, and that this impairment tend to be less severe in schizoaffective disorder compared to schizophrenia and similarly, less severe in cases of psychotic major depression and bipolar disorder. From the perspective of understanding aetiology, it is important to emphasize, however, that affective psychoses are quite similar to schizophrenia in terms of the pattern or profile of cognitive impairment. This finding bolsters the theory that cognitive impairment and psychotic disorders share similar aetiology, as well as the increasing emphasis on identifying underlying brain processes that might manifest as core deficits that transcend diagnostic borders (Barch & Ceaser, 2012).

2.1.3 Cognitive impairment in schizophrenia: quantification

A multitude of studies have demonstrated that working memory impairment is a well-recognised deficit for people with schizophrenia. Poor visuospatial abilities or attentional control issues alone cannot account for cognitive dysregulation associated with working memory deficit (Gold et al., 2010; Hahn et al., 2010). The theory that individuals with schizophrenia have deficits with speed of information processing is also well supported by evidence. In fact, processing speed deficits as shown by performance on tasks of the type "Digit Symbol Coding" constitute one of the largest impact sizes for cognitive impairment in schizophrenia, according to meta-analytic studies (Dickinson et al., 2007). It should be noted that the Digit Symbol Coding Task is comparable to other working memory tasks in that it depends on the capacity to bind working memory representations fast and use them as a cue for performance (Barch & Ceaser, 2012).

In our investigation of classicality, we have utilised scores from Digit Symbol Substitution test (DSST) to quantify cognition in schizophrenia.

In the next section, I present the brief evidence for neural investigation tools that we employed in our research along with brief overview of relevant methods.

2.2 Neural investigation tools

2.2.1 Assessing structural integrity of brain:

Magnetic Resonance Imaging (MRI) is widely used in research and clinical studies to assess the volume of cerebrospinal fluid (CSF), white and gray matter in the brain. One of the methods most frequently used to investigate the neuroanatomy of schizophrenia is voxel-based morphometry, or VBM. It is an automated method which begins by segmenting the brain image into voxel wise measurements of gray matter volume (GMV), also known as gray matter concentration (GMC) (Ashburner & Friston, 2000). After that, these measurements can be subjected to univariate testing to find voxel clusters

where gray matter abnormalities associated with schizophrenia are observed in comparison to healthy individuals. VBM analyses have been shown to be useful for researching schizophrenia in numerous large-scale investigations (Honea et al., 2008; Segall et al., 2009) and meta analyses (Glahn et al., 2008). Gupta et al.,(2015) carried out the large schizophrenia multisite structural imaging study using VBM, totalling 1720 participants (936 controls/784 schizophrenia) from 23 sites. They report that largest gray matter difference between diagnostic groups in the network including the superior temporal gyrus, inferior frontal gyrus, and insula (Gupta et al., 2015)

The majority of VBM investigations have identified the ACC and insula as critical locations exhibiting consistent grey matter abnormalities in patients with schizophrenia, despite the method's inherent limitations (Bookstein, 2001). Glahn and colleagues discovered that the left and right insula had the greatest reduction in grey matter among a distributed network of other regions, such as the anterior cingulate and Para hippocampal gyrus, using anatomic likelihood estimation methods on coordinates reported from 31 VBM studies (1195 patients and 1262 controls) (Glahn et al., 2008).

Picó-Pérez et al. (2022) observed reductions in gray matter volume in multiple regions of brain including anterior insula and dorsal anterior cingulate cortex (ACC). This meta-analysis included a sample of 4,789 patients with schizophrenia. Right anterior cingulate and mesial temporal lobe structures (cortico-striatal-limbic hub regions) have been found to exhibit greatest progressive volume loss from high-risk individuals to patients with chronic schizophrenia after a recent diagnosis (Liloia et al., 2021). Furthermore, people with schizophrenia and psychosis have been found to exhibit greater Sylvian fissures and cingulum sulci compared to healthy controls (Faria et al., 2021; Lee et al., 2016) and concomitant volume decrease in the insula, cingulum, and planum temporalis has been consistently reported from these studies.

Above cited evidence points to the observation that gray matter volume loss in the region of salience network i,e insula and Anterior Cingulate Cortex

(ACC) has been consistently reported in the field of schizophrenia and psychosis research.

In this dissertation work, we have used VBM for deriving region of interest (ROI) volumes from ACC and Insula.

2.2.2 Assessing functional integrity in brain

One of the basic mechanisms for neural communication between various brain regions is represented by neural oscillations (Fries, 2005, 2015). The beta rhythm, or oscillations in the brain that occur between 13 and 30 Hz, is generally linked to sensory and motor processing, but it is also found to be associated with a number of cognitive processes, including working memory (WM) and decision-making and most often, endogenous, top-down regulated processing is linked to beta oscillations (Engel & Fries, 2010; Fries, 2015). Furthermore, oscillations in the beta frequency range are thought to promote long-range interactions on a cortical network level, in accordance with a "communication through coherence" hypothesis (Fries, 2015) (Benchenane et al., 2011; Kilavik et al., 2013). There is growing evidence that aberrant beta oscillations are present in certain neuropsychiatric diseases including schizophrenia (Gaetz et al., 2020; E. B. Liddle et al., 2016).

After a motor response, beta amplitude typically rebounds to values above baseline, a phenomenon known as post-movement beta rebound (PMBR) (Pfurtscheller & Lopes da Silva, 1999). When compared to healthy controls, PMBR has been found to be diminished in schizophrenia patients recruited in their stable phase. This attenuation was more pronounced in those who had more severe disorganization symptoms and a greater impairment of cognitive and role function (Briley et al., 2021; Robson et al., 2016). Findings reported by Robson and by Briley were based on analyses in patient samples overlapping with the samples of patients examined in this thesis, though neither Robson et al nor Briley et al adopted the approach to quantifying classical features as employed in this thesis work.

PMBR attenuation was found to be positively correlated with greater schizotypal personality scores in healthy control adults. This correlation was found to be strongest with subscale scores on a factor representing subclinical disorganized features, indicating that the observed link is not a side effect of the medication (Hunt et al., 2019).

Comprehending PMBR's nature and how it attenuates in psychosis may help to shed light on the mechanisms behind persisting illness . PMBR is related to inhibition of cortical activity (Pfurtscheller & Lopes da Silva, 1999) and is likely to involve GABAergic activity, potentially relevant to the mechanism of classical schizophrenia (P. F. Liddle & Liddle, 2022).

Furthermore, although the role of PMBR remains controversial, substantial evidence indicates that it plays a role in predictive coding that is potentially implicated in classical schizophrenia(Briley et al., 2021; P. F. Liddle & Liddle, 2022).

It is worth noting that beta activity typically occurs in brief bursts lasting several hundred milliseconds (Jones, 2016) and PMBR can be quantified by estimating burst rate measured in bursts /second (Briley et al., 2021).

Method of measuring PMBR:

PMBR can be derived from Electroencephalography (EEG) and Magnetoencephalography (MEG).

EEG method of deriving PMBR: Methods resulting in PMBR values that we utilised in our investigation (Chapter3) have already been published (Briley et al., 2021). To summarise, EEG data was acquired concurrently with fMRI data from 3T MRI. Participants performed two runs of n-back working memory task during scanning, with each run consisting of 0-back,1-back and 2-back subblock tasks. EEG data was recorded using standard electrodes arranged in established electrode system in an elasticated cap. Signals were amplified, stored and the data for each participant goes through pre-processing steps of: gradient artefact correction, band-pass filtering, cardio-ballistic artefact

correction, visual inspection of data, re-referencing to average reference, splitting the dataset into five-second epochs and using Independent Components Analysis (ICA). Epochs were filtered into beta band (13-30 Hz) and concatenated in time dimension to form a single group dataset, which in turn is subjected to ICA and the single component representing beta-band activity is selected. Continuous time courses of neural activity were derived by applying ICA group weights of that component on pre-processed data of each participant. Custom built tool boxes were used to identify the peaks of beta bursts which crossed the selection threshold . Mean beta bursts were computed for each participant, following which PMBR was computed by subtracting the rate in baseline windows (from 3 to 1.5 seconds before button presses) from the mean beta burst rate (from 0.5 to 1 second after button presses).

PMBR from MEG:

Methods which resulted in PMBR scores from MEG during visuomotor task that we have used in our investigations (Chapter4, Chapter6) have already been published (Gascoyne et al., 2020; Rathnaiah et al., 2020; Robson et al., 2016). To summarise, visual stimulation was provided by presenting grating patterns on a computer visual display unit for two seconds and right index finger button presses were recorded (visuo-motor task). MEG data was obtained by a custom-built 275 channel whole head CTF system. All participants completed MRI brain imaging either on the same day or different day. Trails with excessive head movements were excluded. Extracranial field signals were projected into source space by using specialist beamformer. Images consistent with spatial signature of task induced oscillatory power were computed in beta band. A resting baseline signal was estimated for each participant and the percentage change from this baseline was calculated across the trial averaged time series for beta band. In MISP study (reported in Chapter3), the percentage change from baseline for the beta desynchronisation was taken from the 0.5–1.8 s window and beta rebound signal was taken from the 2.3–4.3 s window, by using frequency range of 13-

30 Hz. In SPRING study (reported in Chapter6), noise-normalised source power estimates were obtained for movement-related beta decrease (MRBD; 0.2 to 1.2 s post-grating-offset) and post-movement beta rebound (PMBR; 2 to 3 s post-grating-offset). Furthermore, NUTMEG tool box (Dalal et al., 2008)was utilised in MISP study (Chapter3) and Fieldtrip software (Oostenveld et al., 2011) was used in SPRING study (Chapter 6).

2.2.3 Assessing brain metabolites:

To measure different metabolite levels in vivo in the brain, such as n-acetyl-aspartate (NAA), total creatine (tCr), myo-inositol (mI), glutamate (Glu), glutamine (Gln), glutathione (GSH), and GABA, magnetic resonance spectroscopy (MRS) is an established non-invasive technique. The neurometabolic correlates of alterations in cortical structure or function can be directly evaluated by MRS (Ferris et al., 2021). Glutamatergic and GABAergic systems may be investigated using MRS (Duarte & Xin, 2019).

MRS metabolite results in the field of schizophrenia research have been inconsistent, probably due to heterogeneity of schizophrenia itself coupled with heterogeneity of neuroimaging methods of data acquisition and analysis. In particular, 7 Tesla (7T) MRI has been found to be having better signal-to-noise ratio, small voxel and better spatial resolution compared to 3 T MRI (Karamat et al., 2016; van der Kolk et al., 2013). This is especially important for the assessment of Glu and Gln, as the spectral peaks representing these two metabolites can only be clearly resolved a high filed strength.

Results from proton HMRS (^{1}HMRS) studies in schizophrenia have been inconsistent with regards to the concentrations of metabolites of relevance i.e. Glu, Gln, GSH and GABA. Some studies have found reduction in all these metabolites in psychosis (Sydnor & Roalf, 2020) and some studies have found increased Glu levels (Egerton et al., 2021) particularly in treatment resistant cases. Furthermore, some studies from early phase cases report increased levels of Gln (see review by Marsman et al(2013)).

It would be potentially informative to investigate the levels of Glu, GSH, Gln and GABA, in the context of classical features as described in Chapter1.

Methods of quantifying cortical metabolites:

Values from 7T MRI data acquisition were used for our investigation in MISP study (Chapter3), but for SPRING study (Chapter 6) data was obtained using 3T MRI in Manchester & Cardiff and from 7T MRI in Nottingham. Methods have been previously published (Liddle et al.,(in press)). SPRING study: Brief methods have been described in Chapter6.

Assessing neural inflammation: Brief methods of binding potential of translocator protein (TSPO) are described in Chapter 6.

Chapter 3: Delineating classicality of classical schizophrenia and quantifying the core deficit in a stable sample of psychosis spectrum disorder: MISP

The methods and results of the confirmatory factor analysis of classical features and the investigation of the relationship between factor score and PMBR described in this chapter have been published in:

Rathnaiah, M., Liddle, E.B., Gascoyne, L., Kumar, J., Zia Ul Haq Katshu, M., Faruqi, C., Kelly, C., Gill, M., Robson, S., Brookes, M., Palaniyappan, L., Morris, P., Liddle, P.F., 2020. Quantifying the Core Deficit in Classical Schizophrenia. Schizophrenia Bulletin Open 1, sgaa031. https://doi.org/10.1093/schizbullopen/sgaa031

Abstract

The classical descriptions of schizophrenia by Kraepelin and Bleuler emphasized disorganized and impoverishment mental activity, together with impairments of cognition and function. Subsequently factor analyses have identified latent variables representing the shared variance between these classical symptoms and impairments of function. However it is not clear whether the relationship between these symptoms and disabilities are best described as dimensions of psychopathology with severity distributed continuously across cases of psychotic illness, or alternatively, reflect discrete clusters of patients. In this chapter I report an investigation employing both factor analysis and cluster analysis to examine the relationships between classical clinical features in a sample of patients in a stable phase of illness.

I conducted confirmatory factor analysis (CFA) in the sub-sample of only DSM schizophrenia to test for the feasibility of a potential single classical dimension reflecting the shared variance of disorganization, impoverishment, cognitive impairment and role-function impairment. I then performed two step cluster analysis in the entire sample including schizophrenia (Scz) and Bipolar affective disorder (BPAD) utilising the same core features, seeking to identify discrete clusters. Furthermore, I explored the neural correlates of putative classical dimension and the differences between emergent clusters.

Results from CFA confirmed that a single classical dimension, a putative core deficit, accounts for the shared variance of the classical core features and this dimension was negatively correlated with putative marker of connectivity in the motor system in brain, post-movement beta rebound (PMBR) implying that diminished connectivity in schizophrenia is associated with enhanced core deficit. Results from cluster analysis identified two clusters with good model fit, but overlapping feature of classicality was evident on further examination. Negative correlation between PMBR and putative core deficit was observed in psychosis spectrum, but not statistically significant.

These findings must be interpreted cautiously on account of the small sample size and the cross-sectional nature of the study. Nonetheless, they justify further investigation of the classical dimension as the clinical manifestation of a core pathophysiological process.

3.1 Introduction

3.1.1 Overview

In this chapter I address the challenge of identifying classical schizophrenia in a sample of patients with psychotic illness in a stable phase.

In view of the uncertainty as to whether classical schizophrenia is best described as a dimension of illness or a category of illness, I will adopt two different modes of investigation:

1. Confirmatory Factor Analysis (CFA) which will test for the existence of a single classical dimension.

For this I will only use subsample comprising of schizophrenia and schizoaffective disorder patients (Scz) and do not include participants with Bipolar Affective Disorder (BPAD). Taking into account the fact that the relationships between symptoms may be different in Scz to BPAD, I seek to identify this classical dimension in the Scz group first. It is noteworthy that even in affective disorders, cognitive impairment and role-function impairment would be part of the clinical picture, but the mediating factors might be different set of clusters of symptoms. Hence, to minimise this probable confounding effect, we investigated the pure subsample of only schizophrenia spectrum participants in our quest to unravel the classical dimension, which might share the variance among the classical features of disorganization, impoverishment and cognitive impairment along with role-function impairment. Schizo-affective disorder cases were included with Schizophrenia as one group (Scz) because of the close proximity (Santelmann et al., 2016) and shared neurobiology between both disorders (Madre et al., 2016).

2. Cluster analysis in the entire sample including Scz and BPAD cases, seeking to identify discrete clusters of patients that may include a “pure” BPAD cluster as well as a classical schizophrenia cluster.

In light of that the fact that some BPAD cases might exhibit classical features, we will include the entire sample of Scz+ BPAD in this cluster analysis. This would help ensure that BPAD cases without classical features are not going to confound the analysis.

I will test for neural correlate of the putative classical dimension and also for differences between clusters.

3.1.2 Background

Classical features

As described in Chapter 1, the classical features, identified from the work of Kraepelin (1921) and Bleuler (1950), are disorganization and impoverishment of mental activity, cognitive impairment and impaired role function. I have already laid out the methods utilised to derive the factor of disorganization and impoverishment from three symptom scales (PANSS, SSPI, CASH) in Chapter 1, along with making the case for utilising DSST as a comprehensive measure of cognitive dysfunction in schizophrenia. I made use of disorganization and impoverishment measures from three scales and DSST scores towards the core features driving the classicality of classical schizophrenia.

Dimensions vs Clusters

Current concepts of disorganization and impoverishment were derived via factor analysis (P. F. Liddle, 1987d; Shafer & Dazzi, 2019) suggesting that these features are distributed continuously in schizophrenia, albeit found to be closely related in early phase of psychosis (McGorry et al., 1998). Such dimensional description matches the clinical picture of schizophrenia, supporting our method of investigation utilising CFA of Scz cases.

Kraepelin proposed a categorical separation between BPAD and Scz, however a substantial body of evidence supports the proposition that they lie on a continuum (Craddock & Owen, 2010; Reininghaus et al., 2019; Rodrigue et al.,

2018). Derks et al.(2012) performed a latent class analysis to analyse variation in CASH rated symptoms in a very large sample of 4286 cases and identified a homogenous class of illness that they termed Kraepelinian Schizophrenia. It is noteworthy that a substantial proportion (41%) of Bipolar cases belonged to the Kraepelinian Schizophrenia class.

Hence, I propose to perform a cluster analysis that includes sample of both Scz and BPAD with a view to identify discrete clusters.

Neural measure (PMBR, MEG, visuo-motor task)

As mentioned in Chapter2, PMBR can be tested as a candidate marker for the pathophysiology of classical schizophrenia. We set out to explore the relationship of PMBR with classical dimension or the putative core deficit in the subsample of Scz as well as in the entire sample of psychosis.

3.1.3 Aims & Hypotheses

- To demonstrate through CFA that a putative single classical dimension accounting for shared variance of core features can be identified in Scz
    - To investigate the relationship between classical dimension and PMBR in Scz.
- To identify discrete patient clusters including a potential classical cluster in a sample of cases of stable psychotic illness including Scz and BPAD.
    - To derive a new classical dimension putative factor in the entire sample of Scz and BPAD
    - To delineate potential classical cluster through cluster analysis utilising core features and to confirm that clusters differ.
- Subsequent to cluster analysis, we aim to test the hypotheses that:
    - PMBR will be reduced in classical cluster compared to other clusters.

3.2 Methods and Materials

This study is part of a multimodal imaging investigation of the relationship between clinical features of psychosis and brain structure/function, Multi-Modal Imaging Study of Psychosis (MISP). Recruitment and data collection was completed by the research team before I got involved. Pre-recorded data was available for our analysis.

3.2.1 Participants

Details have been previously published (Palaniyappan and Liddle, 2014) and reproduced here with permission of authors:

Participants were recruited by research team from referrals from the local healthcare teams in Nottinghamshire, Derbyshire and Leicestershire.

Exclusion criteria were:

1) IQ below 70

2) Lifetime history of substance dependence or harmful use in the past 6 months

3) History of significant head trauma or medical conditions likely to have appreciable neurological or psychiatric effects

4) Contraindications for MRI safety assessed by a standardized safety screening questionnaire.

A personal or family history of psychotic illness was an exclusion criterion for controls.

Patients were included if:

a) they satisfied DSM IV criteria for schizophrenia or schizoaffective disorder; this was determined by a consensus meeting in accordance with the best estimate procedure described by Leckman (Leckman et al., 1982)utilizing

evidence regarding current clinical state and a retrospective review of case notes

b) if they satisfied the criteria for stable phase of illness, defined as a change of no more than 10 points in their Social and Occupational Functioning Assessment Scale (SOFAS) score (defined in DSM-IV) between assessment 6 weeks prior to and immediately prior to study participation

Clinical and demographic features of the participants for CFA have already been published in Rathnaiah et al., (2020) and Kumar et al., (J. Kumar et al., 2020) and replicated here with permission of authors:

Table 3-1: Demographic and clinical features

	Healthy controls (n=34)	**Patients with bipolar disorder (n=20)**	**Patients with schizophrenia (n=39)**	**F/X2**
Gender (male/female)	23/11	13/7	30/9	x2=1.2, p=0.55
Handedness (right/left)	31/3	18/2	34/5	x2=4.0, p=0.41
Age in years (SD)	33.76(9.0)	35.25(10.8)	34.18(9.3)	F=0.16, p=0.86
Mean parental NS-SEC (SD)	2.00(1.3)	1.8(1.2)	2.4(1.5)	F=1.33, p=0.27
Mean total SSPI score	-	7.50(8.1)	11.74(7.4)	F=3.78, p=0.06
Mean PANSS total		44.11(8.89)	49.75 (15.60)	

NS-SEC: National Statistics – Socio Economic Status; SD: standard deviation; SSPI – Symptoms and Signs of Psychotic Illness. The total SSPI score can vary between 0 and 80; PANSS – Positive and Negative Syndrome Scale.

Total of 46 healthy controls and 40 patients with schizophrenia and 1 patient with schizoaffective disorder were recruited. Sample for CFA included total of 40 patients with Scz (30 males, 10 females) with mean age of 28.08 years, out of which only one participant was with schizoaffective disorder. Clinical and demographic features of sample of psychosis cases has been previously published (Palaniyappan & Liddle, 2014). Briefly, the sample utilised for cluster

analysis included 14 BPAD patients (8 males, 6 females, mean age 32.7 years) in addition to 40 Scz patients.

3.2.2 Measures

A videotaped semi-standardized clinical interview was conducted by the research team with the aim of eliciting the symptoms of psychotic illness necessary for the SSPI score (P. F. Liddle, Ngan, Duffield, et al., 2002).(Liddle et al., 2002). These videotaped interviews were made available to us, the group of four clinically qualified raters, along with research team lead, Prof. Peter Liddle. We assessed the symptoms based on the video recordings, applying the scoring criteria for each of the three scales accordingly. All symptom items were assessed for the SSPI and PANSS; for the CASH, the symptom subscales related to the disorganization and impoverishment dimensions were scored for the appearance, behaviour, and speech aspects. Since the items on the Avolition and Anhedonia CASH subscales are mostly dependent on social and role function performance, we did not assign scores to them. With α =.87 for the PANSS total, α =.83 for the SSPI total, and α =.79 for the CASH global items, the five scorers demonstrated good inter-rater reliability.

Measures of SOFAS for functioning, DSST for cognitive function and QuickIQ test for Intelligence Quotient (IQ) had been previously scored by the research team and they were made available to us for analysis. Furthermore, for each patient, the dose of antipsychotic medication which was calculated before using the defined daily dose (DDD) was available for analysis.

3.2.3 Quantification of classical features:

As reported in Chapter1, measures of disorganization and impoverishment were derived from three symptom scales (PANSS, SSPI and CASH). Reality Distortion score which was computed by summing up SSPI delusion and hallucination scores, were available for analysis. Furthermore, disorganization and impoverishment derived separately from speech sample using Thought

Language Index (TLI) were available as well. Method of deriving TLI disorganization and impoverishment has already been reported in Chapter1.

3.2.4 Confirmatory Factor Analysis

Methods have been already published in Rathnaiah et al., (2020) as previously mentioned and reproduced here with permission from authors. I used Principal Component Analysis (PCA) at the outset to produce composite scores for the Disorganization and Impoverishment symptom dimensions, respectively. For every dimension, I created a composite score that reflected the variance shared by all three rating scales by entering the three scores from the three symptom scales into a PCA and deriving factor values for the first principal component. Clinical score correlations were calculated using Pearson correlation coefficients.

For statistical analyses, IBM SPSS statistical software version 24.0 was utilized. To determine if a single latent variable could explain the shared variance of the proposed core deficit variables (composite Disorganization, composite Impoverishment, DSST, and SOFAS), I performed a Confirmatory Factor Analysis (CFA) using SPSS AMOS 24.0. In factor extraction, maximum likelihood method was used. The goodness of fit index (GFI) of ≥.95, the root means square error of approximation (RMSEA) of <.06, and the model chi-square test not being statistically significant were among the indices of absolute fit used to assess the fit of the model (Schreiber et al., 2006).

The factor scores for this model were then obtained using the regression imputation method as a measure of putative core deficit (DiStefano et al., 2009). I next calculated the Pearson correlation between the core deficit score and PMBR in Scz sample in order to investigate the possibility that a higher core deficit severity was linked to diminished PMBR. The factor scores for this model were then obtained using the regression imputation method as a measure of putative core deficit (DiStefano et al., 2019).

Cluster analysis

To draw close to the practical real-world measurement of disorganization and impoverishment particularly in clinical settings, PANSS scores of disorganization and impoverishment were used for cluster analysis as candidate measures. These PANSS scores were log transformed (base 10) as they were not normally distributed. DSST was included as cognition measure. Variables included in two-step cluster analysis were: PANSS disorganization, PANSS impoverishment, Cognition (DSST) and role-function measure (SOFAS).

The Two-Step cluster analysis is a hybrid method that selects the best subgroup model using a probabilistic technique akin to latent class analysis, after groups are separated using a distance measure (Gelbard et al., 2007). It has been found to be most reliable in terms of number of subgroups identified, classification probability of individuals to subgroups and the reproducibility of findings on clinical data (Benassi et al., 2020; Kent et al., 2014). Two-step cluster analysis was employed in SPSS version 29.

Distance measure was conducted on the basis of Log-Likelihood. Clustering criterion followed was as per Schwarz's Bayesian Criterion (BIC). Furthermore, the number of clusters were determined automatically.

Putative Core deficit or classical dimension for the entire sample of psychosis (Scz+BPAD) was derived from principal component analysis (maximum-likelihood method) using PANSS derived disorganization and impoverishment, along with cognition measure (DSST) and role-function (SOFAS).

3.2.5 Post movement Beta rebound (PMBR)

Methods of PMBR data acquisition and analysis have been previously published as alluded to before (Rathnaiah et al., 2020; Robson et al., 2016) and reproduced here with permission of authors:

A 275 channel whole head CTF system (MISL, Coquitlam, Canada) Magnetoencephalography (MEG) with a third-order synthetic gradiometer

setup was used to record during a visuomotor task performed by the participants. The task required them to press a button with their right index finger at a regular, self-paced rate for two seconds while a grating appeared on the screen. The visuomotor task and the acquisition of MEG data have been described in previous publications (Robson et al., 2016). Further analysis was carried out following the completion of pre-processing and artifact inspection of the MEG data. Due to insufficient structural MRI brain scans (eight out of forty patients) and patients' excessive movement (four out of forty patients), the PMBR analysis did not include all patients. Due to technical difficulties with data collection and the lack of a structural MRI scan, one participant in the control group was removed from the study. 28 patients and 42 healthy controls were subjected to the PMBR analysis because of this.

To begin pre-processing the MEG data, the data was bandpass-filtered from 1 to 150 Hz, artificial third-order gradiometers were used, and DC offset correction was applied. A researcher well-versed in MEG analysis discarded all experiments containing large blinks or other artefacts (L.G.). Between zero and eight and a half seconds following the commencement of the visual grating, each data point was recorded. All trials had their head motions recorded, and those that deviated more than 7 mm (the standard distance from the starting point) were discarded. Membership in the group was unknown when the data was pre-processed.

For a more thorough evaluation of the pre-processed data, FieldTrip (version 20161011) was utilized (Oostenveld et al., 2011). The participant's coregistered MRI was imported and segmented using FieldTrip's default segmentation. The collected MEG data were downsampled to 300 Hz after de-meaning each trial and bandpass filtering at 13-30 Hz with a 2-pass Butterworth filter. The source was located using an LCMV beamformer on a 5 mm grid that has been distorted to MNI template space using a singleshell forward model. A window of 0 to 8.5 seconds after the grating began was used to construct the covariance matrix in the 13-30 Hz (beta) frequency range.

We identified the source of the movement-associated beta signal by finding

the location of the largest event-related beta desynchronization (ERBD) in the left pre- or post-central gyrus within the window of 0.5 to 1.8 seconds after stimulus onset relative to a baseline period of 7.0 to 8.3 seconds after stimulus onset. Pre- and post-central gyri were identified using the AAL atlas (Tzourio-Mazoyer et al., 2002). Using the previously established beamformer weights, we subsequently retrieved the corresponding MEG timecourse data. After then, a high pass filter (>1 Hz) was used to apply the full 600 Hz sampling rate of this time course data. The post-movement beta rebound was measured by selecting a time window (2.3–4.3 seconds after stimulus onset) that encompassed the rebound peak in both the patient and control groups. After that, we calculated the fast Fourier Transform (FFT) at a frequency range of 13–30 Hz in increments of 0.5 Hz using a Hanning filter inside that time window. After that, we took the average of each person's signal strength across all trials and frequencies. Similarly, we quantified the percentage change from baseline value for both PMBR and ERBD and recalculated the beta power in the ERBD and baseline windows.

Relationship of putative core deficit with formal thought disorder (as quantified by TLI total) was explored, along with its relationship with neural measure PMBR in the entire psychosis sample.

3.3 Results

With an eigenvalue of 2.51, the first PC in the PCA of the three Disorganization scores accounted for 83.6% of the variance. On the first PC, all three rating scale scores loaded strongly. Therefore, a composite Disorganization score was defined for the factor scores of this PC. All three rating scale scores loaded heavily on the first PC in the PCA of the three impoverishment scores, which also had a similarly high eigenvalue (2.29) and accounted for 76.2% of the variance. Thus, a composite Impoverishment score was defined for this PC's factor scores.

Confirmatory Factor Analysis

Measures of the four potential core deficit characteristics—composite Disorganization, composite Impoverishment, DSST, and SOFAS—were included in our single factor model. The assumption of multivariate normality was broken, according to multivariate normality tests (Mardia's coefficient for skewness = 5.88, p =.006; kurtosis = 24.21, p =.93). We used the natural log of the DSST score because the patient group's DSST scores were positively biased. Multivariate normality was reinstated (Mardia's coefficient values, skewness = 4.06, p =.234 and kurtosis = 22.11, p =.389).

The single factor model's fit indices confirmed the good model fit: $\chi 2$ (2)=1.817, p=.403; RMSEA <.001 GFI =.979. Since the modification indices were less than 4, it seemed unlikely that changing the model would result in an appreciably better fit. Forty-six percent of the shared variance and 52.6% of the overall variance were explained by the single factor. Scaled regression weights for all the other variables were substantially different from zero, and the scaled regression weights were matched to the Disorganization scores (Figure 3-1).

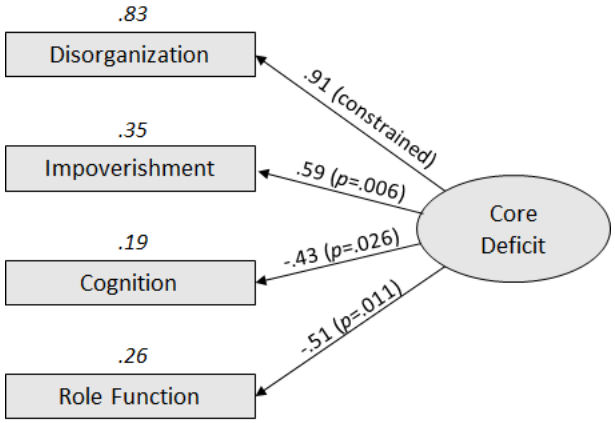

Figure 3-1: Estimated Regression Weights from Confirmatory Factor Analysis for the putative core deficit.

The following variables were examined: role function (SOFAS scores), cognition (log of DSST scores), poverty (composite impoverishment measure), and disorganization (composite disorganization measure). The standardised

regression weights with significance value are indicated by the values adjacent to the arrows. Above the variable boxes, the values indicated in italics are the squared multiple correlations (R^2).

Significant correlation was found between the scores obtained using composite scores and the factor scores when factor analyses were conducted using the symptom scores from each rating scale separately rather than the composite scores (PANSS: r=.964, p<.001, 95% CI [.927,.987]; SSPI: r=.938, p<.001, 95% CI [.891,.967]; CASH: r=.919, p<.001, 95% CI [.865,.954]). A scatterplot shown relationship between these scores is shown in Figure 3-2

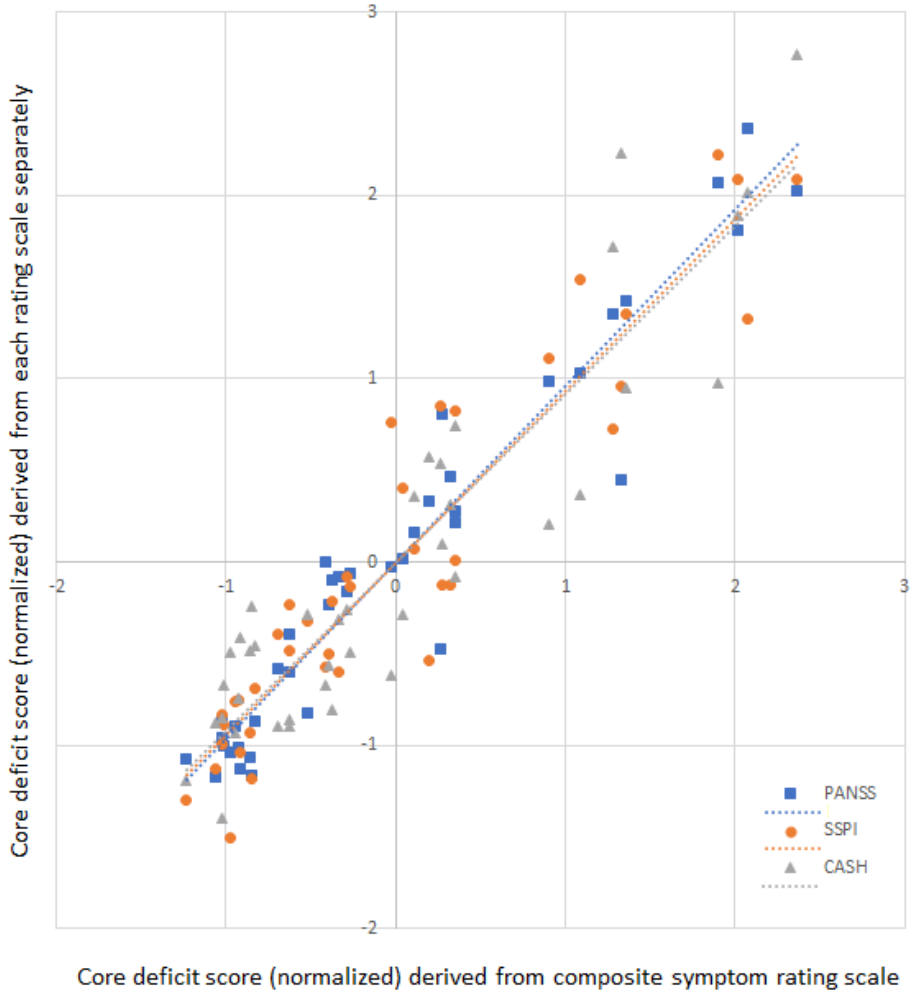

Figure 3-2: Normalized core deficit Factor scores from Confirmatory Factor Analysis (CFA) using composite symptom scores for Disorganization and Impoverishment (horizontal axes) plotted against normalized factor scores derived from factor analyses using PANSS, SSPI, and CASH rating scales, respectively.

In all factor analyses, Role Function scores (SOFAS) and Cognition scores (log of DSST scores) were included in the model. PANSS, Positive and Negative Syndrome Scale; SSPI, Signs and Symptoms of Psychotic Illness; CASH, Comprehensive Assessment of Symptoms and History; SOFAS, Social and Occupational Functioning Assessment Scale; DSST, Digit Symbol Substitution Test. (Prepared for Rathnaiah et al. 2020)

3.3.1 PMBR

When comparing the schizophrenia group to the healthy controls, there was a significant attenuation in PMBR, t (68) = 3.55, p <.001, 95% CI (19.5, 69.3).

PMBR was shown to have a significant negative correlation, r=-.543, p<.01, 95% *CI* (-.730, -.261) with the CFA factor scores that indicate the Core Deficit score within the patient group, suggesting that higher core deficit scores are linked to lower PMBR. Figure 3-3A displays the distribution of PMBR values for healthy controls for comparison and plots Core Deficit scores against PMBR. The average time evolution of the beta signal for each group is displayed in Figure 3-3B.

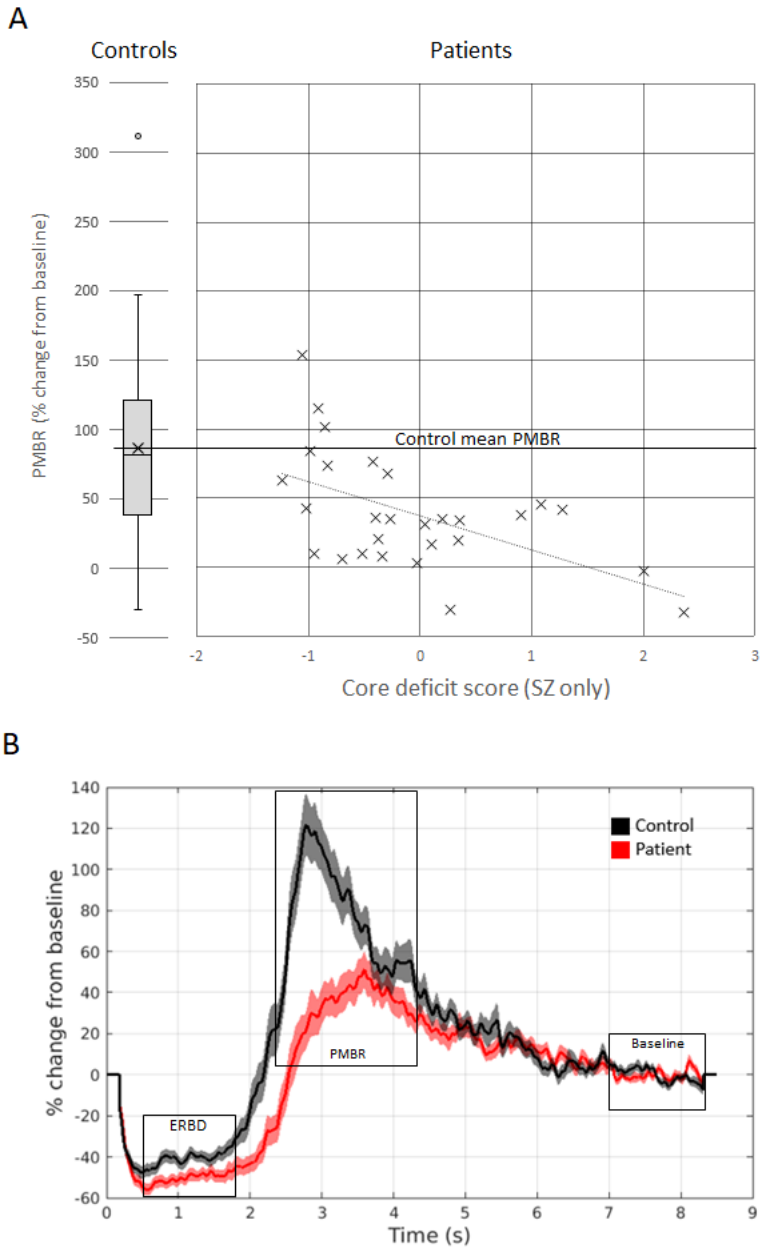

Figure 3-3: PMBR and Core Deficit scores.

Panel A: The patient group's Core Deficit scores are shown against the PMBR scores (vertical axis). On the left, for reference, is a box plot that displays the distribution of PMBR scores among participants who are healthy controls. Panel B: shows the average evolution of beta power over trials and individuals in each group. The ERBD, PMBR, and Baseline time periods are represented, respectively, by boxed areas. The stimuli start at time zero. (Prepared for Rathnaiah et al. 2020).

Even after adjusting for age, medication (DDD), and ERBD, there was still a significant association between PMBR and Core Deficit scores (r(23)=-.513, p<.01, 95% CI [-.718, -.274]. The SSPI Reality Distortion scores and PMBR did not exhibit a significant correlation (r=.222, ns).

3.3.2 Cluster analysis

Two step cluster analysis utilising the standardised log-transformed scores of PANSS disorganization and impoverishment, along with cognition (DSST) and role-function (SOFAS) measures resulted in two clusters with the model fit reaching good optimisation (Figure 3-4).

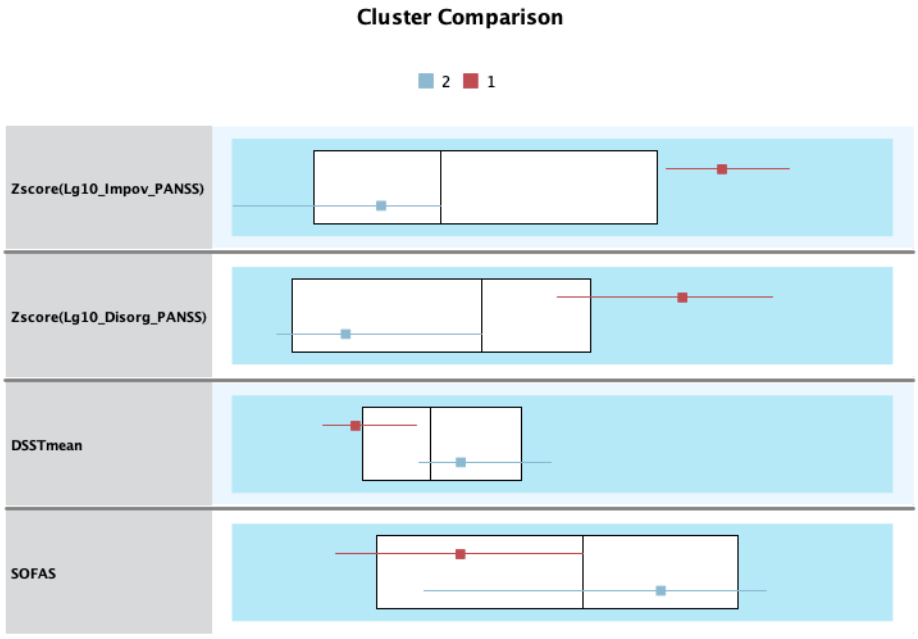

Figure 3-4: Standardised log_{10} transformed scores of impoverishment and disorganization together with cognition (DSST mean) and role-function (SOFAS) used for two step cluster analysis.

Comparison of clusters from two-step cluster analysis results. Cluster1 with enhanced disorganization and impoverishment and markedly diminished cognition and functioning seems to represent higher classicality than cluster2.

Cluster1 can be seen as the cluster with more pronounced classicality (higher classicality) in comparison to cluster2 with less degree of classicality(low classicality). Given the small size of the sample and the fact that classicality is observed to be dimensional in nature lying on a continuum, it can only be propositioned that these discrete clusters reflect varying degree of classicality.

Cluster1 was overrepresented by schizophrenia diagnosis as predicted along with one case of schizoaffective disorder and two cases of BPAD, rest of the BPAD and Scz cases segregated into cluster2 (Figure 3-5).

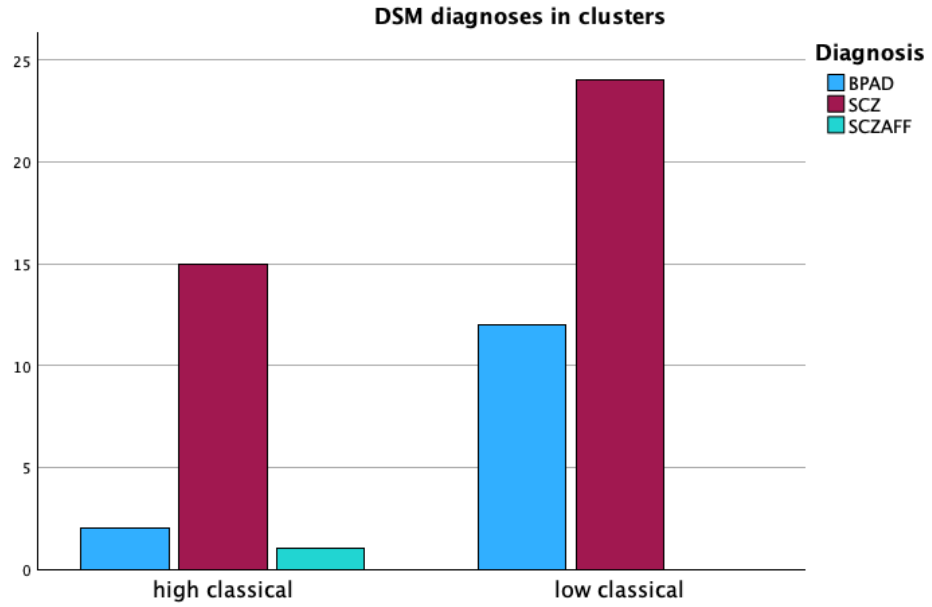

Figure 3-5: Segregation of different diagnoses cases into two clusters.

BPAD: Bipolar affective disorder, SCZ: Schizophrenia, SCZAFF: Schizoaffective disorder

To investigate if these two discrete clusters lie on a continuum of classicality or a point of rarefaction can be identified to help categorise clusters into classical and non-classical, we derived a new classical dimension of putative core deficit by factor analysis (maximum likelihood) of core features in the entire sample of psychosis (BPAD+Scz). Factor loadings for this factor are given in Table 3-2.

Table 3-2: Factor loadings for Core Deficit in the full sample (BPAD + SZ).

Variable	Factor loading
Disorganization	.900
Impoverishment	.763
Role-function (SOFAS)	-.495
Cognition (DSST)	-.425

Log_{10} transformed PANSS disorganization and impoverishment were used along with DSST for cognition and SOFAS for role-function measure. Maximum Likelihood (ML) method was used for factor extraction.

This classical dimension from entire psychosis sample was highly correlated with the composite core deficit derived from only the schizophrenia sample, $r(40)=0.950$, $p<0.001$.

Figure 3-6 shows the distribution of these classical scores as a violin plot, with individual participants represented as jittered data points, the colour of the datapoint (circles or triangles) representing cluster membership, and the shape representing diagnosis. The plot suggests that the clusters are not discrete along the classical dimension, and that these clinical features can also occur in BPAD.

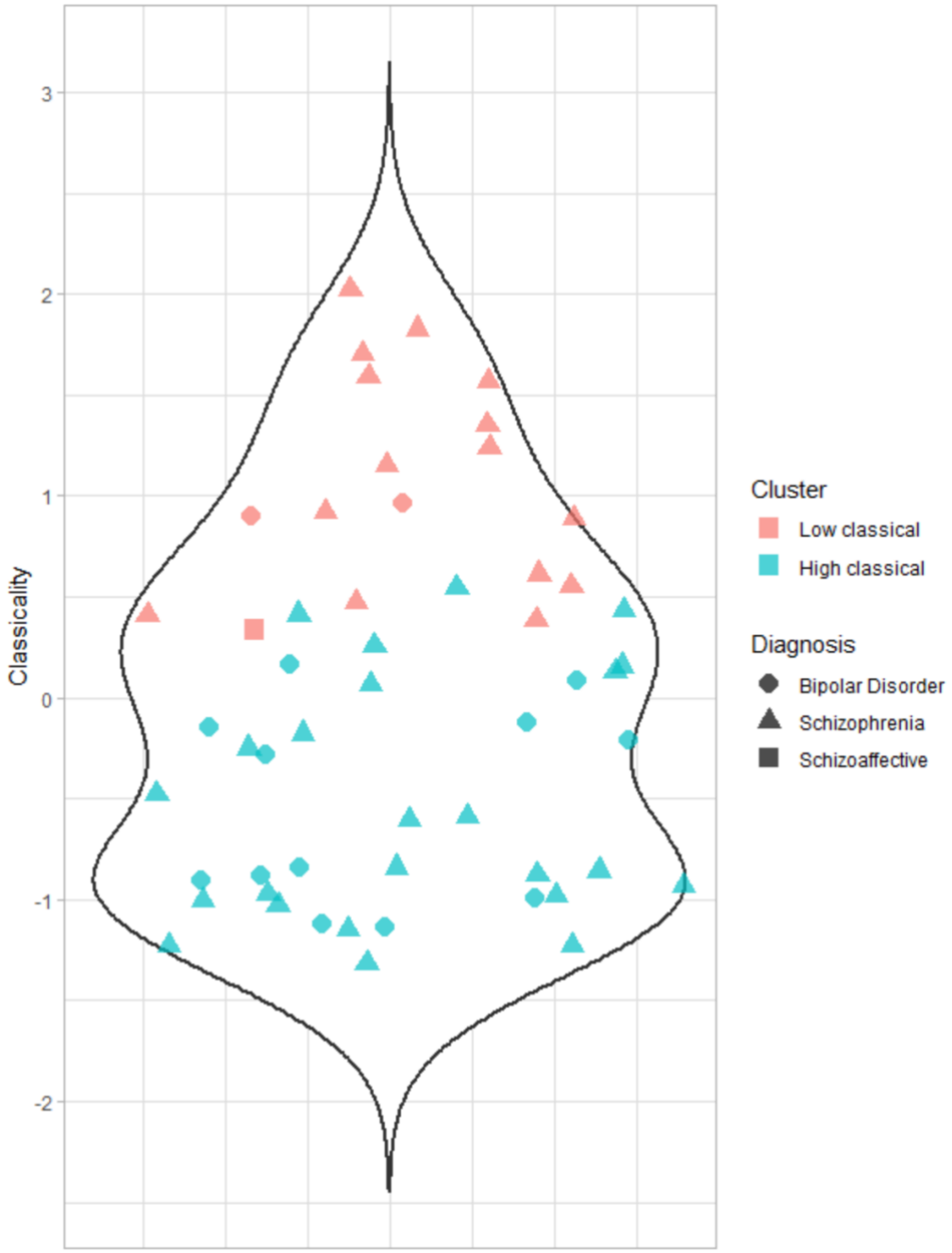

Figure 3-6: Violin plot of two clusters plotted against the axis of core deficit.

There is no evidence of a point of rarefication separating the clusters. Note that while BPAD participants are more prevalent at lower levels of classicality, they nonetheless lie along the same continuum.

Mean differences for clinical and neural features between two clusters are given in Table 3-3.

Table 3-3: Comparison of High and Low Classical Clusters

	High classical (n = 18)	**Low classical (n=36)**	**Significance**
Age	29.11	29.36	t(52)=-0.095,p=0.924,d=-0.028
Illness Duration(months)	59.11	67.83	t(52)=-0.406,p=0.686,d=-0.117
AP_DDD	1.31	0.94	**t(47)=2.501,p=0.016,d=0.741**
Quick IQ	95.59	98.82	t(49)=-1.187,p=0.241,d=-0.353
SSPI reality distortion	3.00	2.00	t(52)=1.509,p=0.137,d=0.429
TLI Disorganization	0.64	0.46	t(49)=1.295,p=0.201,d=0.385
TLI Impoverishment	0.75	0.33	**t(49)=2.561,p=0.014,d=0.761**
PMBR	27.85 (n=13)	50.25(n=29)	t(40)=-1.197,p=0.238,d=-0.400

AP_DDD: defined daily dose of antipsychotic, PMBR: post-movement beta rebound.

It is difficult to draw confident conclusions from the results of mean differences between clusters, as the cluster with high classicality is too small in size to provide a reliable estimate of the mean and variance of the classical group.

Classicality and FTD

Putative core deficit exhibited positive correlation with TLI total, but not statistically significant, $r(51)=.224$, $p=.114$.

Classicality and Reality distortion

Classical dimension exhibited positive correlation with reality distortion, but not significant, $r(54)=.162$, $p=.243$.

Classicality and PMBR

PMBR is significantly diminished in the psychosis group compared to healthy controls, $t(82)=3.281$, $p=.001$, $d= 0.716$, and Core deficit was negatively correlated with PMBR as predicted, but not statistically significant $r(42)=-.227$, $p=.149$.

3.4 Discussion

I demonstrate through CFA that a classical dimension which accounts for the shared variance between measures of mental impoverishment, disorganization, cognitive impairment, and impaired role function in schizophrenia. Furthermore, we obtained similar factor in the larger sample of patients with psychotic illness including bipolar cases in addition to schizophrenia.

I demonstrate that PMBR is reduced in Scz and psychosis, in keeping with the evidence till date and we further support PMBR as a marker of core pathophysiological process in Scz by demonstrating the negative correlation between core deficit and PMBR.

Although correlation between reality distortion and core deficit was weak, this would necessitate further studies to test the theoretical formulation that classicality predisposes to reality distortion. Furthermore, it is plausible that a subset of cases classified according to current DSM standards include cases with the "classical core deficit". Alternatively, it might be more prudent to study the classicality as dimension and to focus efforts on quantifying core features as well as developing targeted interventions to ameliorate putative core deficit.

To further explore whether cases with classical core deficit are categorical in nature, I completed cluster analysis, and we demonstrated that clusters can be identified from cluster analysis of DSM psychosis spectrum disorders. But, in light of the evidence that our results from the factor analysis suggests that Classicality is dimension with severity distributed on a continuum across the full sample. The cutoff between the clusters identified in this sample might reflect idiosyncratic feature of this sample. At this stage we would not be justified in assuming that this cutoff can be generalised to other samples.

We further provide added support to the classicality of the classical cluster by demonstrating significant difference in core feature measures between two

clusters including enhanced disorganization and impoverishment along with reduced cognition and role-function abilities. Furthermore, we confirm this by utilising FTD measures in terms of TLI impoverishment being significantly enhanced in cluster with high classicality and trend for TLI disorganization to be higher and pre-morbid intelligence (Quick IQ) being lower. But antipsychotic DDD is significantly enhanced in the cluster with high classicality and hence any inferences must be taken with great caution as some of these effects might be related to antipsychotic exposure. To make further analysis of any such association, the sample size needs to be bigger, and the study needs to be longitudinal, or the antipsychotic exposure needs to be cumulative rather than a current snapshot.

In addition to the clinical signature, we demonstrate that neural measure of PMBR is diminished in cluster of high classicality, albeit not reaching statistical significance.

The limitations of our study include a small sample size and lack of adequate power to test meaningful correlations. PMBR data was not available is all cases. We cannot exclude possible effects being contributed by cumulative exposure to anti-psychotic medication.

The issue of categorical v/s dimensional classification has influenced psychiatric research for lengthy period of time and schizophrenia is no exception to that. Schizophrenia research has been negatively impacted by recruiting people based on the categorical diagnosis from DSM. Our investigation, albeit based on a small sample size, supports the dimensional nature of classical features and hence supports the notion of continuum of core deficit. Nonetheless, the issue remains undecided. It is important to focus efforts towards replicating the classical dimension as well as further exploring the nature of distribution of core features in psychosis spectrum, in addition to investigating the neural correlates of core deficit. Subsequent chapters in this dissertation work would try to complete investigations in this regard.

Chapter 4: Delineating classicality of schizophrenia in a sample of stable patients with psychosis illness based on persistent and current symptoms

ABSTRACT

Background:

Cross-sectional assessment of current symptoms of disorganization and impoverishment can be confounded by various factors including the antipsychotic medication effect, excitability and acute transient disorganization as part of florid psychosis. To have the best chance to identify the classical dimension reflecting the core pathophysiological process and to test the classicality of classical schizophrenia, it might be important to use the persistent symptoms in chronic patients with stable illness, in addition to analysis based on current symptoms.

Aims and Hypothesis:

I set out to test if clusters can be identified from sample of stable patients with psychotic illness being classified according to the core features, more importantly by using persistent disorganization and impoverishment, in addition to clusters based on current symptoms. Furthermore, I aimed to derive single classical dimension from this sample comprising both Scz and BPAD and test the hypothesis that putative core deficit along with neural measure PMBR will be reduced in cluster with high classicality.

Methodology:

Pre-recorded data of 64 patients with DSMIV diagnosed schizophrenia (n=35), schizo-affective disorder (n=7) and BPAD (n=22) with psychosis was used. Patients were assessed in stable phase of illness. Current disorganization, impoverishment (negative symptoms) and reality distortion (delusions and hallucinations) were derived from Signs and Symptoms of Psychotic Illness

(SSPI) scale. Persistent disorganization and impoverishment symptom domain scores derived from using SSPI scale and retrospective review of case notes, along with measure of cognition (Digit symbol substitution test DSST scores) and functioning (social and occupational functioning assessment SOFAS scale). Post-movement beta rebound (PMBR), a potential neural marker was measured to assess the coordination of brain activity in the motor system. Maximum likelihood factor analysis was employed to identify a latent variable representing the share variance between disorganisation, impoverishment, DSST and SOFAS scores. Two-step cluster analysis was completed in SPSS version 29. Resultant clusters were compared for clinical, demographic and neural characteristics.

Results

Factor analysis identified a single latent variable representing the shared variance between the classical features. Two-step cluster analysis resulted in two clusters, from persistent symptoms as well as current symptoms. Cluster with enhanced classical features identified using persistent symptoms was small in size to make a reliable estimate of mean and variance in the group. But classical cluster identified based on current symptoms was consistent with the concept of classical schizophrenia including enhanced core features and reduced PMBR.

Conclusions and next steps

Our results demonstrate that a single latent variable of core deficit can be derived from classical features and the use of persisting symptom measures in this chapter adds significant support to our conceptualisation of potential core process underlying the classicality. Furthermore, I reiterate observation from previous chapter that classicality presents itself as dimension rather than category. Future research and clinical practice can utilise core deficit as an intermediary dimension to be quantified, studied and targeted to improve outcome for individuals with psychosis illness.

4.1 Introduction

In chapter 1 I introduced the concept of classical schizophrenia: an illness characterised by impoverished and disorganized mental activity, and impairments in cognition and role function that tend to persist. In Chapter 3, I demonstrated the classical dimension by CFA and identified classical clusters from the psychosis spectrum using the current symptoms.

In this chapter, I have the following aims:

1) demonstrate that a latent variable representing shared variance between persisting impoverished and disorganized mental activity, and impairments in cognition and role function can be identified in sample of cases of psychotic illness in the stable phase.
2) to test the relationship between latent variable and formal thought disorder (FTD) to investigate if latent variable is valid measure of classicality.
3) to test the hypothesis that putative latent variable derived from persistent measures predicts reality distortion, consistent with theoretical formulation that severity of persistent core deficit predisposes to current delusions and hallucinations.
4) to determine whether or not a cluster of cases with the clinical features of classical schizophrenia can be identified in a sample of individuals with psychotic illnesses including not only cases satisfying DSM criteria for Schizophrenia (Scz) but also cases satisfying DSM criteria for Bipolar affective disorder (BPAD) using persistent symptoms.
5) to further investigate if classical schizophrenia cluster can be identified from using current symptoms as well, and to compare between the clusters from persistent symptoms and current symptoms.
6) to test the hypothesis that classicality is associated with specific neural abnormality, namely diminished PMBR.

I will also address the question of whether or not classical schizophrenia is best described as a categorical sub-type of schizophrenia or as a continuously distributed dimension of psychopathology occurring in psychotic illnesses.

4.1.1 Background:

Current diagnosis of schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013) is mainly dependent on easily quantifiable clinical features such as delusions and hallucinations. Similarly, diagnosis of Bipolar Affective Disorder (BPAD) is made using easily quantifiable features of affective instability (mania or depression) with or without psychosis. As a result, both schizophrenia and BPAD groups have been found to be heterogenous in several aspects and more importantly, there has been lack of replicability of neurobiological measures and inherent difficulty in delineating the underlying pathophysiological processes.

There has been debate on the applicability of categorical classification in psychiatry in general and psychotic spectrum illnesses in particular. Alternative methods of classification based on psychological and neurological processes have been advocated (Cuthbert, 2014). Remarkably, up to 50% of otherwise typical bipolar patients share some of the cognitive abnormalities that were previously thought to only be characteristic of schizophrenia patients (Glahn et al., 2015). Psychotic symptoms (hallucinations, delusions, formal thought disorder) have been clearly observed during episodes of established BPAD patients (Keck et al., 2003). This has the unavoidable effect of distorting study results because many cases of psychosis are difficult to categorize and are therefore left out of clinical trials and genetic analysis (Pearlson et al., 2016).

There is significant overlap of clinical features among BPAD with psychosis, schizoaffective disorder and schizophrenia. BPAD with psychosis shares genetic (Potash et al., 2001), cognitive (Glahn et al., 2007) and neurochemistry (Pearlson et al., 1995) signature with schizophrenia. There has also been overlap in treatment response and outcome (Pearlson et al., 2016). According

to Litchtenstein et al. (2009), familial expression of illness spans diagnostic boundaries, making certain disorders unable to "breed true." Even though bipolar disorder and schizophrenia are both highly heritable, there is significant overlap in the risk genes that have been identified thus far, and treatment approaches are similar. For instance, second-generation antipsychotics are routinely used to treat bipolar illness, regardless of whether psychotic symptoms are present. Because of these findings, recent proposition is that psychosis is on a spectrum with ill-defined borders, making it impossible to "carve nature at its joints" (Crow et al., 2013).

BPAD with associated psychosis and the schizophrenia can be considered to be part of the psychosis spectrum disorder, although the term psychosis spectrum in its right context should extend from physiological thought anomaly to pathological reality distortion (Loch, 2019). There have been multiple studies comparing and contrasting BPAD and schizophrenia (Yamada et al., 2020). Crucial question that needs answering is: whether there is sub-group of individuals with DSM diagnosed BPAD who share the neurobiological pathophysiology with a subgroup of DSM schizophrenia patients? We wanted to test the hypothesis that there exists a homogenous sub-group comprising of the mix of BPAD and schizophrenia patients, which would meet the criteria for classical schizophrenia, described since the times of Bleuler and Kraepelin.

4.1.2 Pre-morbid intelligence

Premorbid IQ and behavioural functioning predicted post-diagnosis negative symptoms and indirectly predicted social and occupational symptoms through negative symptoms in a study on the course of schizophrenia published by Brill et al. (2009). Conversely, there was no significant correlation found between positive symptoms and functional outcomes.

Addington and Addington (1993) also found that negative symptoms were substantially correlated with poor premorbid functioning and poor outcome. Over the course of the illness, which lasted three years, Bailer et al. demonstrated that premorbid adjustment was strongly related with negative

symptoms and social handicap in 163 patients diagnosed with schizophrenia (Bailer et al., 1996). After analysing 111 cases of schizophrenia, Strous et al. (2004) found that a higher degree of premorbid functioning existed prior to the onset of the illness, and they linked this to worse outcome. According to the evidence available till date in the prodromal psychosis field of research, it can be proposed that schizophrenia would begin long before the onset of the first psychotic episode (Fusar-Poli et al., 2013).

4.1.3 PMBR and beta oscillations

In addition to the review of evidence presented in Chapter2, it is noteworthy that Liddle et al (2016) further supported the proposition that integrative beta oscillations are implicated in the long range connectivity, by demonstrating that modulation by task-relevance of event-related beta-band oscillations in the insula would be disrupted in schizophrenia. It is noteworthy that Beta rebound (PMBR) is reduced in people with schizophrenia and the diminishment occurs in both recent-onset and established stages (Rathnaiah et al., 2020; Robson et al., 2016).

Briley et al (2021) confirmed attenuated PMBR in stable schizophrenia illness and more importantly, strengthened the evidence for association of coredeficit reflecting the disorganization, impoverishment and cognitive impairment with attenuated PMBR (Briley et al., 2021). Gascoyne et al. (2020) have demonstrated that the frequency, amplitude and duration of bursts in the PMBR window are diminished in the established phase, that suggests the relationship between the generation process of the beta bursts with the manifestation of disorganization.

4.2 Methods

4.2.1 Participants

Pre-recorded data from multimodal connectivity study (CONN) was used for this investigation. Methods from the research team have been previously

published (Briley et al., 2021) and reproduced here with permission of authors:

The study involved 112 patients (ages 18–50), 41 healthy controls, and 71 cases with psychotic illness.The Early Intervention in Psychosis Team and other community-based Mental Healthcare Teams in Nottinghamshire and Leicestershire, England, referred patients who had a clinical diagnosis of psychotic disorder. Retrospective case notes review, standardized symptom assessment with the Signs and Symptoms in Psychotic Illness scale (SSPI, Liddle 2002), and multiple clinical consensus meetings involving two or three research psychologists and two or three research psychiatrists who were trained in the use of research diagnostic criteria were used to confirm the presence of psychosis. According to the Best Diagnostic Estimate procedure outlined by Leckman et al., a positive lifetime history of psychosis was established. Diagnoses were assigned based on DSMIV criteria, as determined by consensus, and confirmed using the Operational Criteria Checklist (OPCRIT)(McGuffin et al., 1991).

The following inclusion criteria had to be met in order for a case meeting DSM IV criteria for schizophrenia, schizoaffective disorder, or bipolar disorder (with psychotic characteristics) to be included in the study:

between the ages of 18 and 50.

absence of significant medical condition or head injury

no history of harmful substance uses or dependence

estimated IQ based on the Quick Test to be at least 70 (Ammons & Ammons, 1962)

no contraindications for MRI safety.

All patients were in a stable phase of illness (defined as a change of no more than 10 points in their Global Assessment of Function (GAF) (Endicott et al.,

1976) score between assessment six weeks prior and immediately prior to study participation.

Advertisements were used to find 38 healthy controls who were free of any neurological or psychiatric disorders. The controls were matched to the patient group in terms of age and parental socioeconomic status, as determined by the National Statistics - Socio Economic Classification (Rose & J.Pevalin, 2003). Control participants met the same inclusion and exclusion criteria as the patients, as previously mentioned, and were further restricted from participation if they had a personal or family history of mental disease. To confirm that the controls had no history of neurological disorders or psychotic illness, as well as no current axis 1 condition, a clinical interview conducted by a research psychiatrist was utilized.

The study was conducted with ethical approval by the National Research Ethics Committee, Derbyshire, UK. Written informed consent was obtained from all study subjects in accord with the procedure approved by the Ethics Committee.

We included the pre-recorded data from 64 patients with stable psychotic illness.

4.2.2 Symptom and cognitive Assessment

Clinical symptoms using SSPI were assessed on the day of EEG acquisition. The administration and scoring of the Thought and Language Index (TLI) was in accord with the procedure described in Chapter1. DSST scores were obtained as measure of cognition. Retrospective assessment of lifetime history of symptoms was completed to derive persistent symptoms of disorganization and impoverishment.

Methods of deriving persistence symptoms has previously been published (Briley et al., 2021), but to briefly summarise, persistence score was computed by independent retrospective case notes review of all the available patient care records by two psychiatrists who achieved good inter-rater reliability. Persistence scores were computed for each of five cluster of symptoms on

SSPI namely psychomotor excitation, psychomotor poverty, disorganization, anxiety/depression and reality distortion from each of the episodes of psychosis documented. Persistence was scored for each cluster on a scale of 0 to 6 with 0 for absent symptoms and 6 for chronic presence of symptoms since the first episode. We utilised the scores of psychomotor poverty for impoverishment and disorganisation cluster scores for disorganization in our cluster analysis investigation.

Social and Occupational Functioning Assessment Scale (SOFAS) score assigned on the basis of enquiry about occupational social function; recreational interests and family relationships assessed during the SSPI interview (Morosini et al., 2000).

Global Assessment of Functioning (GAF)

The Global Assessment of Functioning (GAF) is a modified version of the Global Assessment of Severity (Endicott et al., 1976). The score, in the range 0-100, was assigned on the basis of disruption due to symptoms; occupational social function; recreational interests and family relationships, assessed during the SSPI interview. In addition, for the purpose of determining that the participant satisfied the requirement regarding stability of the mental state, a retrospective GAF score was assigned for the period 6 weeks preceding the index assessment was completed using all available information, including direct questioning of the participant about any change in mental state, medication or function in the preceding 6 weeks.

An estimate of IQ was obtained using form A of the Quick test (Ammons & Ammons, 1962).

Handedness scale: The 12 item Annett scale was administered (Annett, 1970).

4.2.3 Beta bursts and PMBR

These methods have previously been published (Briley et al., 2021). To briefly summarise, PMBR and Beta bursts were derived from EEG data. Participants completed a behavioural task of back-to-front working memory exercise

presented in software. Research team obtained 3TBOLD fMRI data at the same time as the EEG.

Using analyses of variance, mean beta burst rates were computed for every subject and experimental condition, and the results were compared using SPSS Statistics (version 25) (IBM Corp.). The mean beta burst rate in windows extending from 0.5 to 1 second after button presses minus the rate in baseline windows extending from 3 to 1.5 seconds before button presses provided the values for PMBR.

Average PMBR data for each participant was made available to us for our analysis in this investigation.

4.2.4 Core deficit

Classical dimension was derived from maximum likelihood factor analysis of core features: persistent disorganization, persistent impoverishment, cognition (DSST) and role-function (SOFAS). Relationship of classical dimension with neural correlate of PMBR was explored.

Core deficit was derived from using current symptoms of disorganization and impoverishment as well, together with cognition (DSST) and role-function (SOFAS) measure. Mutual relationship between these two classical dimensions in the same sample was examined, along with relationship of core deficit measures with reality distortion, FTD quantified by TLI and neural measure PMBR. Spearman correlation analysis was completed to test these relationships.

4.2.5 Cluster analysis

Initial two-step cluster analysis was performed using persistent disorganization, persistent impoverishment from SSPI, cognition (DSST) and role-function measure (SOFAS). Symptom scores of disorganization and impoverishment were log transformed as they were not normally distributed. Fitness of the model was determined by using Schwartz's Bayesian

Information Criteria (BIC). Two step cluster analysis predicts the model and segregates the clusters automatically. Identified clusters were compared for potential differences in clinical and neural characteristics. Exploratory analysis using violin plot was completed to test if classical schizophrenia is more on the continuum of classical features or a categorical entity in itself.

Same process of two step cluster analysis was completed utilising the current symptoms of disorganization and impoverishment (instead of persistent symptoms). Identified clusters were further examined for differences, for relationship with classical dimension particularly to explore if classical schizophrenia can be studied as a homogeneous category.

4.3 Results

Pre-recorded data of 64 patients with DSMIV diagnosed schizophrenia (n=35), schizo-affective disorder (n=7) and BPAD (n=22) with psychosis was used. 10 patients were receiving treatment with antipsychotics (clozapine n=1, other atypical antipsychotics n=2, typical antipsychotics n=3, combined typical and atypical agents n=4) and had no change in their prescriptions for the 6 weeks preceding the scan. The median Defined Daily Dose (WHO Collaborating Centre for Drug Statistics and Methodology, 2003) of antipsychotics was 1.32 (range from 0 to 10).

4.3.1 Classicality using persistent symptom scores

Classical Dimension

Classical dimension derived from a psychosis sample (N=64) using the maximum likelihood method of factor analysis on persistent disorganization, impoverishment (from SSPI), cognition (DSST) and role function (SOFAS), resulted in single latent variable with Eigenvalue more than1. Factor loadings for this component are given in Table 4-1.

Table 4-1: Core deficit derived by using persistent symptom measures together with cognition (DSST) and role-function (SOFAS).

Variable	**Core Deficit (persistent) factor loadings**
Persistent Impoverishment	-.475
Persistent Disorganization	-.372
Cognition	.551
Role Function	.579

This single component accounting for 43% of variance resulted which was termed putative core deficit from persistent features. Because impoverishment and disorganization were negatively loaded onto this factor, it was inverted for better visualisation of results (multiplied by -1).

This putative core deficit was significantly positively correlated with formal thought disorder (FTD) as measured by TLI total, $r(64)=.415$, $p<.001$, confirming the validity of core deficit measure to quantify classicality.

This putative core deficit (persistent) was positively correlated with persistent reality distortion scores, ***r*(64)=.237, *p*=.060**, and positively correlated with current reality distortion scores, ***r*(64)=.283, *p*=.025**, confirming our hypothesis that severity of persistent classicality predisposes and predicts current florid psychosis features of delusions and hallucinations (reality distortion). A scatterplot showing this relationship is give in Figure 4-1.

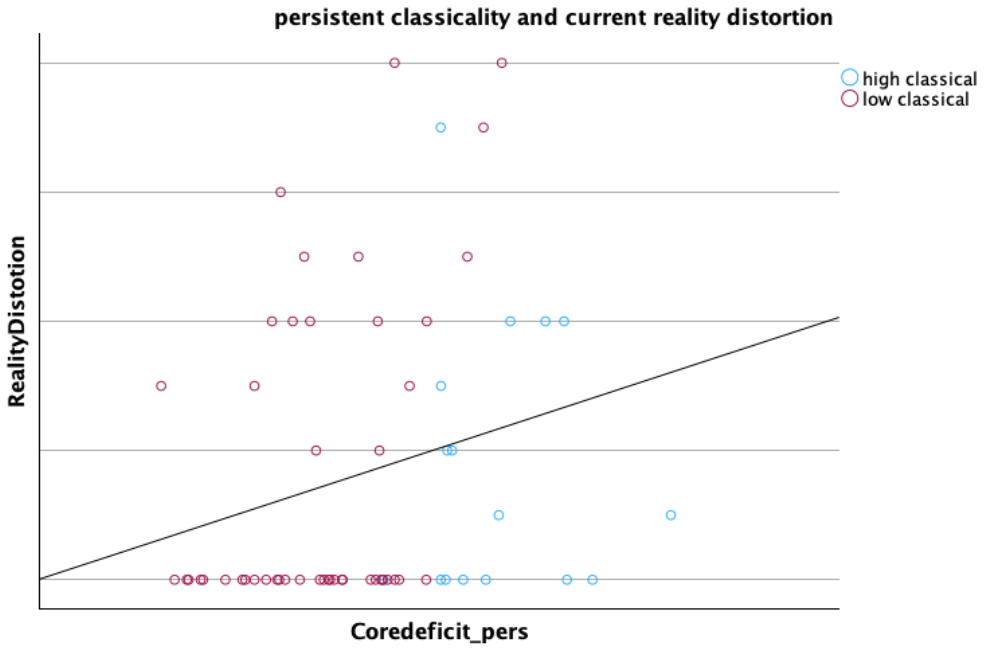

Figure 4-1: persistent core deficit predicts current reality distortion, and this relationship is more pronounced in cluster with high classicality.

Clusters were identified from two step cluster analysis using persistent symptom measures together with cognition (DSST) and role-function (SOFAS).

Classical clusters:

Cluster analysis resulted in two clusters, with one cluster (n=17) characterised by pronounced classical features (Figure 4-2).

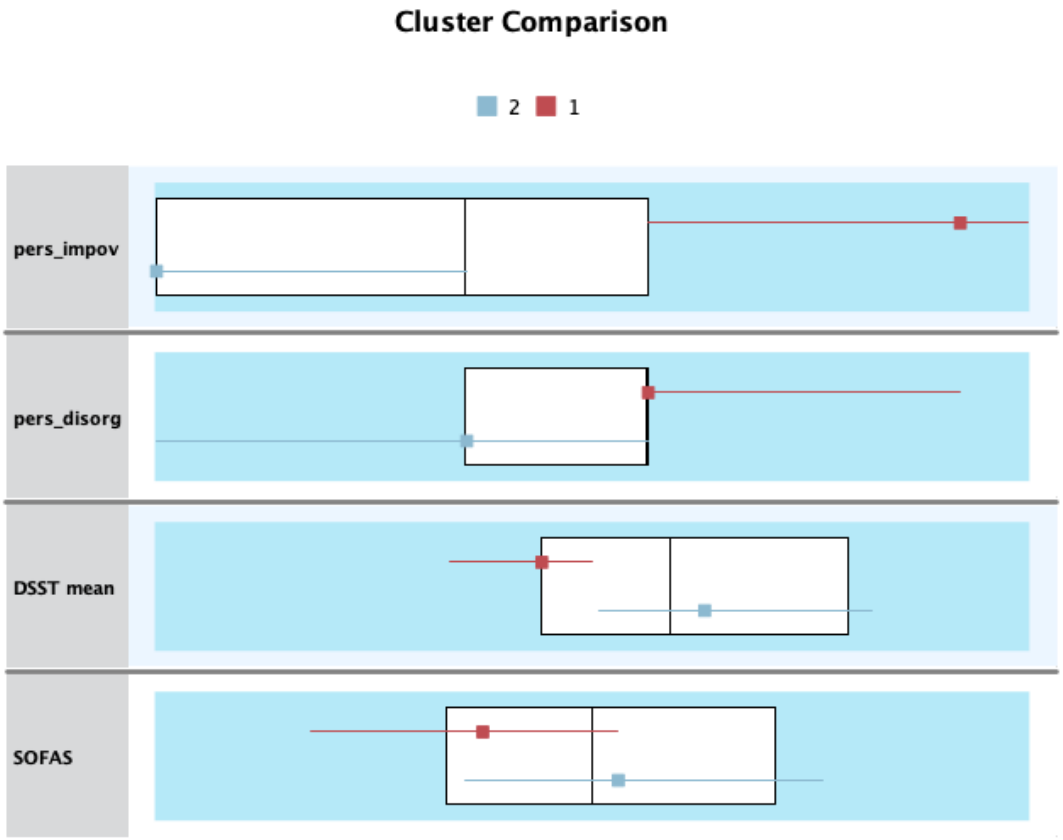

Figure 4-2: Cluster comparison, Cluster 2-with low classicality, Cluster1-high classicality. SOFAS – Social and Occupational functioning scale (role/functioning), DSST – Digit Symbol Substitution test (cognition).Log_{10} transformed standardised scores of persistent disorganization and impoverishment (pers_impov and pers_disorg) were used in cluster analysis.

Significant proportion of cluster 1 cases were schizophrenia cases, but couple of bipolar and schizoaffective cases segregated into Cluster1 as well. This cluster of enhanced core features is termed as cluster with high classicality in contrast to second cluster with less classicality (Figure 4-3) .

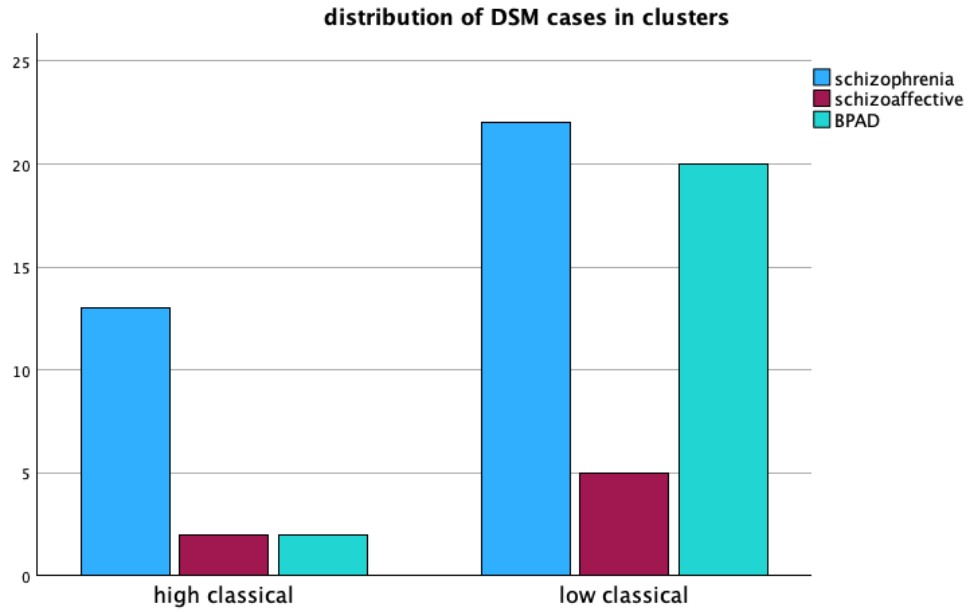

Figure 4-3: Distribution of diagnosis in two clusters

Differences between these two clusters (persistent) are given in Table 4-2**Error! Reference source not found.**:

Table 4-2: Mean differences between two clusters

	High classical (n=17)	**Low classical (n=47)**	**significance**
Age	35.82	33.55	t(62)=0.82,p=0.42,d=0.23
Illness Duration (years)	12.59	9.09	t(62)=1.62,p=.055, d=0.46
DDD Antipsychotic	1.18	0.97	t(62)=0.75,p=0.45, d=0.21
GAF	47.59	53.66	t(62)=-1.74,p=0.087, d=-0.49
Quick IQ	97.29	99.17	t(62)=-0.48,p=0.63,d=-0.14
Persistent PsychExcit	0.71	1.30	t(62)=-1.64,p=0.11,d=-0.46
Persistent RealityDis	3.53	3.11	t(62)=0.83,p=0.42,d=0.23
TLI Total	0.88	0.77	t62)=0.42, p=0.68,d=0.12
TLI Impov	0.58	0.26	t(62)=1.86, p=0.068, d=0.53
Current SSPI Impov	4.53	1.26	**t(61)=3.68,p<0.001, d=1.04**
Current SSPI Disorg	1.65	1.17	t(61)=1.07,p=0.29, d=0.30
Average PMBR	0.042 (n=12)	0.084 (n=36)	t(46)=-0.94,p=0.35,d=-0.31

DDD Antipsychotic: WHO defined daily dose of antipsychotic, GAF: Global assessment of functioning, Quick IQ: measure of pre-morbid intelligence, Persistent PsychExcit: persistent psychomotor excitation, Persistent RealityDis: persistent reality distortion, TLI Total: measure of FTD from Thought Language Index, TLI Impov : Impoverishment score from TLI scale, Current SSPI Impov: current score of psychomotor poverty (impoverishment) on SSPI scale, Current

SSPI Disorg: current disorganization score from SSPI scale, PMBR: Post movement beta rebound. Differences significant at p<.05 are shown in bold.

The cluster with higher classicality was too small in size to provide a reliable estimate for mean and variance for the group, but the trends can be inferred from the results. Effect of illness duration on the classicality needed to be further explored as the duration was significantly higher in the cluster with higher classicality. Psychomotor excitability was more pronounced in the second cluster with lesser magnitude of classicality as expected. Persistent reality distortion was greater in the high classicality cluster, consistent with the expectations that classical features predispose to reality distortion but is not possible to draw a confident conclusion. Higher classicality cluster was noted to be characterised by significant impoverishment as confirmed by symptom scales as well as speech manifestations (TLI).

Among the neural measures, trend for reduction in PMBR in higher classicality cluster was evident, but not reaching statistical significance.

Relationship with PMBR

Persistent core deficit was significantly negatively correlated with PMBR, $r(48)=-.402$, $p=.005$ (Figure 4-4).

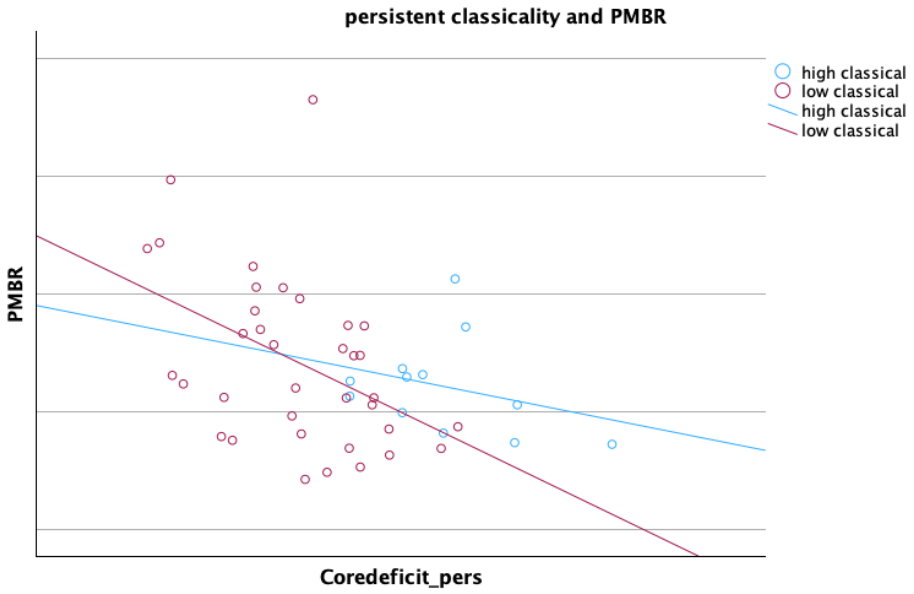

Figure 4-4: Relationship between persistent core deficit and PMBR.

Diminished PMBR was found to be negatively correlated with enhanced core deficit in both the clusters.

To investigate if the classicality is on a continuum as a dimension or there is possibility of categorical separation based on a rarefication point, a violin plot was constructed plotting the clusters against the classical dimension (Figure 4-5). The plot provides no evidence for a separation between clusters, and instead shows a continuous gaussian distribution along the classical dimension.

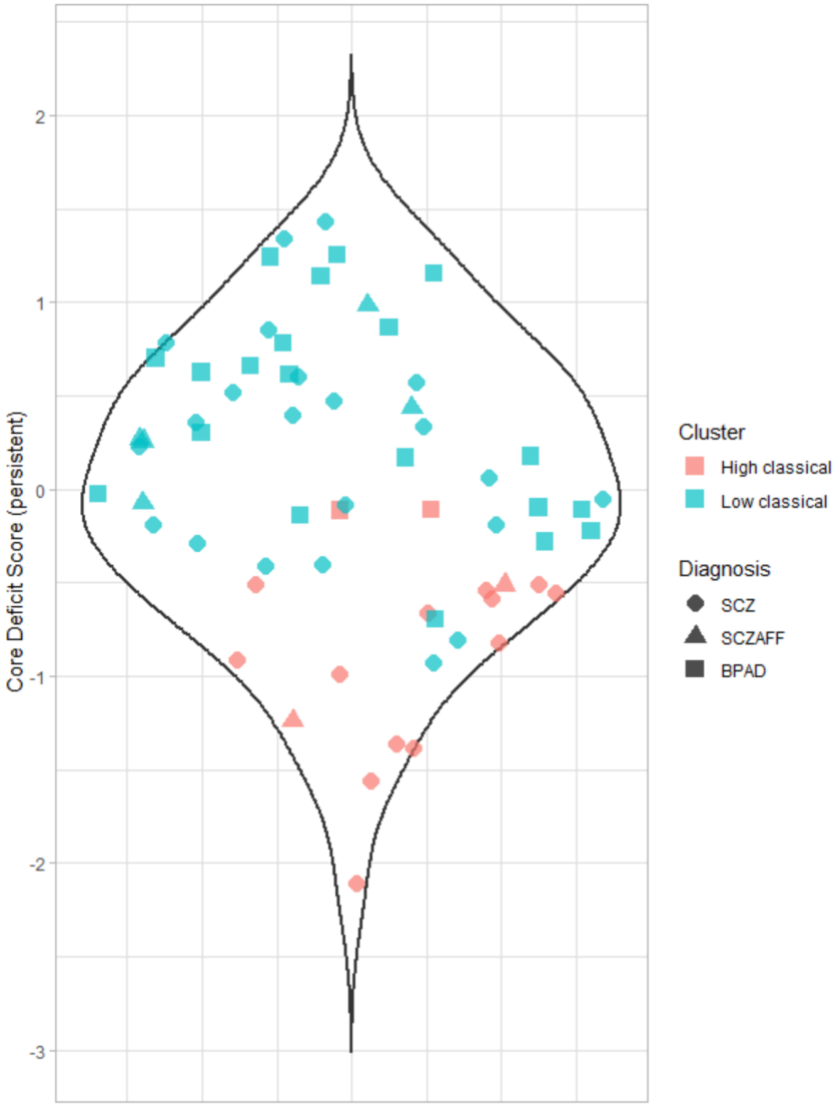

Figure 4-5: Violin plot showing the distribution of classical scores derived from persisting symptom scores. Datapoints represent individual patients, coloured to indicate cluster assignment. The shape of the datapoint indicates diagnosis.

4.3.2 Classicality using current symptom scores

Classical dimension

Maximum likelihood factor analysis was used to derive a new core deficit score using scores of current disorganization and impoverishment together with cognition (DSST) and role-function (SOFAS). This resulted in a single latent variable with Eigenvalue more than 1, which accounted for 51% of shared variance. Factor loadings for this putative core deficit (current) factor are given in Table 4-3.

Table 4-3: Factor loadings for core deficit component, using current symptoms.

Variable	**Core deficit (current) Factor loadings**
Current Impoverishment	.749
SOFAS	-.647
DSST mean	-.496
Current Disorganization	.460

The correlation between this core deficit (current) measure was highly correlated with the core deficit (persistent) measure previously derived from persistent symptom scores, $r(63)=.754$, $p<.001$.

The core deficit (current) measure was also significantly positively correlated with FTD as quantified by TLI total, $r(63)=.422$, $p<.001$ (Figure 4-6), indicating that the more practical measure of current symptoms would be a valid method to quantify classicality.

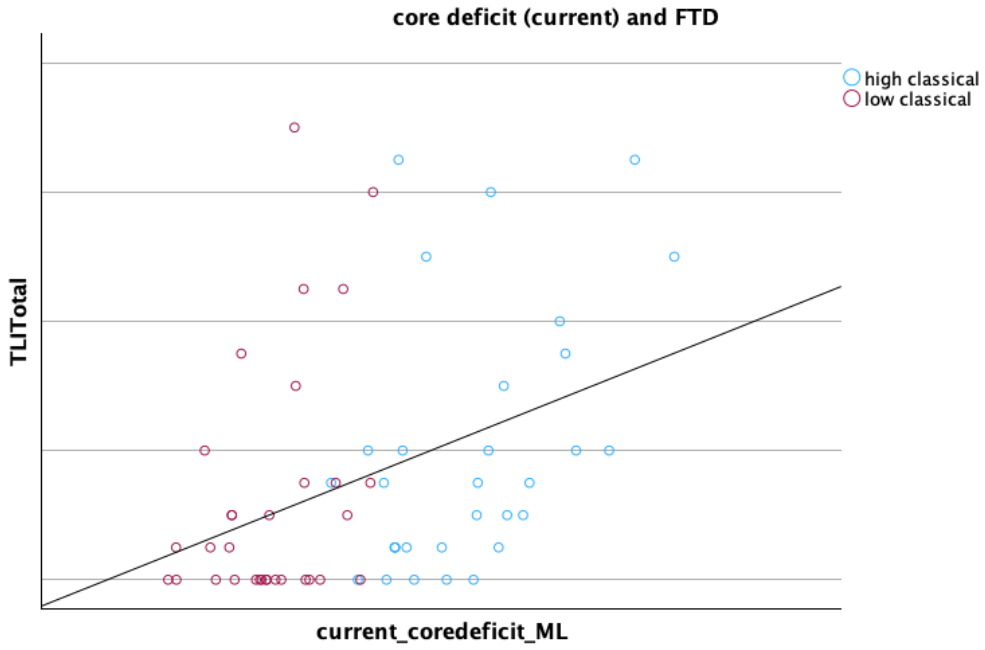

Figure 4-6: Scatter plot of current core deficit against Formal thought disorder (FTD) as measured by TLI total, confirming that severity of core deficit is proportionately related to severity of FTD

This relationship is more marked with cluster of high classicality as would be expected. Clusters obtained from two step cluster analysis using current measures of SSPI disorganization and impoverishment together with cognition (DSST) and role-function (SOFAS).

Furthermore, core deficit (current) was positively correlated with both persistent reality distortion, $r(63)=.220$, $p=.083$, and significantly positively correlated with current reality distortion, $r(63)=.400$, $p=.001$, further supporting the hypothesis that severity of core deficit predicts reality distortion (Figure 4-7).

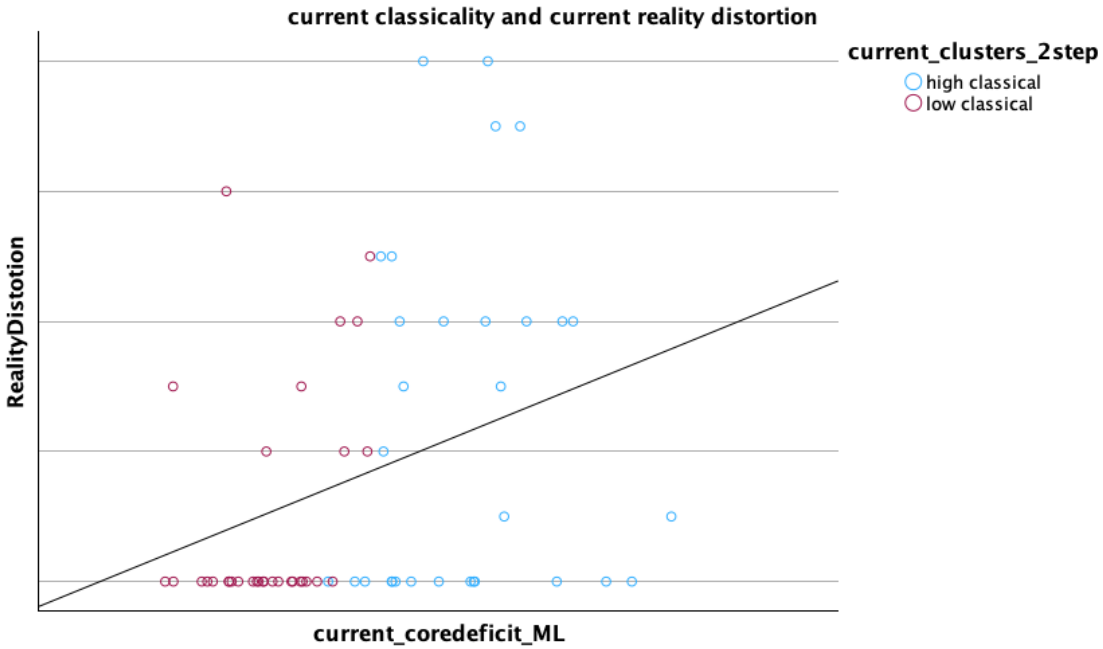

Figure 4-7: Scatter plot of current core deficit against current reality distortion confirming that severity of core deficit predicts delusions and hallucinations

This relationship is more marked with cluster of high classicality as would be expected. Clusters obtained from two step cluster analysis using current measures of SSPI disorganization and impoverishment together with cognition (DSST) and role-function (SOFAS).

Classical clusters

Two clusters were identified with one cluster representative of classical schizophrenia, as shown in Figure 4-8.

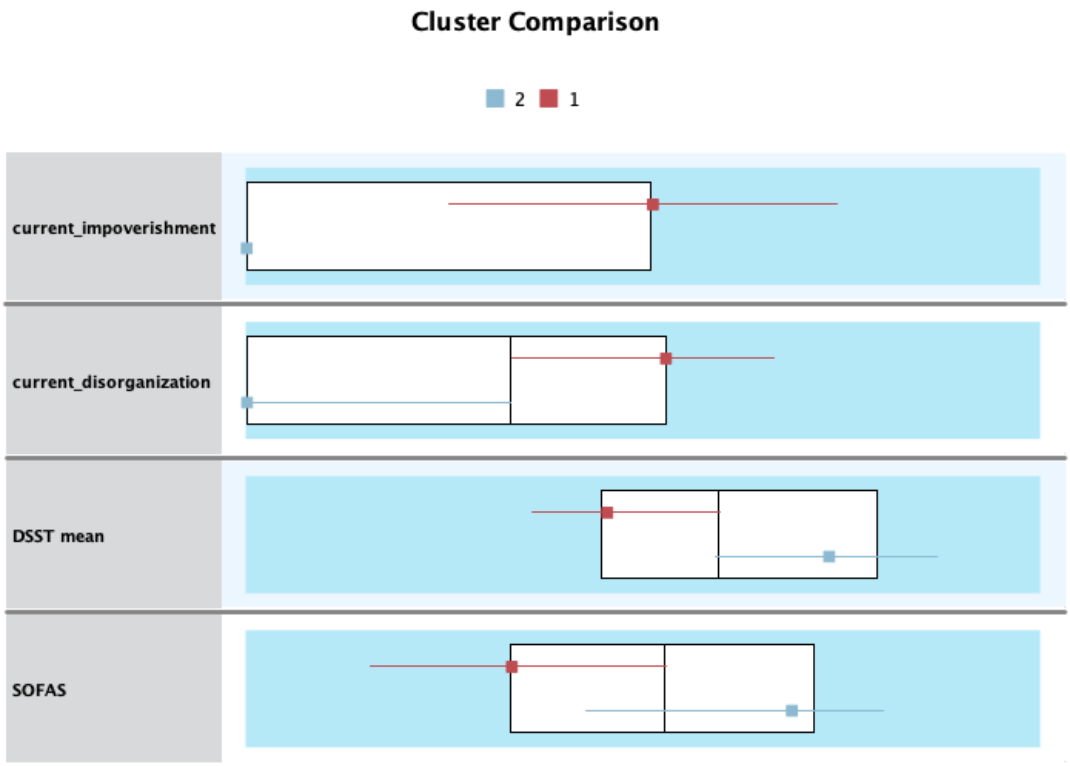

Figure 4-8: Cluster analysis using two-step cluster analysis. Cluster 2-low classicality, 1-high classicality. Current SSPI scores of psychomotor poverty (impoverishment) and disorganization used along with cognition (DSST mean) and role-function (SOFAS) measures. DSST – Digit Symbol Substitution test, SOFAS – Social and Occupational Functioning Scale.

The cluster with high classicality (n=31) was characterised by markedly pronounced core features as predicted, in contrast to the other cluster (n=32).

Substantial proportion of schizophrenia patients segregated into high classical cluster as expected, along with noticeable number of BPAD and schizoaffective patients (Figure 4-9).

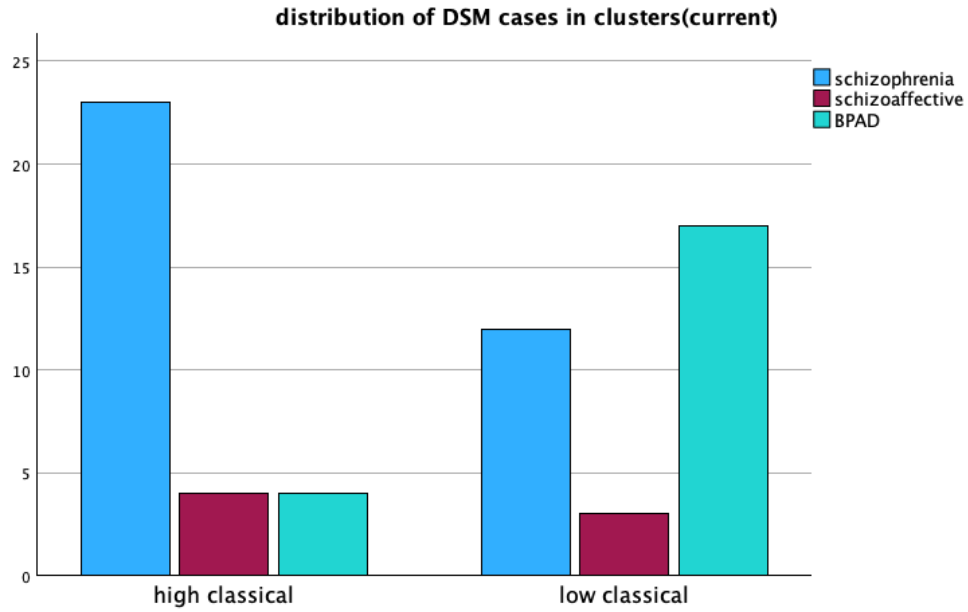

Figure 4-9: Distribution of DSM diagnosis cases in two clusters derived using current SSPI scores.

Differences between two clusters (current) are given for a range of variables in Table 4-4.

Table 4-4: Differences between cluster means for a range of variables.

	High classical (n=32)	**Low classical (n=31)**	**significance**
Age	32.71	35.19	t(61)=-1.01, p=0.32, d=-0.25
Illness Duration (years)	9.19	10.31	t(61)=0.29, p=0.77, d=0.07
DDD Antipsychotic	1.05	0.98	t(61)=0.29, p=0.77, d=0.07
GAF	45.71	58.63	**t(61)=-4.76, p<0.001, d=-1.2**
Quick IQ	91.58	105.00	**t(61) = -4.67, p<0.001, d=-1.13**
Persistent Disorg	1.94	1.41	t(61)=1.40,p=0.17, d=0.37
Persistent Impov	2.10	0.94	**t(61) =2.38,p =0.021, d=0.60**
Current Reality Distor	2.39	0.97	**t(61)=2.48,p = 0.008, d=0.627**
TLI total	0.99	0.63	**t(61)=1.67, p=0.036, d=0.37**
Average PMBR	0.02[a]	0.12[b]	**t(45) =-2.46, p=0.014, d=-0.74**

DDD Antipsychotic: W.H.O defined daily dose of antipsychotic, Persistent Disorg: persistent disorganization, Persistent Impov: persistent impoverishment, Current Reality Distortion: current score of reality distortion on SSPI scale, PMBR: Post movement beta rebound.[a] N=24; [b]N=23. Differences significant at p<.05 are in bold font.

Cluster with high classicality identified based on current symptoms seems to be representative of classical schizophrenia. Pre-morbid intelligence is significantly low in this group of individuals along with pronounced core features. Age, antipsychotic dose and duration of illness do not seem to differentiate between two clusters and formal thought disorder as reflected by TLI total and persistent measure of impoverishment is enhanced in high classical group as expected.

Figure 4-10 shows a violin plot similar to that in Figure 4-5, showing the distribution of classical scores, this time with the scores derived using current symptoms. Again, the plot provides no evidence for a separation between clusters, and instead shows a continuous gaussian distribution along the classical dimension.

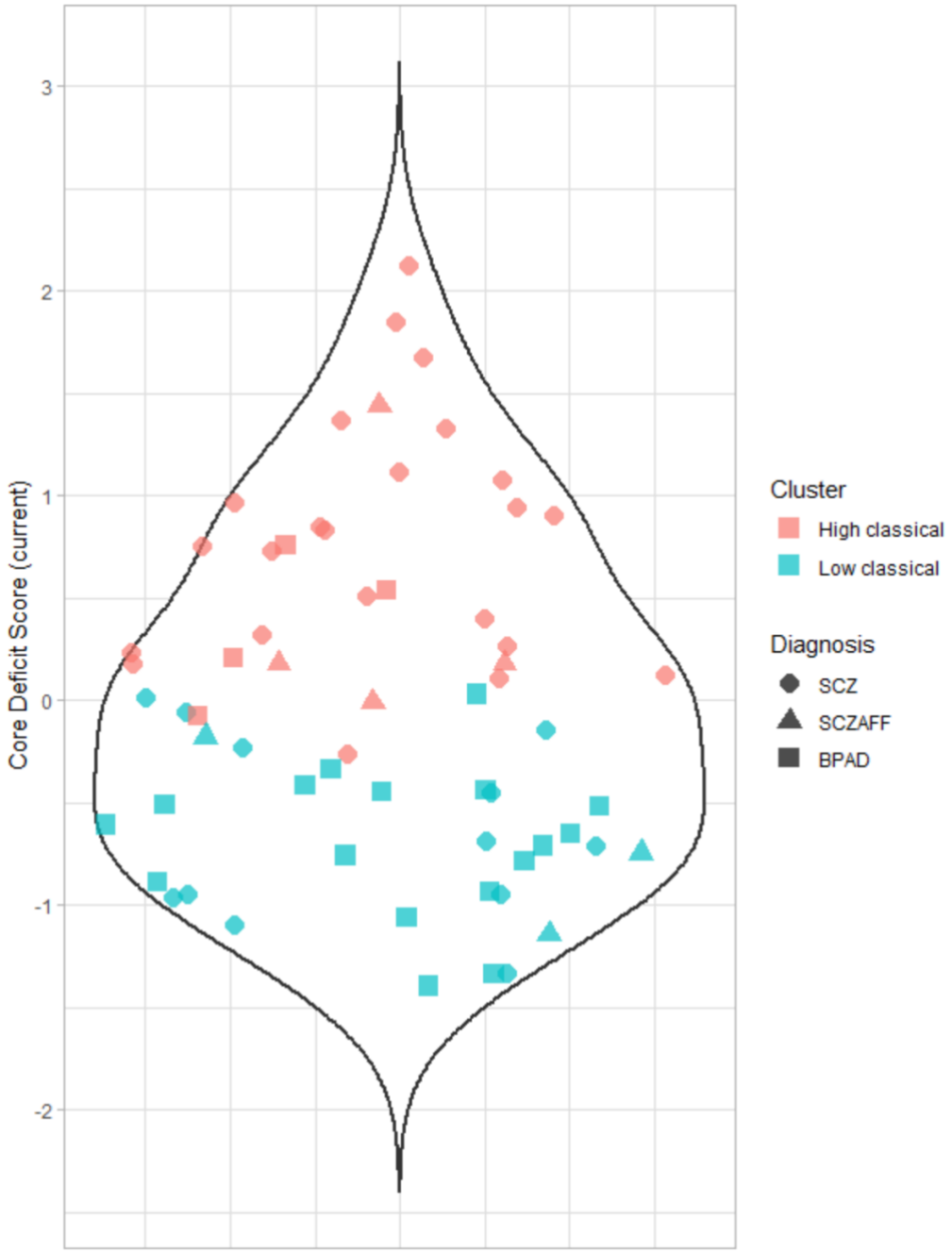

Figure 4-10: Violin plot showing the distribution of classical scores derived from current symptom scores. Datapoints represent individual patients, coloured to indicate cluster assignment. The shape of the datapoint indicates diagnosis.

Relationship with PMBR

Diminished PMBR was associated with corresponding enhanced severity of core deficit (current) scores, as evident in Figure 4-11.

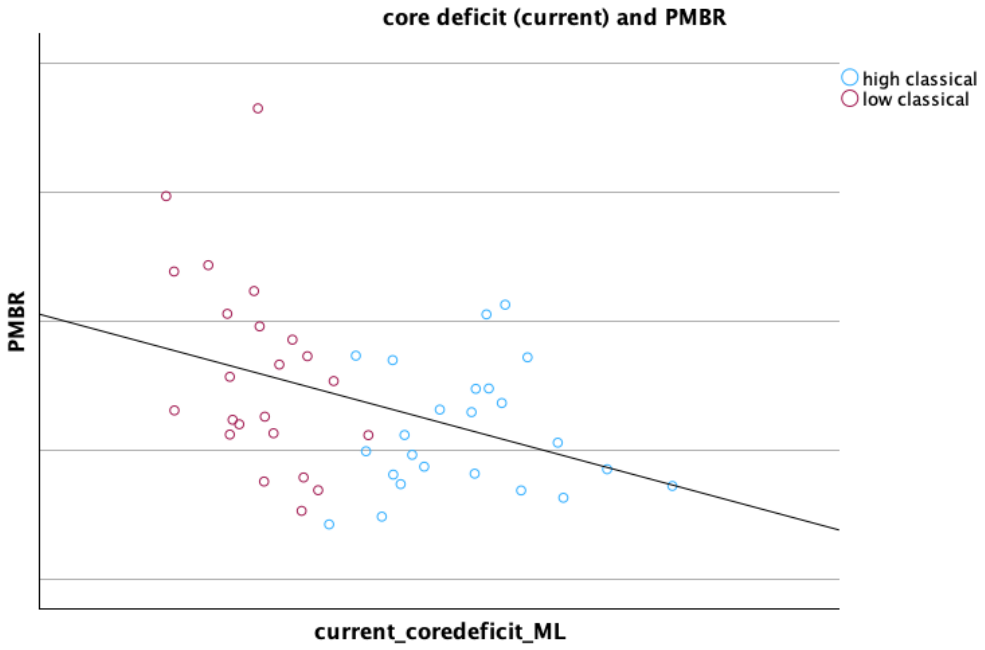

Figure 4-11: Relationship between core deficit (current) and PMBR

4.4 Discussion

Our results demonstrate that a single latent variable of putative core deficit can be identified by maximum likelihood factor analysis, using both persistent disorganization and impoverishment as well as current disorganization and impoverishment. These two core deficit measures are highly correlated with each other pointing to underlying core processes that need to be uncovered.

By demonstrating the significant positive correlation between core deficit measures and FTD as quantified by TLI total, I confirm that core deficit can be a valid measure to quantify the classicality. This is even more promising on the backdrop of our results that core deficit from current measures of disorganization and impoverishment is significantly positively correlated with FTD measure. Keeping in mind that numerous efforts have been made in the past to quantify FTD and to have replicability of results, our demonstration that core deficit can serve as that valid measure of classicality will have useful clinical implications as well as future research influence.

Furthermore, both the core deficit measures are significantly positively correlated with current reality distortion confirming the conceptualisation that severity of core deficit predisposes and predicts delusions and hallucinations. Speculative theoretical formulation can be extended to imply that severity of core deficit precipitates the episodes of florid psychosis that is commonly observed in clinical practice with delusions and hallucinations. This notion would mean that by ameliorating the severity of core deficit with targeted interventions, it seems plausible that the frequency and intensity of episodes of florid psychosis can be significantly reduced.

I demonstrated that clusters can be identified by utilising both persistence symptoms and current symptoms. This study has the unique advantage of having both persistence scores and current scores for the symptom dimensions. Furthermore, the sample studied consists of individuals in their stable phase of illness. Hence, this can be considered best opportunity to explore the classicality of classical schizophrenia.

Cluster of high classicality identified from persistent symptom scores was characterised by increased illness duration, pronounced impoverishment evident from symptom scales (current and persistent SSPI impoverishment scores) and from speech manifestations (TLI impoverishment). This would make us wonder if this cluster is more representative of predominant negative symptom schizophrenia which has been described previously under different terms of ‘deficit schizophrenia’ and ‘residual schizophrenia’. Residual schizophrenia can be conceptualised as the tail end of classical schizophrenia. However, it is important to consider that above results were based on persistence symptoms and persistent impoverishment was the main predictor of importance in deriving these two clusters. It is worth taking into account the fact that the clinicians would readily observe and document impoverishment phenomenon such as flat affect, underactivity, poverty of speech and anhedonia. It is plausible that the scores obtained from persistence symptom measurement are positively skewed towards recognising

impoverishment but not the disorganization as the persistence symptoms were derived from retrospective scrutiny of clinical case records.

Classical cluster identified based on current symptoms of disorganization and impoverishment supports this proposition with disorganization sharing the predictor of importance status with impoverishment. But it needs to be acknowledged that disorganization continues to be a difficult to quantify symptom dimension.

Our results from clusters based on persistence symptoms and also examination of classical dimension (core deficit) would support the dimensional model for psychosis. Previous studies comparing specifically the validity of categorical and dimensional models to classify psychotic disorders have supported the superiority of dimensional approach in several domains (Peralta & Cuesta, 2007; Van Os et al., 1999). Peralta and Cuesta, in their critical analysis of dimensional and categorical architecture for classification of psychotic disorders (2007), propose that a dimensional model to describe psychotic disorders needs to be developed in a systematic and stepwise basis, including developing new scales that can assess entire range of the dimensions of interest and natural grouping of symptoms into dimensional syndromes. Our results would lead us to propose dimensional model based on putative core deficit which can satisfy criteria for being developed in such systematic and stepwise manner. First step proposed by Peralta and Cuesta for dimensional model for psychosis disorders is that the new scales need to be developed that can assess the entire range of dimensions of interest and attention to items should be paid in particular because previously excessive emphasis has been placed on delusions, hallucinations and negative symptoms. We advocate for a new scale utilising putative core deficit or classical dimension, which would include the entire range of core features and the symptom items included would be representative of cognitive, behavioural, motor and thought manifestations of underlying core pathophysiological process. Second step proposed by Peralta and Cuesta is the natural grouping of symptoms into dimensional syndromes. By deriving the

dimension of disorganization and impoverishment from systematic review of factor analysis of three symptom scales (as described in chapter1), we demonstrate that symptoms are naturally grouped into dimensional syndromes. Furthermore, Peralta and Cuesta advocate for assessments in both stable phase and active psychosis phase. We have already demonstrated classical dimension in two samples of patients in stable phase of psychosis. Assessment in non-stable phase of psychosis is described in the next chapter. Final step would be to incorporate dimensional syndromes into categorical classification, which seems plausible if future research efforts are focussed towards identifying a threshold on the severity of putative core deficit.

Having demonstrated the clinical signature of classicality, I demonstrate the neural signature mainly through PMBR. Diminished PMBR consistently comes across as candidate marker of classicality through its negative correlation with putative core deficit in schizophrenia sample and in psychosis sample in both previous and current chapter. Furthermore, classical schizophrenia cluster identified based on current symptoms in this investigation presents itself as a representative group with enhanced core deficit. One can foresee that classical schizophrenia can render itself open to further research into molecular and genetic basis of underlying core pathophysiological processes based on further investigations into putative core deficit.

Limitations of this investigation include the fact that persistence symptom measures were obtained from retrospective scrutiny of case records and hence it is plausible that disorganization dimension in particular is underrepresented. Small sample size and cross-sectional nature of investigation would limit the extent to which inferences can be made. Confounding effect of variables such as age and antipsychotic exposure haven't been investigated in a robust way. Nevertheless, from our preliminary exploratory analysis, it can be argued that putative core deficit can be the valid and replicable marker of classicality which predicts reality distortion, and which opens up new doors for research and clinical efforts to improve the outcome for individuals with psychosis.

Chapter 5: Delineating classicality of classical schizophrenia and exploring clinical correlates in a multi-centre study: SPRING

Abstract

Having demonstrated the existence of a single latent variable of putative core deficit in two independent stable psychosis samples, I set out to investigate whether a single classical dimension can be identified from factor analysis in a heterogenous multi-centre mixed sample of both recent-onset and established cases of schizophrenia. We further tested our theoretical formulation that core deficit will predict reality distortion. Furthermore, I continued examination of nature of classicality in the context of dimensional or categorical distribution, towards which we completed cluster analysis.

Our results demonstrated that a single latent variable can be derived in a multi-centre mix sample and confirmed that core deficit predicts reality distortion. Cluster analysis resulted in two clusters, but classicality came across as a dimensional entity rather than discrete categories in keeping with our previous observations.

By identifying single latent variable of classical dimension in this chapter, in addition to similar results from previous two chapters, I provide evidence to support core deficit as a robust measure to be utilised for future research and clinical purposes. Furthermore, I provide more evidence towards dimensional nature of classicality and evidence to support conceptualisation of core deficit predicting florid psychosis of reality distortion.

5.1 Introduction

5.1.1 Overview

The preceding chapters of this thesis have examined sample of participants during a stable phase of psychosis illness, defined as no appreciable change in function in the preceding 8 weeks. Furthermore, the samples of patients studied in previous two chapters were in their established phase or chronic schizophrenia. Having demonstrated the existence of a single classical dimension in such stable psychosis sample, we wanted to explore if such classicality can be delineated from a mix of recent onset and established cases of schizophrenia. It is plausible that the disorganization quantified from a realistic sample of mix of both recent-onset and established schizophrenia patients, might be confounded by excitation and acute transient disorganization. Acute cases of schizophrenia of recent onset exhibit pressure of speech, excitation and flight of ideas which can confound the quantification of disorganization dimension. Equally, quantification of impoverishment can be confounded by secondary negative symptoms as a result of antipsychotic exposure or associated with sedentary lifestyle and metabolic syndrome.

This current chapter describes the study of classicality or core features of classical schizophrenia in a heterogenous practical sample of patients from multi-centre study, with two arms of the study, one arm with patients of recent onset schizophrenia and their matched controls and the other arm being patients with chronic schizophrenia (>10 years duration) and their matched controls.

5.1.2 Background

Further to the evidence presented in Chapter 1 for core features defining classicality, it is worth emphasising the relationship between core features and reality distortion. Previous studies have demonstrated that

disorganization and impoverishment predict overt psychosis and poor functional outcome (Dominguez et al., 2010; Ziermans et al., 2014), contributing to theoretical formulation that core deficit might predict the reality distortion associated with episodes of florid psychosis (P. F. Liddle, 2019). Overarching unified mechanisms such as predictive coding (P. F. Liddle & Liddle, 2022) and dysfunctional plasticity (Guterman et al., 2021) have been proposed to bring together the underlying pathophysiological processes leading to manifestations of symptoms in schizophrenia.

5.1.3 Recent onset versus established schizophrenia

Clinical signature of early phase schizophrenia illness might be different compared to established chronic phase of schizophrenia. Negative symptoms and cognitive impairment might predominate the presentation in the established phase. As alluded to before, impoverishment might be contributed additional confounds rather than the underlying pathophysiological process of classicality. Similarly, there might be more contribution from psychomotor excitation and acute processes such as disorientation to both reality distortion and disorganization phenomenon. It would be helpful to explore if there is a common shared underlying dimension of psychopathology between early phase and established phase schizophrenia.

5.1.4 Antipsychotic exposure

Evidence from PET studies (Kapur et al., 2000) indicates that antipsychotic effects are small at doses below 50% DA receptor occupancy, in the therapeutic range for 60-80% and are in excess of antipsychotic needs above 80%. However, occupancy data is not available for all antipsychotics and is not directly relevant to therapeutic effect for all antipsychotics (especially clozapine). Therefore, it is more practical to define broad ranges (low, medium and high, relative to the doses that have become established in clinical practice, even though these are only an approximate indicator of

effects on brain chemistry or brain function (Leucht et al., 2016). WHO defines the Defined Daily Dose (DDD) as

> "The defined daily dose DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults."

In the case of olanzapine, DDD is 10mg. According to the PET data reported by Kapur et al. (2000), during sustained treatment, olanzapine produces 50% occupancy at approximately 5mg/day: 70% occupancy at 10 mg/day and 80% occupancy at 20 mg/day. Thus, in the case of olanzapine, assuming that the therapeutic range is 50-80% DA occupancy, the therapeutic range is from 0.5 DDD to 2 DDD. For other antipsychotics, DDD is likely to be less closely related to DA occupancy. Typically, DDD for first generation antipsychotics is associated with high occupancy due to the establishment of customary practice an era when higher doses were widely used, whereas for clozapine, DDD corresponds to a lower DA receptor occupancy reflecting the evidence that therapeutic effects occur at lower DA receptor occupancy than for other antipsychotics. Nonetheless, if we seek a definition of dose range based on customary practice, 0.5 DDD to 2 DDD is an appropriate estimate.

Dose ranges

- Low: dose < 0.5 DDD
- Medium: 0.5 DDD =< Daily Dose =< 2 DDD
- High: Daily dose > 2 DDD

Duration of exposure

With regard to the neural effects of lifetime exposure, there is little evidence to provide firm guidance, as studies are inconsistent, possibly reflecting variation between individuals based on predisposition and phase of illness, and within individual depending on brain region. Nonetheless, significant decreases in brain tissue volume have been reported in longitudinal studies of 3-5 years in the early phase of illness (Haijma et al., 2013; Kubota et al., 2015; van Haren et al., 2008). Neeltljee et al reported excessive focal decreases in

cortical thickness during the 5-year interval ranging from 0.05 to 0.19 mm (compared with a mean of 0.01 mm in healthy controls). Overall, evidence indicates that illness duration of 5 years is associated with substantial tissue loss in predisposed individuals with schizophrenia. If medication contributes an appreciable portion to this tissue loss, a time scale of 5 years is likely to be relevant to appreciable tissue loss.

5.1.5 Aims

1. To test the hypothesis that a single classical dimension of core deficit can be delineated from a heterogenous mixed sample of both recent-onset and established DSM schizophrenia cases.
2. To investigate the relationship between core deficit and reality distortion based on the theoretical formulation that the severity of core deficit predisposes to reality distortion and florid psychosis.
3. To further examine if discrete clusters of varying classicality can be identified from the mixed sample of acute and chronic schizophrenia.
4. To test for differences in clinical and demographic characteristics including purpose-designed measure of cumulative antipsychotic exposure between clusters of varying severity of classicality

5.2 Methods

Details of the study protocol and the participant criteria are previously published (Conen et al., 2020; Gascoyne et al., 2020). Salient features relevant to our investigation are given below:

SPRING Study: The Study of Psychosis and the Role of Inflammation and GABA/Glutamate

Number of study institutes: 3 – University of Manchester, University of Nottingham, Cardiff University.

The study was conducted across three sites: Cardiff University, University of Manchester, and University of Nottingham. The three sites recruited the same

number of participants but undertook different complementary imaging techniques to investigate the research objectives.

1. Cardiff University – 3T 1H MRS, and MEG.
2. University of Manchester – 3T 1H MRS, 3T 13C MRS, and PET.
3. University of Nottingham – 7T 1H MRS, 7T 13C MRS, and MEG.

5.2.1 Study population

The study population consisted of three groups:

1. Patients with recent onset psychosis (less than 5 years since diagnosis): target n=60 in total; 20 per site, recruited n=62.
2. Patients with established psychosis (10 or more years since diagnosis): target n=60 in total; 20 per site, recruited n = 76.
3. Healthy volunteers matched for age, sex and parental occupational status: target n=60 in total; 20 per site, recruited n = 74.

Patient criteria

Inclusion/Exclusion criteria are shown below.

Inclusion criteria

1. Male or female aged 18 - 55 years.
2. Ability to understand and willing to give written informed consent.
3. English as first language or fluent.
4. Current DSM IV criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder.
5. <5 years from onset for early psychosis group; or >10 years for established illness group.

6. Antipsychotic drugs: no exposure, discontinued or minimal (<12 weeks) exposure for early psychosis group; or for established illness group 8 weeks of stable treatment.

Exclusion criteria

1. Clinically significant neurological disorder
2. History of head injury, which in the opinion of the investigator, may significantly affect the results of the study.
3. Any other relevant findings on investigation, examination or medical history at screening which, in the opinion of the investigator, may significantly affect the results of the study, or may make it unsafe for the participant to take part.
4. Current harmful use of, or recent dependence on, psychoactive substances (excluding nicotine) in the opinion of the investigator.
5. Current use of any medication which may interfere with the study, in the opinion of the investigator.
6. Contraindications for MR scanning (e.g. claustrophobia, pregnancy etc).
7. Taken part within the previous month as a participant in a clinical trial that involved taking an experimental drug.
8. A blood-borne virus that would preclude the research protocol being followed.

Healthy control criteria

Healthy persons matched by sex, age and parental occupational status.

Inclusion criteria

1. Male or female, aged 18 - 55 years.
2. Ability to understand and willing to give written informed consent.
3. English as first language or fluent.

Exclusion criteria

1. Personal history of psychosis or related disorder as determined by MINI (-international neuropsychiatric interview) (Sheehan et al., 1998a).
2. Current or recent (within 2 years) presence of depressive symptoms or treatment with antidepressant medication.
3. Current use of any medication which may interfere with the study, in the opinion of the investigator.
4. First degree relative with a history of psychosis.
5. Clinically significant neurological disorder
6. History of head injury, which in the opinion of the investigator, may significantly affect the results of the study.
7. Current harmful use of, or recent dependence on, psychoactive substances (excluding nicotine) in the opinion of the investigator.
8. Contraindications for MR scanning (e.g. claustrophobia, pregnancy etc).
9. Taken part within the previous month as a participant in a clinical trial that involved taking an experimental drug.
10. A blood-borne virus that would preclude the research protocol being followed.

5.2.2 Assessments completed:

Clinical assessments:

Patient sample only:

1. Consensus diagnosis from interview and case notes (Leckman et al., 1982)
2. The PSP (The Personal and Social Performance) scale (Morosini et al., 2000)
3. Current and lifetime therapeutic drug exposure:

Cumulative lifetime antipsychotic exposure scores were quantified for both any antipsychotic exposure (Total Exposure Score) and for Clozapine exposure.

Total exposure score

Range 0-10 based on duration and dose:

0 no antipsychotic exposure
1 Low dose exposure only (any duration)
2 Less than 1 year total exposure including some medium but no high dose exposure:
3 Less than 1 year of total exposure including some high dose exposure:
4 One to five years total exposure including medium but no high dose exposure lasting more than one month.
5 One to five years total exposure including with some high dose exposure lasting more than one month.
6 Five to 10 years total exposure including medium dose but no high dose exposure lasting more than one month.
7 Five to 10 years total exposure with some high dose exposure lasting more than one month.
8 Greater than 10 year exposure including medium but no high dose exposure lasting more than one month.
9 Greater than 10 years total exposure including with high dose exposure of between one month and 5 years in duration.
10 Greater than 10 years total exposure including high dose exposure of greater than 5 years in duration.

Clozapine exposure score

Taking into account that DDD is not likely to be meaningful for Clozapine exposure, four-point scale capture the relevant information was utilised.

0 no evidence of exposure to clozapine
1 exposure to clozapine for less than 1 year
2 exposure to clozapine for greater than 1 year, less than 5 years
3 exposure to clozapine for greater than 5 years.

For measure of role-function, the Personal and Social Performance (PSP) scale was used. Originally developed by Morosini, Magliano, Brambilla, Ugolini, and Pioli (2000), PSP consists of four main areas:

1. Socially useful activities (e.g., housework, voluntary work) including work and study.

2. Personal and social relationships (i.e., partner, family relationships, friends)
3. Self-care (i.e., personal hygiene, care of one's appearance)
4. Disturbing and aggressive behaviour

The patient's degree of severity in the four domains was rated on a six-point scale from absent (which means no problems on this dimension) over mild, manifest, marked, severe to very severe difficulties in the given area. Out of the ratings on the four subdimensions, one total score on a 100-point scale was created.

Control participants only:

The MINI (The Mini-international neuropsychiatric interview) (Sheehan et al., 1998)

The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicentre clinical trials and epidemiology studies and to be used as a first step in outcome tracking in non-research clinical settings.

Patient and control participants:

- Handedness (Motor Dominance Demonstration Test) (Seisdedos et al., 1999; Tabarés et al., 1997)
- Parental Occupational Status (Rose & J.Pevalin, 2003)
- Drugs of abuse, alcohol and nicotine questionnaire

Cognitive tasks

All cognitive tasks were completed for patient and control participants.

IQ was measured - premorbid, current and the decline associated with functional outcome.

- Wechsler Test of Adult Reading (WTAR)(Whitney et al., 2010)
- *Wechsler Adult Intelligence Scale* (WAIS) (Leeson et al., 2009)
    - Digit Symbol
    - Arithmetic
    - Information
    - Block Design

Assessment of working memory, processing speed and other functions associated with psychomotor poverty or disorganised symptoms was done via tasks from the MATRICS (MCCB) battery (Nuechterlein et al., 2008)

- Category fluency (5mins)
- Letter number span (5mins)
- Spatial span (5mins)

The MATRICS Consensus Cognitive Battery (MCCB) was developed to be an endpoint for clinical trials aiming to enhance cognition in schizophrenia. The MCCB is sensitive to the cognitive impairments observed in schizophrenia. The reported frequency distribution of the overall composite MCCB score is strikingly different in SZ and HC populations, demonstrating the sensitivity of the battery to the type of impairment observed in schizophrenia. MCCB is highly sensitive to the types of impairments observed in schizophrenia. The composite score appears to be a measure of broad intellectual ability and the individual domain scores demonstrate significant inter-correlations. MCCB performance is related to functional outcome in the area of vocational performance (August et al., 2012)

Symptom assessments

Below symptom scales were administered to all participants during either the Screening visit or a scanning session visit:

- Signs and symptoms of psychotic illness, (Poverty, disorganisation and reality distortion syndrome scores) [SSPI] (P. F. Liddle, Ngan, Duffield, et al., 2002)

- Positive and Negative Syndrome Scale [PANSS] (Kay et al., 1987)
- Thought Language, and Communication Index [TLI] (P. F. Liddle, Ngan, Caissie, et al., 2002)

Both the SSPI and PANSS were scored from a same semi-structured interview with the participant. The interview was audio recorded to aid the scoring of the scales and also to ensure inter-rater reliability across sites. After the study visit, to ensure participant confidentiality, any participant identifiable data in the recording was removed by the researcher.

For the TLI, participants were shown three pictures from the Thematic Apperception Test (Murray, 1943) (a rural scene; a river scene; and a picture of two people in conversation) one at a time and asked to describe each of them for 1 minute. The participants utterances were recorded on audiotape, and subsequently transcribed.

To further establish inter-rater reliability for PANSS/SSPI and TLI, some of the interviews were video recorded. This was optional for participants. The patient videos were only available to members of research team who were involved in the rating exercise. The data was stored in a secure locked computer hard disk at the coordinating centre at each site, with videos password protected and not available on shared drives.

Smoking Pack Years measure was computed for all the participants based on the available data about age when started smoking and number of years and quantity of smoking daily. Number of packs smoked per day multiplied by number of years of smoking resulted in the measure of Smoking Pack Years.

Body Mass Index (BMI) of 27 has been proposed as a good threshold to differentiate between high propensity of metabolic syndrome versus less likelihood of the same (Ofer et al., 2019).

5.2.3 Analysis:

As discussed in previous chapters, in terms of the quantity of subgroups found, the likelihood that an individual will be classified into a subgroup, and

the repeatability of results on clinical and other types of data, comparative studies consider Two-Step cluster analysis to be among the most reliable (Bacher et al., 2004; Gelbard et al., 2007; Kent et al., 2014). IBM SPSS Statistics (version 29.0) was used to implement the Two-Step cluster analysis (Chiu et al., 2001; Bacher et al., 2004). The cases are pre-clustered in the first stage (pre-clustering) using a sequential technique based on the definition of dense regions in the analyzed attribute-space. During the second phase, known as clustering, each pre-cluster is combined statistically until all of the clusters are part of a single cluster. The solution with the strongest change and the fewest clusters is regarded as the optimal cluster solution. This makes it possible to assess which parsimonious cluster solution offers the best fit. In SPSS, this process is carried out automatically for the Two-Step cluster analysis.

Variables included in cluster analysis:

Disorganization and Impoverishment clusters derived from PANSS (methods have been described in chapter 1), along with DSST from MATRICS cognitive battery for cognition and PSP for role-function measure. PANSS symptom measures of disorganization and impoverishment were log-transformed (base 10) as they were not normally distributed.

Medication exposure: Cumulative antipsychotic exposure, clozapine exposure and their relative effect on the clusters were explored.

Core deficit:

The maximum likelihood method of factor analysis was conducted, similar to the procedure in previous chapters to derive the core deficit of classical schizophrenia. Measures of the core features of disorganization (PANSS), impoverishment (PANSS), cognition (DSST_scaled) and functioning (PSP) were used to derive this classical dimension. The relationship of core deficit with reality distortion was explored.

5.3 Results

Core deficit:

Maximum likelihood factor analysis of the schizophrenia group (N=128) resulted in a single factor with Eigenvalue more than 1, accounting for 42.4% of the variance. Factor loadings are shown in Table 5-1.

Table 5-1: Factor loadings for core deficit.

	Core Deficit factor loading
Role-function	-.545
Cognition	-.312
Disorganization	.381
Impoverishment	.693

Maximum-likelihood factor analysis resulting in single latent variable of classicality

Characteristics of clusters identified from two-step cluster analysis, are given in Figure 5-1. Similar proportions of the established and recent-onset cases were represented in each cluster (Figure 5-2).

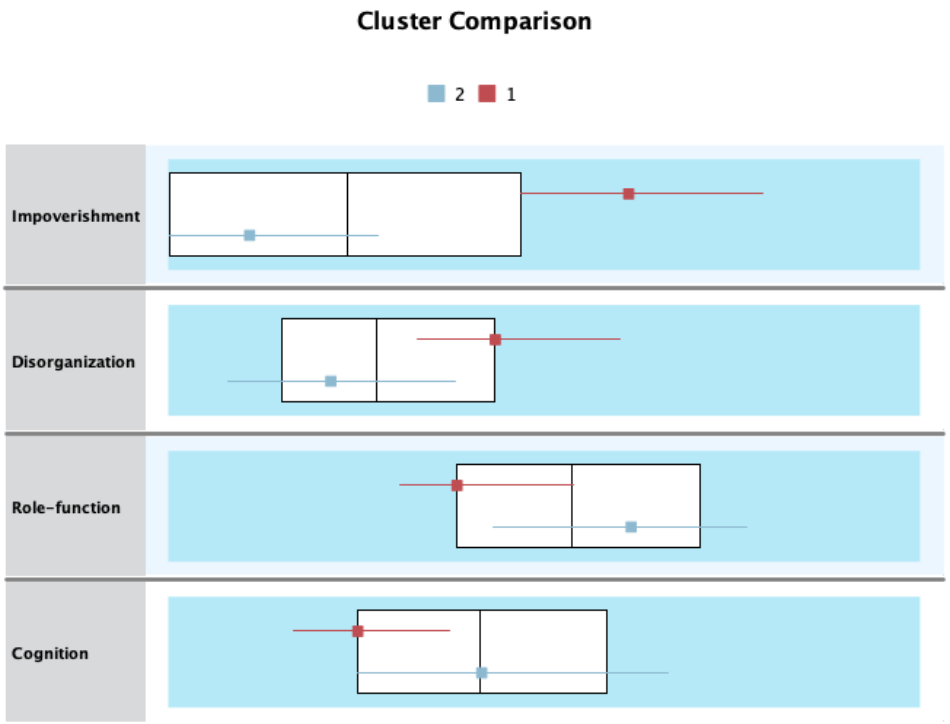

Figure 5-1: Cluster Comparison, 2-Low classicality , 1-high classicality.

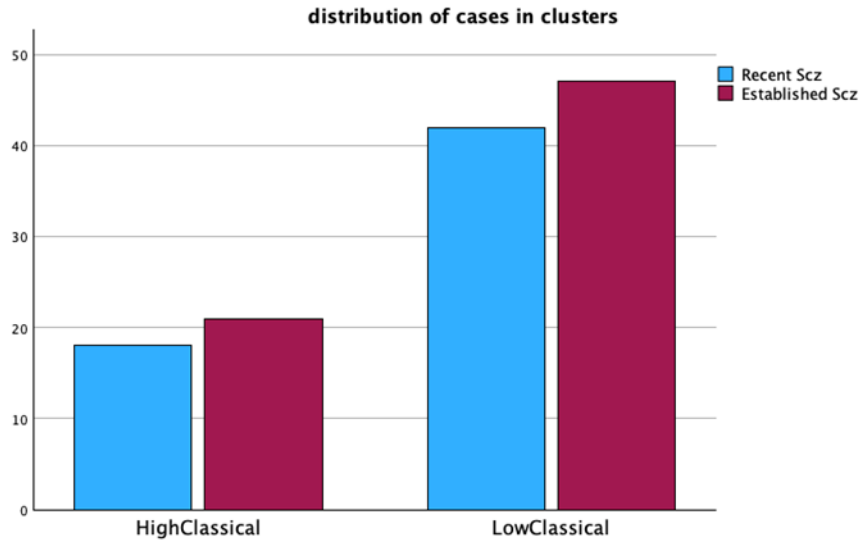

Figure 5-2: Distribution of recent-onset and established cases of Scz in clusters of high v/s low classicality

Table 5-2: Differences between clusters

	Highclassical (N=39)	**Lowclassical (N=89)**	**Significance**
Age	33.10	33.80	t(126)=-0.32,p=0.74,d=-.062
Father_SES	3.19	2.76	t(118)=1.24,p=0.22,d=.250
Cumulative_AP_exp	5.00	4.98	t(126)=0.04,p=0.97,d=.007
BMI	27.30	27.80	t(123)=-0.36,p=0.65,d=-.088
Duration of Illness (months)	112.4	114.4	t(124)=-0.09,p=0.92,d=-.018
Smoking_PackYears	19.01	14.05	t(99)=1.05,p=0.29,d=.229
PANSS Positive symp	16.13	9.14	**t(126)=3.08,p=0.003,d=0.591**
PANSS Negative symp	19.72	9.91	**t(126)=14.90,p<.001,d=2.859**
PANSS Total	68.31	48.64	**t(126)=8.18,p<.001,d=1.571**
Clozapine Exposure Sc	0.74	0.48	t(126)=1.20,p=.231,d=.608
WTAR_total	97.13	101.11	t(126)=-1.16,p=0.248,d=-.223
WAIS_FSIQ	85.74	94.31	**t(126)=-2.93,p=0.004,d=-.562**
SSPI_reality_distortion	4.13	2.65	**t(126)=2.79,p=0.003,d=0.537**
SSPI_Excitability	.46	.40	t(126)=0.31,p=.759,d=0.059

Father SES: Socioeconomic Status of parent (father), Cumulative_AP_exp: cumulative antipsychotic exposure, BMI: Body Mass Index, WTAR: Wechsler test of adult reading, WAIS_FSIQ: Wechsler Adult Intelligence Scale _full-scale intelligence quotient, PANSS: Positive and negative symptom scale, SSPI: Symptoms and Signs of Psychotic Illness. Differences significant at p<.05 are indicated in bold font.

As evident from Table 5-1, Age, BMI, socio-economic status or duration of Illness did not exert significant effect in differentiating clusters with varying classicality. Similarly antipsychotic exposure was not significantly different between clusters, but clozapine exposure is more pronounced in the cluster with high classicality implying that the cases from this cluster might be the ones with persisting symptoms from multiple domains which are resistant to traditional treatment with antipsychotics. This inference is further supported by the results of symptom dimensions from above table. Delusions and hallucinations (reality distortion) is significantly enhanced along with PANSS positive, negative and total symptom scores in the cluster of high classicality. Furthermore, WTAR which is a measure of pre-morbid intellectual functioning (Venegas & Clark, 2011), is significantly reduced in this cluster along with full scale IQ measure of WAIS. These results would imply that the cluster with high classicality is representative of classical schizophrenia in its purest form in which the disease begins from pre-morbid stage and persists onto older adult age, characterised by enhanced core features and resistant to the current antipsychotic interventions.

Relationship between Core deficit and Reality distortion

Core deficit was positively correlated with reality distortion, ***r*(128) = .306, *p*<.001**, in keeping with our hypothesis that severity of core deficit would predict florid psychosis of reality distortion. A scatterplot showing this correlation is given in Figure 5-3.

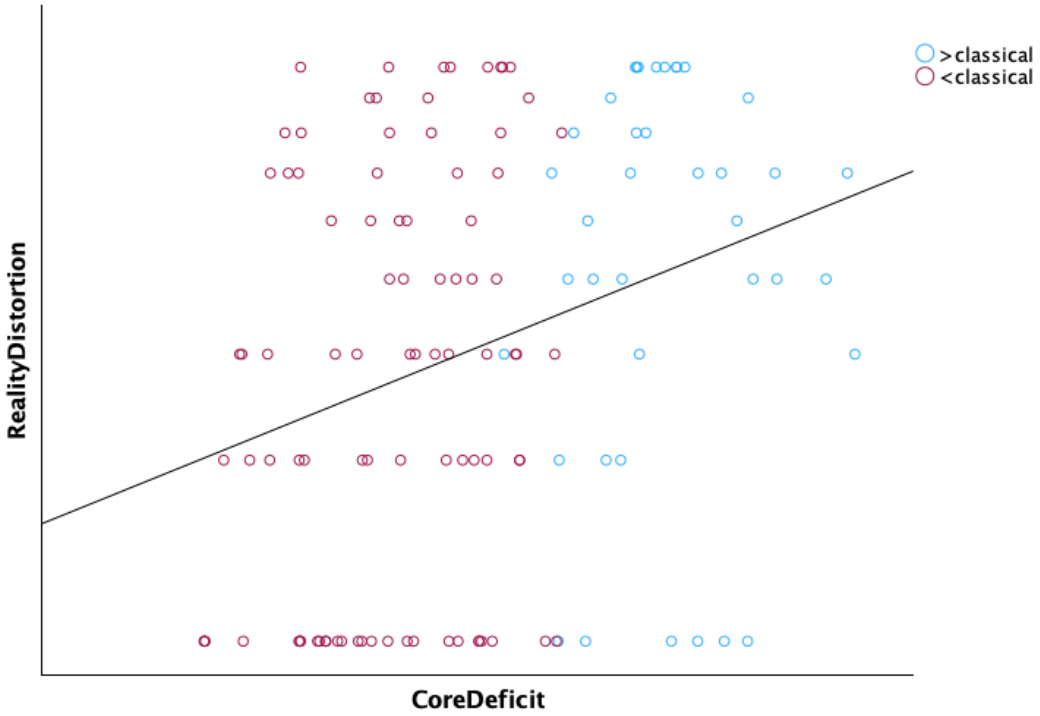

Figure 5-3: Relationship between the core deficit and Reality Distortion, exhibiting proportionate increase in reality distortion with core deficit severity.

Furthermore, to investigate if metabolic syndrome as a risk factor drives the relationship between core deficit and reality distortion, we completed partial correlation controlling for BMI and results including zero order correlations confirmed that BMI does not account for the relationship between core deficit and reality distortion, ***r*(122) = .291, *N*=125, *p*<.001**. This is further illustrated by in the scatterplot shown in Figure 5-4.

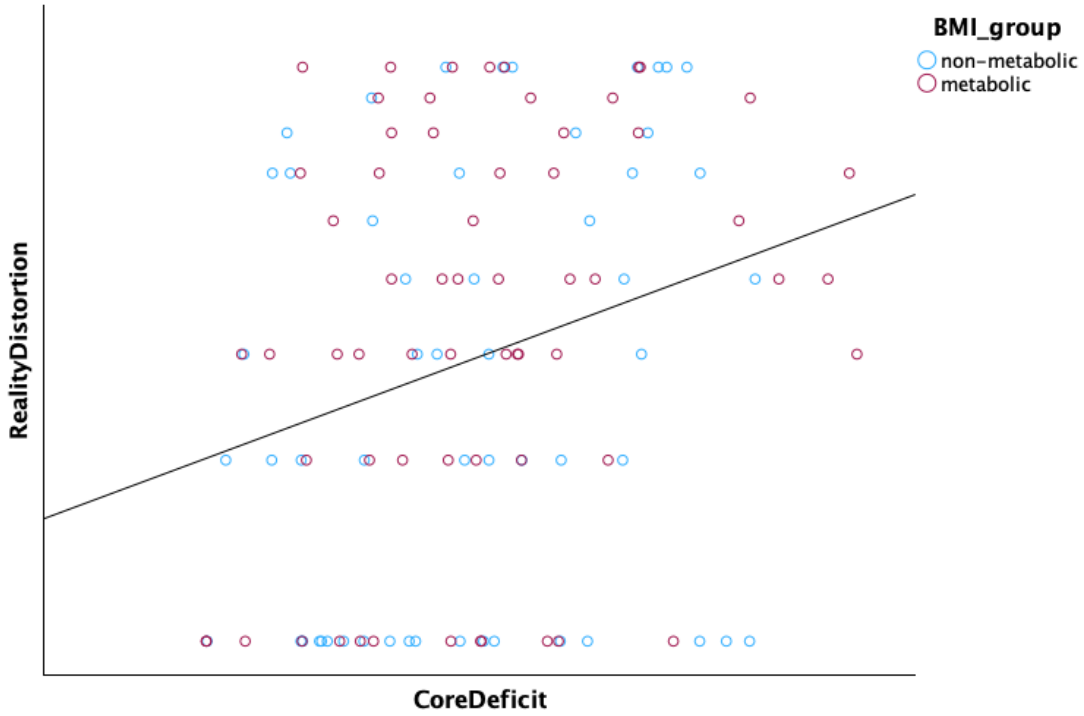

Figure 5-4: Relationship between core deficit and reality distortion in the context of high v/s low BMI.

Metabolic group = BMI equal to or more than 27. Non-metabolic group = BMI less than 27.

Figure 5-5 is a violin plot showing the distribution of core deficit scores for this data set, with individual participants represented as jittered data points, coloured to indicate cluster membership . As with the two datasets reported earlier, the plot provides little evidence of discrete clusters along the classical dimension. There is also little evidence in the plot of an association between phase of illness and cluster membership.

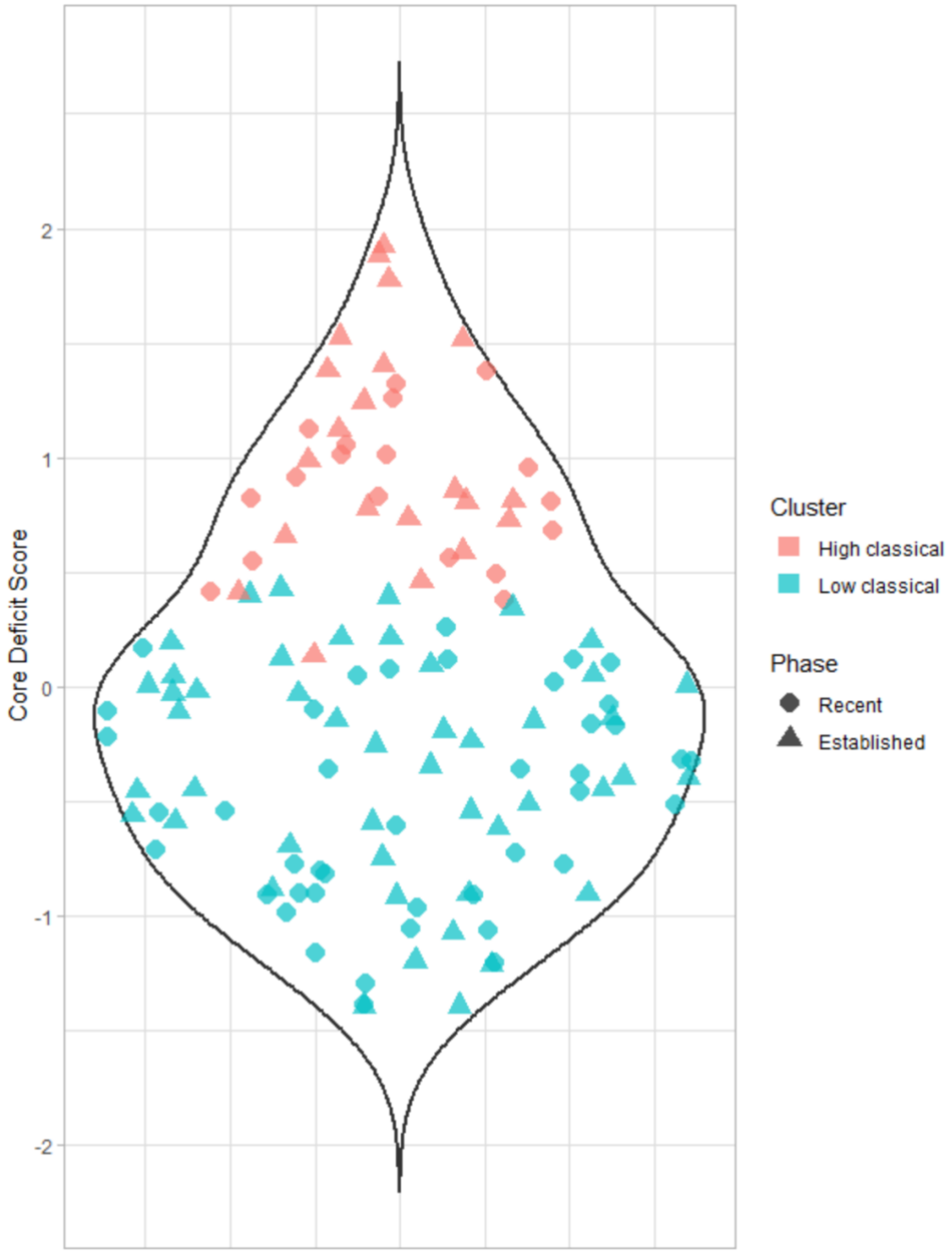

Figure 5-5: Violin plot showing distribution of Core Deficit scores in the SPRING sample. Each datapoint represents a patient with schizophrenia, coloured according to cluster membership. The shape of each datapoint indicates whether they were from the Recent onset or from the Established group.

5.4 Discussion:

By identifying two clusters from a heterogenous multi-centre mixed sample of both recent-onset and established schizophrenia, we have demonstrated the

utility of classical features (disorganization, impoverishment, cognition and role-function) in segregating groups with high versus low classicality, which would have clinical implications including targeted interventions with future research. Furthermore, by demonstrating that a single classical dimension can be derived in a large multi-centre heterogenous sample, through factor analysis using the same core features, we have provided further avenues for direct utility in clinical and research settings. Classical dimension derived in our previous investigations (Chapters 3 and 4), had predominant loadings from disorganization, but that's not the case in this study. As described in the introduction, there might be overlap of symptoms between different dimensions, particularly among reality distortion and excitability, as the stability of illness was not possible to ensure in this heterogenous sample. However, given the practical difficulties in recruiting a big sample and the challenges in quantification of symptom dimensions, our investigation provides credible support for reliable quantification of core features along with confirmation of shared variance among them.

By utilising the maximum likelihood method and demonstrating a single classical dimension, we add evidence towards an underlying intermediate process of shared variance which can be derived from items of widely used symptom scales and performance measures. By identifying a factor with similar loadings to that reported in chapters 3 and 4, the analysis in this chapter has added to the accumulating evidence that this factor can be identified in a robust manner.

Furthermore, severity of classical dimension is significantly enhanced in the cluster with high classicality. From our results, we can infer that the classicality lies in a continuum, although it would be beneficial to further isolate a categorical group of severe core deficit which can be studied for targeted interventions. On that note, putative core deficit emerges as the consistent clinical dimension which can be targeted to improve outcomes and to ameliorate the persisting disability in psychosis illness.

Limitations of investigation in this chapter include the possible confounding effect of medication exposure, inflammation, age on the clinical variables as well as metabolic variables. Mediation/moderation analysis might help understand the complex nature of such relationship, which is being currently undertaken (Liddle et al., (in press)), but it is beyond the scope of this dissertation work.

It is reasonable to conceptualise this classical dimension as an intermediate biomarker for psychosis illness, similar to blood pressure (B.P) for vascular disorders. B.P lies on a continuum, but consensus guidelines come-up with threshold criteria to categorise people with or without Hypertension and these guidelines change with accumulated evidence. Furthermore, in individuals with genetic predisposition, high B.P is combined with other vascular risk factors such as metabolic syndrome, chronic smoking and physiological stress, can lead to severe manifestation such as ischaemic stroke. Theoretical formulation discussed earlier in the chapter, would support similar concept of core deficit precipitating episodes of florid psychosis involving reality distortion. Longitudinal studies can try to answer with data, but through our study, we demonstrate a significant correlation between core deficit and reality distortion. Taken together with the results of differences between two clusters particularly on symptom severity, it can be argued that higher classicality can be a surrogate marker for group of psychosis patients who are quite unwell, and their symptoms are resistant to traditional antipsychotic medications. If these individuals can be identified in their early phase of illness by potentially utilising putative core deficit, then treatment interventions can be person-centred and away from traditional medications of dopamine antagonism. Options backed by evidence such as neuromodulation techniques of rTMS and tDCS, cognitive remediation therapy, lithium augmentation of effective antidepressant use can be studied in trials, along with research into exploring genetic basis.

Chapter 6: Neural correlates of classicality in schizophrenia: SPRING

Abstract

There is heterogeneity in clinical manifestations as well as neuroimaging and neuropathological findings in schizophrenia. Structural deficits of GM volume, functional aberrations of neural oscillations, cortical metabolic activity measures of varying heterogeneity have been reported. Picture is even further complicated by the challenge of current classification system and in particular, the shortfalls of studying schizophrenia as a category or dimensional illness.

Having previously demonstrated the consistent finding of a single latent variable of classicality from three independent heterogenous sample of schizophrenia patients, we set out to investigate the relationship of classicality with neural features namely PMBR, Cortical metabolic factor from ACC, GM volume in salience network region as well as neuroinflammation(TSPO binding).Furthermore, I tested the potential association between neuroinflammation and peripheral inflammation in the context of classicality potentially being associated with multi-system manifestations.

Our main results indicated that neural measures of cortical metabolic activity and PMBR are diminished with severity of core deficit, albeit not a statistically significant association of PMBR with classicality. Our results demonstrated a positive association of Insula volume and TSPO binding with classicality, along with significant association between central and peripheral inflammation.

I put forward theoretical formulation of possible underlying unified core pathophysiology in neurons and glia which might lead to diminished cortical metabolic activity, diminished long range oscillations and enhanced core deficit manifestations in the salient network region of brain. Backed by accumulating evidence, I speculate mitochondrial dysfunction as one of the potential core pathophysiology mechanisms, which would have significant implications for research and clinical practice.

6.1 Introduction

This chapter presents an investigation of possible neural mechanisms underlying the clinical features of classical schizophrenia. A cardinal feature of classical schizophrenia is a tendency towards persisting symptoms and disability, suggesting a relatively persistent disorder of brain structure and/or function. Schizophrenia is associated with both microscopic and macroscopic damage to the brain (Bakhshi & Chance, 2015; Harrison, 1999). Substantial evidence indicates that the underlying pathological process is progressive in many cases, though the time course of the pathological processes remains a topic of debate (Haren et al., 2008).

Although the exact pathophysiology of brain morphometric changes in schizophrenia remain elusive, immune dysregulation has been suggested as underlying mechanism (Bergink et al., 2014; Boerrigter et al., 2017; Fillman et al., 2016; Kirkpatrick & Miller, 2013; Laskaris et al., 2016). Aberrant synaptic plasticity (Forsyth & Lewis, 2017) and disorganised cortical-subcortical connectivity (Howes & McCutcheon, 2017) have been reported to be part of schizophrenia at the molecular level. Inflammation has been found to be contributing to abnormalities of brain connectivity, synapse organization and neuronal signalling (Anderson et al., 2013; Aricioglu et al., 2016; Parellada & Gassó, 2021) in schizophrenia.

Both Bleuler and Kraepelin implied that the core issue in schizophrenia encompasses deficits in specialised domains of mental activity. Such core deficit would comprise impaired ability to initiate or co-ordinate mental activity. Integration of mental activity in brain is facilitated by network of neural connections. Disruption of such networks may lead to disruption of integration between specialised domains of mental activity, resulting in the manifestations of core features of schizophrenia (P. F. Liddle, 2019)

As emphasised in previous chapters, putative core deficit has shared variance of disorganization, impoverishment, cognitive dysfunction and impaired role-function, forming the foundation for the classical concept of schizophrenia as

described by Kraepelin and Bleuler. Some particular brain areas have been found to play crucial roles. One of the critical roles is facilitating the orderly recruitment of appropriate brain circuits (and mental processes) to efficiently handle the current demands. The insula and anterior cingulate cortex, which make up the salience network, are crucial for such orderly recruitment (Sridharan et al., 2008). The finding by Nenadic et al. (Nenadic et al., 2010) that decreased gray matter in the insula cortex is linked to both impoverished and disorganized mental activity in schizophrenia is significant in this context. But, it is essential to emphasise that brain circuits extending from frontal to occipital lobes are implicated in explaining the neural correlates of the core features of schizophrenia (P. F. Liddle, 2019)

Pro-inflammatory cytokine levels have been found to be negatively correlated with decreased gray matter volume in schizophrenia patients (Meisenzahl et al., 2001). Similarly, diminished frontal cortex gray matter has been linked to higher levels of pro-inflammatory cytokines in individuals at risk of psychosis who developed psychosis (Cannon et al., 2015). Thus, synaptic pruning may be disrupted by microglial activation, leading to the gray matter volume loss observed in schizophrenia (Laskaris et al., 2016). But it is noteworthy that recent review has found that binding potential of translocator protein (TSPO), which is considered a proxy measure for microglial activation/neuroinflammation has been found to be reduced in schizophrenia (Plavén-Sigray et al., 2018).

Elevated levels of markers of peripheral inflammation, particularly cytokines IL6, TNF-alpha along with c-reactive protein (CRP), have been consistently reported from meta-analyses and reviews in schizophrenia (Goldsmith et al., 2016; Miller et al., 2011; Potvin et al., 2008).

Furthermore, Escobar et al. (2023) emphasise the bi-directional interaction between neuroinflammation and peripheral inflammation and propose vicious cycle of interaction as a common factor in the aetiopathogenesis mechanisms of addictive disorders, neurological disorders and aging related pathology.

Classical schizophrenia can be considered a multi-system disease with crosstalk between brain and periphery on the background of underlying core pathophysiology. Exploring the role of inflammation in general and the association between central & peripheral inflammation, in particular, would have significant implications for further research and treatment of patients with classical schizophrenia.

6.1.1 Diminished cortical metabolic activity/defense in brain:

There have been previous studies of schizophrenia patients in which reduction of multiple metabolites including Glutamate (Glu) and Glutathione (GSH) have been reported, particularly in the region of medial frontal cortex (mPFC), but the interpretation has been different based on the group of researchers conducting the particular study (Dixon et al., 2022; Iwata et al., 2021; Natsubori et al., 2014).

Despite some studies suggesting increased glutamate levels in treatment-resistant schizophrenia (Egerton et al., 2023), it is worth emphasising that the reduction of metabolites including glutamate, glutamine have been consistently observed in mPFC, particularly when studying the group of patients of chronic schizophrenia in stable phase (Merritt et al., 2021; Nakahara et al., 2022). This evidence would suggest that there might be underlying process of diminished metabolic activity which might account for such uniform reductions in various metabolites of significance. In this regard, diminished GABA levels have been found to be negatively correlated with severity of symptoms (Liddle et al., in press).

J Kumar et al.,(2020) pursued the mechanism of probable metabolic integrity factor in stable schizophrenia patients. Following 7T MRS study of metabolites in chronic schizophrenia, they imply that the observed reduction in glutamate and glutathione in the ACC in stable schizophrenia, and especially in cases satisfying criteria for residual schizophrenia, is part of a more extensive reduction in a set of metabolites that might be regarded as indicator of metabolic integrity (J. Kumar et al., 2020). In this context, it is worth noting

that the cases satisfying criteria for residual schizophrenia might be the cases that probably meet the criteria for classical schizophrenia as we describe in this thesis work, provided such criteria can be designed based on the quantification of the classical core features.

Above account of reduction in metabolites needs to be considered with the caveat that there is considerable heterogeneity in the findings including numerous studies presenting evidence to support the notion of Glu mediated excitotoxicity in the early phase of schizophrenia, followed by reduction of mPFC Glu in the established phase (Marsman et al., 2013). Furthermore, in their meta-analysis Marsman et al. (2013) also found elevated mPFC Gln in early schizophrenia.

6.1.2 Common mechanism linking inflammation, diminished metabolic activity and brain changes:

During normal oxidative metabolism a small portion of the energy generated in the electron transport chain in Mitochondria is diverted to produce Reactive Oxygen Species (ROS). ROS are very reactive small molecules with unpaired electrons that readily oxidise biological molecules, including DNA and proteins, damaging them (Lenaz, 1998). It is also noteworthy that glutamatergic neurotransmission is associated with the generation of ROS. Coyle and Puttfarken (1993) review the evidence that oxidative stress and excessive glutamatergic neurotransmission are interacting processes that lead to cellular damage in the brain in various neurodegenerative disorders. Chronic oxidative stress is thought to be primarily caused by mitochondrial dysfunction, namely disruption of the electron transport chain (ETC), which damages DNA and the cell membrane and intensifies oxidative stress.

Previous studies have already suggested such mitochondrial dysfunction and the vicious perpetuating cycle in Bipolar Affective Disorder (BPAD) (Lima et al., 2022) and in DSM diagnosed Schizophrenia (Konradi & Öngür, 2017; Ni & Chung, 2020; Rajasekaran et al., 2015; Roberts, 2021; Whitehurst & Howes, 2022).

Whitehurst and Howes (2022) in their comprehensive review of the role of mitochondria and mitochondrial complex 1 (MCI) in schizophrenia point out that : "This review highlights the evidence that refines our understanding of the well-established finding of reduced cortical metabolic activity in schizophrenia, by implicating reduced mitochondrial complex one (MCI) protein and expression in the pathophysiology of schizophrenia".

Furthermore, correlation between symptoms, particularly cognitive dysfunction, and impaired MCI functioning has been previously observed (Ben-Shachar, 2017).

Further evidence comes from the proposal that elevated dopaminergic activity in schizophrenia causes excessive MCI inhibition and subsequent cytotoxicity (Ben-Shachar, 2017; Pivovarova & Andrews, 2010; Smaili et al., 2011). In order to explain how greater striatal dopamine synthesis capability results in lower cortical dopaminergic firing and diminished cortical metabolic activity more generally, and progressive volume loss in schizophrenia, MCI inhibition by dopamine may be the underlying mechanism as suggested by (Rajasekaran et al., 2015).

In light of the fact that persisting symptoms and disability are a cardinal feature of classical schizophrenia, it is plausible that persisting damage arising from mitochondrial dysfunction plays a major role in the mechanism of classical schizophrenia.

It seems plausible that subgroups of psychosis spectrum disorder which meet the criteria for classical schizophrenia would possibly have mitochondrial dysfunction as the cardinal underlying aetiopathogenesis. Classical schizophrenia can be seen as a multisystem inflammatory disease. Within this context, classical schizophrenia is likely to be associated with dysfunctional mitochondria, leading to metabolic disturbance in neurons and glial cells, which demand much energy.

Many of the brain conditions, including schizophrenia, are studied in the context of dysregulation of balance between excitatory and inhibitory

processes in the brain. Glutamatergic system is known to be the predominant excitatory influence, whereas GABA system is the inhibitory component of balance. During acute insult of local areas in brain, cortical Glu will be overexpressed above the inhibitory control of GABA. Furthermore, Glu, Gln and GSH need to work in a synergistic balanced way to keep oxidative stress under control and to prevent Glu-mediated excitotoxicity. But, if there is underlying aetiopathological processes such as mitochondrial dysfunction, then it is conceivable that both Glu and GABA metabolic activity will be diminished.

We have demonstrated in previous chapters that severity of classical dimension of putative core deficit is the candidate marker of classicality and plausible intermediate mechanism influencing clinical manifestations related to underlying aetiopathological processes. If our concept of core deficit is right, then it can be expected that severity of core deficit will be related to neural markers of metabolic activity, connectivity, inflammation and volume changes in the salient regions of brain.

This would lead us to propose the below hypotheses:

6.1.3 Hypotheses:

1. Candidate neural marker of pathophysiology, PMBR, will be reduced in the group with higher classicality and putative core deficit will be negatively correlated with PMBR.
2. Metabolites of relevance Glu, Gln, GSH will be correlated with each other in ACC and factor of metabolic activity in ACC will be diminished in proportion to severity of core deficit. Furthermore, factor of GABA will be diminished as well.
3. Markers of neuroinflammation, TSPO_binding in ACC and peripheral inflammation (IL6, TNF-alpha,CRP) will be associated with putative core deficit. Furthermore, neuroinflammation will be correlated with peripheral inflammation.

4. Gray matter volume in ACC will be diminished in group of higher classicality and will be associated with severity of core deficit.

6.2 Methods

Details of the SPRING study and clinical symptom scales have been provided in Chapter5. Here, a brief summary of the methods and the relevant details of neuroimaging and cytokines data acquisition and analysis will be provided.

6.2.1 Sites

The data for this study is from a multimodal collaboration between the Universities of Manchester, Nottingham and Cardiff (The Study of Psychosis and the Role of Inflammation and GABA/Glutamate). MRS spectroscopy data were acquired at 3T at Cardiff and Manchester, and at 7T in Nottingham.

6.2.2 Participants

Inclusion and exclusion criteria

Participants were patients with psychosis and healthy controls, recruited locally at each study site. Inclusion criteria for all participants were: aged 18–55 years; ability to understand and willing to give written informed consent; English as first language or fluent. Exclusion criteria were: current use of any medication which may interfere with the study, in the opinion of the investigator (not including treatment for schizophrenia); clinically significant neurological disorder; history of head injury with loss of consciousness > 5 min; current harmful use of, or recent dependence on, psychoactive substances (excluding nicotine); contraindications for magnetic resonance imaging (MRI) (e.g., claustrophobia, pregnancy, ferrous metal implants); taken part within the previous month as a participant in a clinical trial that involved taking a drug, being paid an inconvenience allowance, or having an invasive procedure (e.g., venepuncture > 50 ml, endoscopy).

All patient participants met current DSM IV criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder. Participants who met criteria for a schizophreniform disorder were followed up after six months and the DSM diagnosis of schizophrenia confirmed using information from case records.

Recruitment

Two groups of patients were recruited at each site, from populations at contrasting early and established 'Phases' of illness: a recent onset, minimally treated group (Recent) and an 'Established' group with 10 years if illness. Criteria for the Recent group were psychosis onset less than five years, and initiation of treatment less than 12 weeks prior to recruitment. The criterion for the Established group was psychosis onset at least ten years prior to recruitment.

Two groups of healthy Control participants were recruited locally by public advertisement and selected so as to match the site's two patient groups for age, sex and NS-SEC parental occupation category. Additional exclusion criteria for controls were: a personal history of psychosis or a related disorder (as determined by the MINI-international neuropsychiatric interview v5.0.0 for DSM-IV (Sheehan et al., 1998b); current or recent (within 2 years) presence of depressive symptoms or treatment with antidepressant medication; first degree relative with a history of psychosis. Informed consent was obtained, and participants were paid an inconvenience allowance for their participation. All procedures were approved by the UK National Research Ethics Service.

Sample size

The intended final sample size was 60 patients (20 per site) for each Phase Group, and 30 healthy controls (10 per site) age matched to each of the patient groups. For structural neuroimaging data analysis subpart of this study, only the sample from Nottingham was used because 7T MRI was used in Nottingham whereas 3T MRI was used in other sites.

6.2.3 Measures

Patient History measures

Patient history measures included: duration of illness; smoking history (in pack years); current antipsychotic defined daily dose (AP-DDD); cumulative antipsychotic exposure dose (AP-cum); height, weight, and body-mass index (BMI). Where height was missing, proxy BMI value was computed using mean height in each sex category.

Symptom measures

Symptoms of psychosis were assessed in all patients using the PANSS (Kay et al., 1987). Scores were obtained for Positive Symptoms; Negative Symptoms as per protocol and for three syndromes of Reality Distortion, Impoverishment and Disorganisation from the SSPI (P. F. Liddle, Ngan, Duffield, et al., 2002). As symptom scores were positively skewed, they were log transformed (base 10) to give a more symmetrical distribution across the patient sample.

Cognitive and psychosocial function

Cognitive function in all participants was assessed using a short-form of the WAIS-III (Wechsler, David, 1997) validated for schizophrenia (Blyler et al., 2000). It comprised four subtests: Digit-symbol coding (Processing Speed); Information (Verbal Comprehension); Block Design (Perceptual Organisation); and Arithmetic (Working Memory). Subtest scores were combined to give a Full-Scale IQ Standard Score (FSIQ). We used the Wechsler Test of Adult Reading (WTAR) (Whitney et al., 2010) as a proxy for pre-morbid IQ.

Psychosocial functioning was assessed using the Personal and Social Performance Scale (Morosini et al., 2000).

Clusters of classicality

Method of segregating two clusters with high versus low classicality has already been described in the previous chapter. Clinical variables and neuroimaging measures were compared in these two groups of schizophrenia.

Putative Core deficit

Method of deriving a single classical dimension has already been described in Chapter5. Correlation of core deficit with neural measures was examined for each neural measure.

MRS spectroscopy

Proton MRS at 3T and 7T: GABA, glutamate and glutathione

^{1}H MRS was used to measure steady state levels of metabolites in all 3 centres, at 7T in Nottingham and at 3T in Manchester and Cardiff. PRESS (3T) or STEAM (7T) localized 27ml volumes were located in the anterior cingulate and occipital cortex. Glutamate, glutamine, GABA and glutathione were quantified.

At 7T all metabolites were measured in one simple/standard acquisition. At 3T, due to unreliability in glutamine measurements related to overlaps with glutamate and the aspartyl resonance of NAA, spectral editing using the MEGAPRESS sequence (Puts et al., 2011; Terpstra et al., 2003; Waddell et al., 2007) was used to measure GABA and glutathione. Due to low concentration of these metabolites (1-2 mMol/kg) longer acquisitions than the standard ^{1}H spectrum was used. LCModel (Provencher, 2001)(Provencher, 2001)or jMRUI/QUEST (Stefan et al., 2009) approaches were used to estimate the concentrations of the metabolites of interest (GABA, Glu, Gln and GSH). High resolution images were acquired prior to the spectroscopic acquisition(s) in order to segment the spectroscopic volumes into gray matter (GM), white matter and cerebrospinal fluid. Regional GM volumes were utilised as dependent variables in secondary analyses as indices of possible neurotoxicity

of MRS changes. They were also used to co-register PET images. Metabolite measures were corrected for tissue fraction before using in analysis. Nonparametric site normalisation was completed for MRS variables by subtracting site median and dividing by median absolute deviation (MAD).

6.2.4 PK11195 PET method:

[^{11}C](R)-PK11195 PET was performed in Manchester only. In total, 20 recent onset patients (14 males; mean ± standard deviation [SD]: 24.2 ± 5.1 years); 21 established patients (13 males; mean ± SD: 46.0 ± 6.0 years); and 21 age- and sex-matched controls: 10 matched to recent onset (8 males; mean ± SD: 25.5 ± 4.1 years), 11 matched to established patients (7 males; mean ± SD: 47.0 ± 5.0 years) completed the study. Total gray matter as well as regions of interest were defined apriori. Parametric images of [^{11}C](R)-PK11195 binding potential (TSPO binding_ACC) were created using MICKpm 5.2 (in-house MATLAB based software), using the simplified reference tissue model and the time activity curve from the bilateral gray matter cerebellum as reference tissue input function. TSPO binding_ACC for each ROI were read out from the parametric maps by applying the object maps.

For the current study described in this chapter, TSPO binding_ACC from anterior cingulate cortex (ACC) was utilised to test the correlation with core deficit and other relevant measures. ACC has been implicated in the aetiopathogenesis of schizophrenia, both in morphological changes (Lahutsina et al., 2023) and as part of salience network (Palaniyappan & Liddle, 2012). Studying central inflammation with ACC as candidate region would serve as a sound scientific method in schizophrenia research, given the cardinal role of ACC in structural and functional connectivity.

6.2.5 Cytokines

Up to 40 ml blood samples was taken from each participant for cytokine and genetic analysis. These samples were taken from all three study sites. Blood

samples were centrifuged, and plasma stored locally at -80°C, then transferred at intervals throughout the trial to Kings College, London for batch analysis. A number of relevant cytokines were analysed.

Plasma assay: Plasma cytokines were measured as per the standard protocol. Venous blood samples were collected and centrifuged within one hour at 1300–2000g for 10 min. Cytokines were measured in duplicate using Meso Scale Discovery (MSD) V-plex immunoassays (MSD, Maryland, USA) according to the standard protocol provided by MSD. The standard Pro-inflammatory Panel 1 (human) kit was used for the measurement of IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNF-α.

For this current study described in this chapter, relationship of IL6, TNF-α and CRP was mainly tested with the clinical and neuroimaging variables, based on the previous evidence that these are the relevant markers of peripheral inflammation in schizophrenia (Boerrigter et al., 2017; Fillman et al., 2016; Goldsmith et al., 2016; Miller et al., 2011). As cytokine measures were positively skewed, they were log transformed (base 10) to give a more symmetrical distribution across the patient sample. Cytokine values were site-normalised log 10 values, as there were systematic site effects which we concluded must have been due to centrifuge effects as they were not correlated with time between collection and assay.

6.2.6 Structural Neuroimaging:

Voxel Based Morphometry (VBM) analysis was completed for the patients and healthy control sample from only the Nottingham site as all the neuroimaging acquisition was done in 7T MRI in Nottingham, whereas 3T MRI was utilised in Cardiff and Manchester sites. Analysis of 3T data is not presented in this thesis.

One of the most used methods to examine the neuroanatomy of schizophrenia is voxel-based morphometry (VBM). The segmentation of the brain picture into voxelwise estimates of gray matter volume (GMV) or GMC is

the first step in the automated process of VBM (Ashburner and Friston, 2000). These measurements can then be used in univariate testing to locate voxel clusters that differ from healthy patients in terms of gray matter alterations in schizophrenia. The usefulness of VBM analyses for schizophrenia research has been demonstrated by meta-analysis (Glahn et al., 2008) and large-scale investigations (Honea et al., 2008; Hulshoff Pol et al., 2001; Segall et al., 2009).

Deriving ROI Insula volumes for Nottingham Subjects:

Out of the 64 participants from Nottingham site, T1 weighted 7T structural MRI scan images 63 were analysed, one scan was discarded due to persistent contrast issue and inadequate quality of the image. Of the 63 scans, 17 were recent onset schizophrenia group, 22 established schizophrenia and 24 matched healthy controls. VBM analysis of all viable images were performed using SPM12 on MATLab12b, pre-processing and segmentation was completed on Computational Anatomical Box (CAT12) and smoothing for gray matter segmented images were achieved on SPM12. Data quality and VBM data homogeneity was checked on CAT 12. Prior to preprocessing, all images were double-checked for alignment with the CAT12 toolbox (https://neuro-jena.github.io/cat/) and SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The VBM image preprocessing pipeline was executed on MATLAB using SPM 12. For the preprocessing processes, the default parameters of the VBM toolbox were used. In a nutshell, MRI inhomogeneities were removed and noise was avoided by bias-correcting the T1-weighted images and by using a spatially adaptive non-local means filter. A combination of a linear affine transformation and nonlinear deformation employed high dimensional DARTEL normalization was required for registration into standard MNI space. Brain tissue was sectioned into white matter, cerebrospinal fluid, and grey matter after non-brain tissues were removed. The next step was to multiply the segmented white matter and grey matter images with the nonlinear components obtained from the normalization matrix. In the end, the volumes

of grey and white matter were determined by generating modulated pictures of these brain regions. The unsegmented normalized images were examined visually to ensure high-quality normalization. A Gaussian kernel filter with an 8 mm full with half maximum (FWHM) setting was used to spatially smoothen the segmented and modulated pictures. Regarding the quantities of grey matter, an absolute threshold masking value of 0.3 was chosen. Two-sample t-test in SPM12 with a voxel-level and cluster-level height threshold of $P < 0.05$ (FWE-corrected) to identify regions was completed where there were significant differences in grey matter volume between controls and schizophrenia patients. The total intracranial volume (TIV) must be included as a covariate in the model of the statistical analysis in order to account for inter-individual differences in brain size, since the resultant volume of each tissue type represents the absolute volume of the corresponding tissue in a voxel, which is dependent on the total brain size. After estimating the volumes of GM, WM, and CSF using CAT12 during the VBM analysis, the total intracranial volume (TIV) was determined. Total Intracranial Volume was used as covariate during estimation. Univariate analysis,
for smoothed gray matter volumes was performed on SPM 12, Basic Model.

Region of interest identification:

ROI was built for predetermined coordinates (Insular region 39 15 –15, -44 2 –5, 46 8 –4). Regions-of-interest (ROIs) of clusters that showed a significant group difference were extracted using MarsBaR extension (Brett et al., 2002). Mean grey matter volumes of the significant ROI was calculated for each patient using Matlab. Image intensity values (Y values), representing local grey matter density, were extracted for statistical analysis.

ACC Metabolic activity factor:

Principal component analysis (PCA) of metabolites of relevance; Glu, Gln, GSH and GABA from ACC, was completed to explore if there is mutual relationship among metabolites and if factor of shared variance can be derived.

6.2.7 Analysis:

For all variables, outliers, defined as values greater than three standard deviation above mean, were excluded from analysis. Means were compared between two clusters using independent t-tests. Correlation analysis was completed using Spearman correlation coefficient. SPSS version 29 was used for all statistical analysis.

Above mentioned analysis to test our hypotheses embraced multiple statistical tests, implying that correction for multiple comparison would be required to justify firm conclusions. In fact the multiple variables are expected to be interrelated and the appropriate correction for multiple comparisons would be complex. Therefore, we will present uncorrected statistical results with the caveat that these exploratory findings might provide a basis for subsequent more definitive testing.

6.3 Results:

6.3.1 Classicality and PMBR

Putative core deficit exhibited no correlation with PMBR: r (62) =-.097, p=.455. A scatterplot showing this correlation is shown in Figure 6-1.

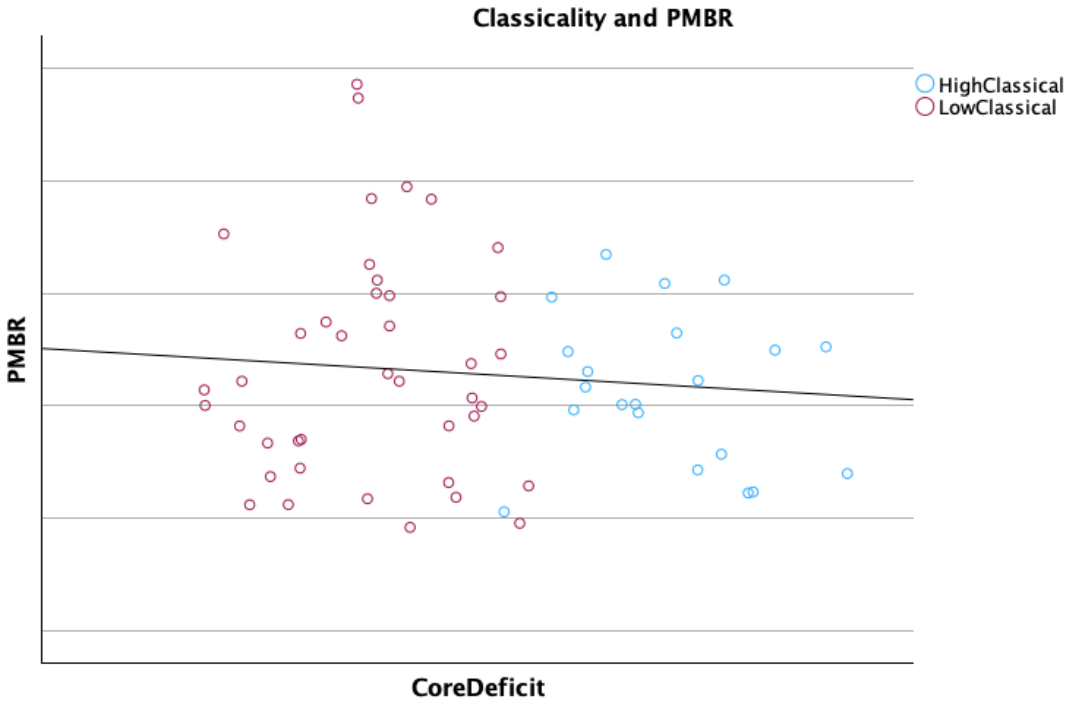

Figure 6-1: Relationship between putative core deficit and post-movement beta rebound (PMBR) in the schizophrenia patient group.

Core deficit (classicality) was derived from Maximum Likelihood factor analysis of disorganization, impoverishment, cognition (DSST) and role-function (PSP), with a single factor extracted.

6.3.2 Classicality and cortical metabolic factors:

PCA of Glu, Gln, GSH and GABA from ACC resulted in two factors, each with Eigenvalue more than 1. Component 1 which accounted for 39% of variance and had high positive loadings from Glu, GSH and Gln and was termed ACC Glutamatergic Metabolic Factor. Component 2 which accounted for 26% of variance and had a high GABA loading was termed ACC Metabolic GABA factor. Factor loadings are given in Table 6-1.

Table 6-1: Factor loadings from Principal Component Analysis of ACC metabolites.

Variable	Component	
	1	2
ACC Glutamate	.822	-.103
ACC Glutamine	.700	.226
ACC Glutathione	.628	.000
ACC GABA	-.075	.979

Two components were extracted. All MRS values were reference to water and normalised by site (site median/site MAD)

Both components were significantly negatively correlated with putative core deficit scores, indicating that greater severity of core deficit was associated with proportional reduction in both metabolic factors.

For the ACC Glutamatergic Metabolic factor (Component 1) the correlation was r (99) =-.238, p = .018, and for the ACC GABA Metabolic factor (Component 2) it was r (99) =-.203, p= .044.

Scatterplots showing the relationship between the core deficit factor scores and these two brain metabolic factors are shown in Figure 6-2.

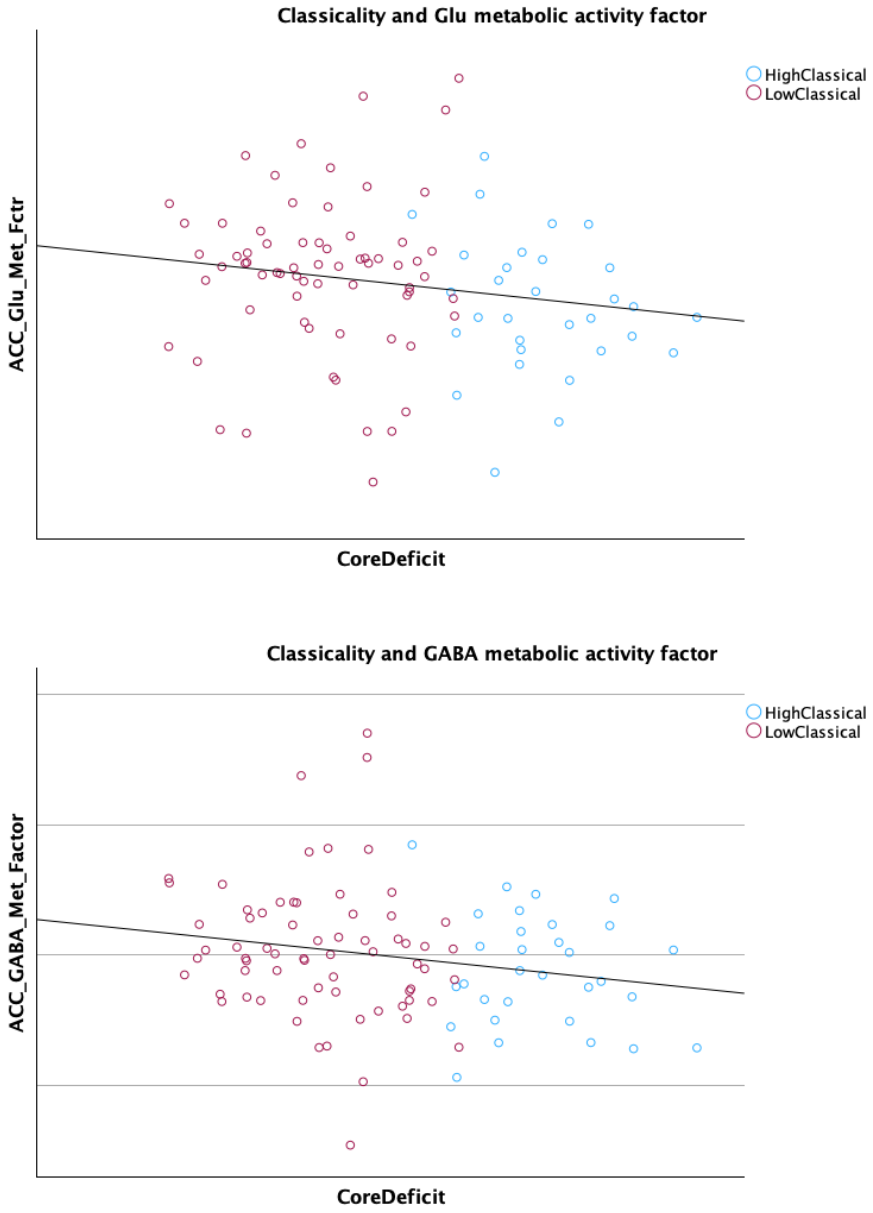

Figure 6-2: Relationships between Putative core deficit and the two ACC metabolic factors.

Core deficit (classicality) scores (horizontal axis) were derived from Maximum Likelihood factor analysis of disorganization, impoverishment, cognition and role-function. Higher values of the Core Deficit scores represent higher symptom scores and lower cognitive and social function scores. Upper panel: ACC Glutamatergic Metabolic factor (vertical axis); Lower panel: ACC GABA metabolic factor (vertical axis). For both metabolic factors, higher values of metabolic factors indicate higher metabolite concentrations.

6.3.3 Classicality and inflammation

Central inflammation

Core Deficit scores were positively, but non-significantly, correlated with TSPO binding potential in the ACC, $r(41)=.255$, $p=.108$, and in the insula, $r(41)=.254$, $p=.110$. A scatterplot showing the relationship between Core Deficit scores and TSPO binding potential in the insula is shown in Figure 6-3. Note that TSPO values were only obtained for Manchester participants.

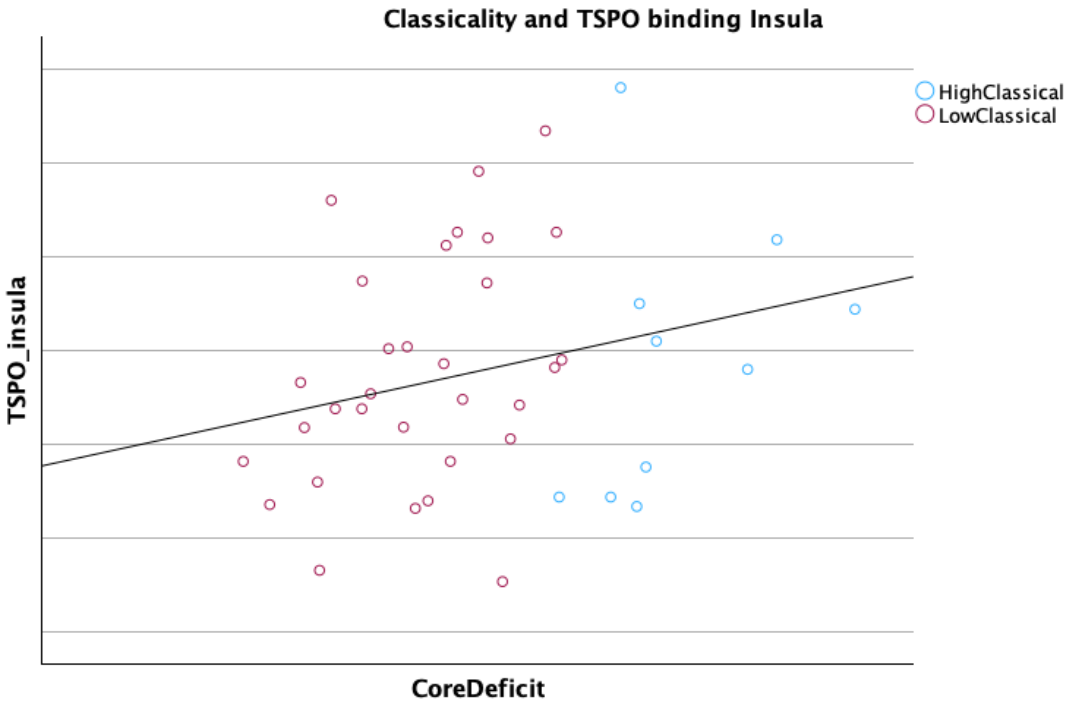

Figure 6-3: Relationship between binding potential of TSPO in Insula with Core deficit. TSPO Insula.

Binding potential of TSPO protein measured in Insula, Core deficit (classicality) was derived from Maximum Likelihood factor analysis of disorganization, impoveris cognition and role-function.

Correlations between these brain measures of neuroinflammation and peripheral inflammatory cytokines il-6, CRP, and TNF-α are given in

Table 6.5

Table 6-2: Correlations between neuroinflammatory markers (TSPO binding potential in ACC and insula) and peripheral cytokines IL-6, CRP and TNF-α.

	TSPO ACC	**TSPO Insula**
IL-6	*r* (41) =.414, *p* =.007	*r* (41) =.138, *p* =.391
CRP	*r* (41) =.215, *p* =.177	*r* (41) =.066, *p* =.680
TNF-α	*r* (41) =.416, *p* =.007	*r* (41) =.376, *p* =.015

IL6: Interleukin-6, CRP:C-reactive protein, TNF-α: tumour necrosis factor α, representative of cytokines and potential peripheral inflammation, TSPO_ACC: binding potential of TSPO protein in ACC from PET results, TSPO Insula: binding potential of TSPO protein measured in Insula representative of potential neuroinflammation.

6.3.4 Classicality and GM volume

Core deficit scores were positively but non-significantly correlated with grey matter volume in left insula, $r(35) = .261$, $p = .130$, and dorsal ACC, $r(38) = 0.205$, $p = .216$. A scatterplot showing the relationship between Core Deficit scores and left insula grey matter volume is given Figure 6-4. Note that grey matter volume values were only obtained for the Nottingham participants.

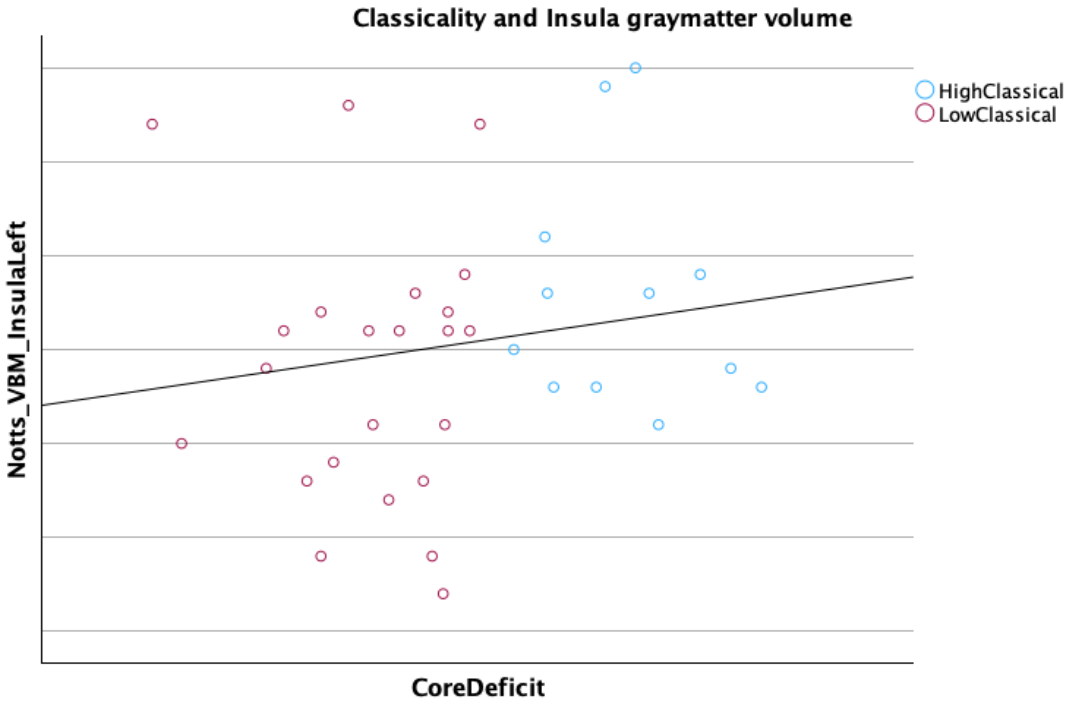

Figure 6-4: Relationship between classicality and gray matter volume from Insula.

Vertical axis: Grey Matter Volume from Left Insula obtained from VBM results for Nottingham study centre: Horizontal axis: Core deficit (classicality) was derived from Maximum Likelihood factor analysis of disorganization, impoverishment, cognition and role-function.

6.3.5 Cluster differences

The results of t-tests comparing the High Classical and Low Classical clusters on the above variables are shown in Table 6-3: Mean differences between High Classical and Low Classical Clusters (High minus Low). Table 6-3.

Table 6-3: Mean differences between High Classical and Low Classical Clusters (High minus Low).

		High Classical	Low Classical	*t* value	*df*	*p*	Effect size *d* (95% CI)
Brain function	PMBR	57.65	67.66	-0.82	60	.286	-0.22 (-0.75, 0.30)
Brain metabolites	ACC Glu	-.37	.05	-1.78	112	.077	-0.36 (-0.76, -0.04)
	ACC Gln	-.08	.20	-1.04	109	.298	-0.21 (-0.62, 0.19)
	ACC GSH	-.23	.09	-1.66	112	.099	-0.33 (-0.73, 0.06)
	ACC GABA	-.35	-.01	-1.35	105	.223	-0.28 (-0.69, 0.13)
	ACC Glut. Met Factor	-.27	.14	-1.99	97	**.049**	-0.43 (-0.86, -0.01)
	ACC GABA Met Factor	-.23	.08	-1.45	97	.151	-0.31 (-0.73, 0.11)
Neuro-inflammatory markers	TSPO ACC	.09	.10	-0.30	39	.767	-0.11 (-0.82, 0.60)
	TSPO Insula	.04	.03	0.25	39	.800	0.09 (-0.62, 0.80)
Peripheral inflammatory markers	IL-6	.37	.16	1.11	120	.268	0.22 (-0.17, 0.61)
	TNF- α	.20	.05	0.70	120	.768	0.14 (-0.25, 0.53)
	CRP	.13	.27	-0.78	120	.485	-0.16 (-0.54, 0.23)
Grey matter	GM Insula(L)	.47	.43	1.58	33	.123	0.56 (-0.15, 1.27)
	GM DACC	.51	.46	1.39	36	.173	0.48 (-0.20, 1.13)

P values <.05 shown in bold font. Abbreviations: PMBR: Post-movement beta rebound; ACC: Anterior Cingulate Cortex; Glu: Glutamate, Gln: Glutamine, GSH: Glutathione, GABA: gamma amino butyric acid; TSPO: Translocator Protein (binding potential); IL-6: interleukin-6; TNF-α: Tumour Necrosing Factor-α; CRP: C-Reactive Protein; GM: Grey Matter.

6.4 Discussion

Our results demonstrate that metabolites from ACC (Glu,GSH and Gln) are highly correlated with each other and two orthogonal factors can be derived from PCA of ACC Glu, GSH, Gln and GABA. One factor with high positive loadings of Glu-Gln-GSH is considered the Glu associated cortical metabolic activity factor and the other one with high loading from GABA and negligible loadings from other metabolites is considered GABA associated cortical metabolic factor.

Furthermore, having demonstrated the putative core deficit as a consistent single latent variable from three independent heterogenous sample of schizophrenia patients from previous chapters, we report in this investigation that classical dimension is negatively correlated with cortical metabolic factors as predicted, but weakly associated with PMBR contrary to our prediction. PMBR results add to the ongoing challenges in the field of schizophrenia research including confounding effects from multiple sites and the combined

sample of recent-onset and established schizophrenia cases in this investigation. MRS metabolites were site-adjusted to minimise the confounding effect of site but that was not the case with PMBR values.

The negative correlation of classicality score with both Glu and GABA activity factors raises important challenges in trying to understand and uncover the possible associated pathophysiology. It is worth reminding ourselves that glutathione cycle not only supports antioxidant activity but might also act as a storehouse for intracellular neuronal glutamate (Sedlak et al., 2019). Reduced glutamate release from the glutathione cycle results in lower glutamate levels in cortical neurons, whereas reduced glutamate consumption raises overall glutamate levels by approximately 25%. It is possible to accomplish these changes in glutamate pools without raising oxidative stress or causing cell death (Sedlak et al., 2019).

GABA deficit has been discussed as one of the cardinal markers in classical schizophrenia (Liddle & Liddle, 2022), taking into account the inconsistent findings from multitude of studies in schizophrenia field of research. Kumar et al (2021) report hypo-GABAergic state from ACC following their meta-analysis, but substantial heterogeneity is noted in the studies included.

Our results of preserved volume in ACC found in the cluster with high classicality, is in contradiction to the most robust finding in schizophrenia of reduced gray matter volume (Gupta et al., 2015). Furthermore, association of reduced Insula volume with disorganization (Nenadic et al., 2010) and psychomotor poverty (Stein et al., 2021) has been reported. Although the evidence till date from diverse studies is inconsistent, it is worth considering the recent evidence from machine learning study of a large set of cases of schizophrenia (PRONIA study) which has found persistent FTD to be associated with extensive GM abnormality including increased GM density in Insula and ACC (Buciuman et al., 2023). Furthermore, our theoretical formulation would argue for dysregulation of synergistic balance between Glu-Gln coupling and GSH cycle in ACC leading to reduced defense/metabolic integrity, along with reduced GABA mediated inhibitory defence as well, both processes being

contributed by possible underlying unified pathophysiology. If this were to be true, then it is possible that shift in Glu pools will reflect as diminished cortical metabolic activity, yet preserved volume in ACC can be observed. This is in contrast to the mechanism in neurodegenerative disorders in which increased Glu levels leading to Glu mediated excitotoxicity and related neuronal death, and loss of GM volume would be strikingly evident. We have come to understand that schizophrenia is not dementia praecox, but perhaps classical schizophrenia is more of diminished multi-modal neural mechanisms associated with unified underlying core pathophysiology which may or may not be related to structural volume loss. But it is worth emphasising that our results are from preliminary exploratory analysis and hence must be considered with great caution, particularly given the limitations of lack of robust methods of statistical analysis along with small sample size and the heterogeneity of sample.

Taking these limitations into account, results from our investigation would provide preliminary substance to speculate that Glu mediated excitotoxicity may characterize a subgroup of schizophrenia which might share underlying processes similar to neurodegenerative disorders, where as another subgroup might be characterized predominantly by the widespread reduction of metabolic activity in Glu and GABA systems reflecting underlying unified pathophysiology such as mitochondrial dysfunction. Classical schizophrenia can be conceptualized as the second subgroup, but the small sample size and the cross-sectional measurement of data, along with neuroimaging results taken from only one region of the brain, would make it difficult to come up with any satisfying answers. Nevertheless, our preliminary exploratory analysis should help guide future research to establish or rule-out if core pathophysiology leading to reduced cortical metabolic activity characterizes classical schizophrenia.

Furthermore, we found that central inflammation was significantly positively correlated with peripheral inflammation as predicted. But simplistic inferences about multi-system involvement and crosstalk between brain and periphery

cannot be undertaken because various confounding factors such as exposure to antipsychotic medication, can influence this relationship. Detailed analysis of mediation/moderation might uncover the complex relationship between these measures, and it is being undertaken (Liddle et al., in prep), but it is outside the scope of this thesis work. Similarly, antipsychotic exposure is negatively correlated with gray matter volume in ACC, but the modulating role of medication is not attempted here. Similarly, the modulating role of age, BMI and smoking habits needs to be further investigated, but that work is currently under progress and is not included in this dissertation scope. Furthermore, there are questions about whether TSPO binding can be considered as marker for neuroinflammation (Notter et al., 2018), hence our simplistic narration of TSPO binding in ACC as a marker for central inflammation needs to be taken with great caution. Similarly, elevated levels of IL6, CRP and TNF-alpha by themselves do not necessarily represent the plethora of peripheral inflammation, which is a complex process of interplay between multiple factors (Sun et al., 2022).

On the backdrop of limitations, none of the above-mentioned confounders, including antipsychotic exposure, had any association with core deficit. Putative core deficit emerges as the consistent latent variable even in this investigation of multi-centre heterogenous sample of mix of recent-onset and established schizophrenia patients, opening up the possibility for future research and clinical investigations to quantify core deficit towards diagnosis as well as targeted interventions.

As pointed earlier in the discussion, conceptual formulation of unified core pathophysiology leading to diminished glutamatergic-GSH defense, diminished GABA activity, diminished long range communications reflected through PMBR, may manifest in enhanced core classical features represented by latent variable of putative core deficit. But we must be cautious in drawing conclusions from this preliminary cross-sectional analysis, and we propose for future longitudinal studies of large samples to further explore and validate or refute our theoretical formulation.

Chapter 7: Summary, Conclusions, Limitations and Future research

7.1 Summary

Having recognised the heterogeneity of schizophrenia in multi-dimensional aspects including clinical features, response to treatment, prognosis, neural correlates and persisting disability (P. F. Liddle, 2019), I and my colleagues put forward the notion of classicality defined by the core features of disorganization, impoverishment, cognitive dysfunction and role-function impairment. In chapter1, I narrated the systematic method of deriving the scores for disorganization and impoverishment from three common symptom scales (PANSS, SSPI and CASH), along with method of deriving from speech and language manifestations (TLI). Furthermore, I described the notion of classical schizophrenia characterised by core features. In chapter2, I further provided the evidence for supporting cognition as core feature of classicality along with introducing the methods of neural investigations that we employed.

I then narrated our investigation of quantifying the classicality in Chapter3. We were able to successfully identify a single latent variable of shared variance among core features, a putative core deficit, in a sample of schizophrenia cases in their stable phase. It is noteworthy that I and my colleagues published this research work in schizophrenia bulletin (Rathnaiah et al., 2020). I further demonstrated that putative core deficit is negatively correlated with candidate neural marker, PMBR. I also examined if discrete clusters can be segregated from sample of stable psychotic illness individuals. Although two clusters were identified, numbers were small, and dimensionality of core deficit was more evident than categorical groups.

I then tested if latent variable can be derived in another independent sample of psychosis in which measures of persistent disorganization and impoverishment were available (Chapter4). I confirmed that single latent

variable of core deficit does emerge from both persistent symptom measures as well as current measures of disorganization and impoverishment in stable psychosis sample. Furthermore, cluster analysis identified two clusters but again dimensionality seems to account more for the data than discrete categorical groups. I was able to replicate the finding that neural marker PMBR is diminished in proportion to the severity of putative core deficit, importantly derived from persistent symptom measures.

In the next chapter (5), I investigated if classicality can be identified in a multi-centre heterogenous sample of mix of both recent-onset and established cases of schizophrenia and demonstrated that single latent variable can be identified. This putative core deficit was closely related to reality distortion in keeping with our theoretical formulation that classicality predisposes to delusions and hallucinations. Two clusters were again identified from this mixed sample by cluster analysis and close examination was again completed to confirm our observation that our data from three independent samples would support dimensionality of core deficit than distinct categories of illness. Given the profound heterogeneity of schizophrenia and the lack of replicability of results, the fact that a single latent variable of core deficit was identified from three different samples provides a promising approach to clarifying an aspect of the heterogeneity of schizophrenia relevant to long term outcome.

I then examined neural correlates of classicality (Chapter6) and demonstrated that ACC Glu and GABA metabolic activity factors are diminished in proportion to severity of core deficit. But magnitude of PMBR reduction was not in keeping with our prediction. Furthermore, through demonstrating diminished cortical metabolic activity in the presence of preserved GM volume in ACC, our results open up the possibility of formulating and studying core pathophysiology such as mitochondrial dysfunction.

Due to lack of correction for multiple comparisons and the impracticality of an adequate investigation of potentially confounding factors such as effects of medication, these findings must be interpreted with caution. They

nonetheless provide a promising foundation for further research into the pathophysiological mechanism underlying classical schizophrenia. Furthermore, our findings provide some support for the proposal that reduced PMBR might be a useful marker for classicality. However, it remains uncertain whether or not reduced PMBR is a marker specific to persistent disorganization (as indicated by the finding of Gascoyne et al (2020) and Briley et al (2021), or marker for the full syndrome of classical schizophrenia).

7.2 Conclusions

1. A single latent variable of classicality, a putative core deficit, can be identified from three independent heterogenous samples of psychosis and schizophrenia. This is established by exploratory factor analysis (maximum likelihood) as well as confirmatory factor analysis.
2. Our results provide support for formulation that this core deficit might predispose to reality distortion.
3. The core deficit can be identified from persistent symptoms as well as current symptoms.
4. Three independent samples provide evidence that classicality is dimensional in nature.
5. Severity of the core deficit is associated with diminished PMBR, and this result is evident from our investigations reported in Chapter 3 and Chapter 4, although not statistically significant in the study reported in Chapter 6. PMBR should be further studied to investigate whether it is neural marker specifically for disorganization severity or alternatively a marker for the severity of the core deficit.
6. Core deficit severity is significantly associated with reduced cortical metabolic activity in ACC and taken together with other results, this would suggest potential role of underlying core pathophysiology such as mitochondrial dysfunction.
7. Evidence also suggests a possible positive correlation between neuroinflammation and peripheral inflammation, but we refrain from deriving conclusions because of limitations as stated below.

7.3 Limitations

1. Size of sample was small particularly for investigations reported in Chapters 3 and 4 as well as some investigations in Chapter 6 where we

employed results from only one site. Hence significant control needs to be exercised whilst interpreting and extrapolating the results.

2. All results reported from three independent samples can be taken as preliminary exploratory analyses as the role of confounders such as age, BMI, antipsychotic exposure were not analysed. This is particularly important for the results reported in Chapter 6, as it is possible that neural measures and/or core features might have been significantly influenced by confounder such as antipsychotic exposure.
3. Some of the results were contrary to established evidence such as preserved GM volume in ACC reported in Chapter 6. This might be related to various issues including methodology, confounding effects and small subsample. Hence, results need to be taken as preliminary exploration.
4. All data collected is cross-sectional although persistent symptoms from life course were utilised for the investigation in Chapter 4. But it is worth emphasising that conceptualisations such as underlying mitochondrial dysfunction are speculative in nature. Similarly, the conceptualisation that classicality predisposes to reality distortion (delusions and hallucinations) needs to be taken with great caution because the studies included in this work are mainly cross-sectional in nature and the reality distortion is heterogenous and so is classicality. Unless the future research comes up with scientifically robust methods to quantify classicality and reality distortion as well as demonstrating this formulation through longitudinal research studies with a large population cohort, this remains a speculative formulation based on our observations from studying three independent samples.

7.4 Future research

Significant contribution from this dissertation research is presenting the single latent variable of putative core deficit of psychosis. This can serve as intermediate phenotype, the effective modulation of which might ameliorate the clinical manifestations and at the same time, effective investigation of this core deficit including in tandem with candidate neural markers such as PMBR and cortical metabolic activity might help uncover the core pathophysiology as well as genetic/molecular basis. Future research involving large cohorts and longitudinal samples should focus on quantifying core deficit and testing targeted interventions both through psychopharmocolgy and neuromodulation. This core deficit might open up possibility of novel

interventions away from traditional dopamine antagonists towards molecules modulating intracellular mechanisms, transduction pathways and mitochondrial enzyme aberrations. Along with scope for basic science research utilising core deficit, future research should focus on clinical implications and hence a simple tool designed to quantify classicality can be the first step. By combining the tools we have utilised through-out this research work, it seems plausible that clinical translation can be achieved in the coming years. DSST is easy to administer and score, and PANSS or SSPI are similarly easy to administer tools. Focussed training would help identify subtle signs of disorganization and impoverishment, following which all the core features can be elicited and quantified. A new scale which can incorporate these classical features can be the way forward. With the advent of artificial intelligence algorithms and the availability of large datasets shared across the research world, it would be a matter of time before normative data can be computed and even a threshold point to help categorise the severity of core deficit for the benefit of clinical practise might be achieved. Furthermore, the complexity of brain processes involved in manifestations of psychosis might be uncovered and modulated utilising the conceptualisation of core features and classical schizophrenia. Proposal of imprecise predictive coding by Liddle & Liddle (2022) can be seen as that important step to unravel brain complexity in psychosis through guided investigation of classical features.

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