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MASTERS THESIS

Exploring developmental correlates between preterm birth and schizophrenia using a machine learning approach

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Author*:*

Paul Fisher

Supervisors:

Prof. Dr. Nikolaos Koutsouleris,

Dr. Dominic Dwyer

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Abstract

Neurodevelopmental theories of schizophrenia state that early disruptions in development can lead to anatomical vulnerabilities that are associated with transition to psychosis. One such disruption in development stems from the obstetric complications relating to preterm birth (PTB). Currently, research shows that PTB increases the likelihood of transition to schizophrenia but the mechanisms at work are not well understood. This thesis aimed to use multivariate pattern analysis (MVPA) techniques to examine the relationship between schizophrenia and PTB by applying cross-over support vector machine (SVM) signatures to each respective group as unseen data. Initially, SVM signatures were created by testing each patient group with an age-matched control sample. Following this, out-of-sample cross-validation (OOCV) style analyses applied these signatures to an age-matched version of the opposing patient group. Initial results demonstrated high performance in classification balanced accuracy (BAC) for PTB vs control (86.2%), and a moderately high BAC for schizophrenia vs control (67.2%). PTB signatures featured patterns of reduced grey matter volume (GMV) across a large network of subcortical regions including: basal ganglia, putamen, caudate, and hippocampus, as well as cortical regions including: temporal lobe, and premotor cortex. There were also patterns of enlarged GMV for the PTB group in: frontal, parietal, cingulate, and occipital regions and lateral ventricles. The schizophrenia patient signatures featured patterns of reducted GMV in cortical regions including: the frontal, temporal, limbic, occipital, superior motor area, and postcentral gyrus. Further subcortical reductions of GMV were found in: cingulate gyrus, basal ganglia, para-hippocampus, caudate, and precuneus. Enlargements of GMV were noted in the putamen, paracentral lobule, and lateral ventricles. OOCV BAC results performed at chance level in both cross-over directions indicating that the signatures were not reliable for classifying PTB using schizophrenia signature or schizophrenia using PTB signature. Several subgroup analyses were also conducted to examine classification boundaries with more stringent unseen data, these results also peformed at chance level. This thesis demonstrated that age-matched datasets of PTB and schizophrenia patients were poor classifiers of each others condition, this result was unexpected and lead to the conclusion that more work should be done to narrow down the mechanisms at work. It is suggested that looking at Ultra High Risk (UHR) patients may be informative as UHR participants typical present with less severe GMV reductions than transitioned patients, and perhaps schizophrenia patients have already had too much influence from psychosis and treatment.

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Contents

Introduction

In the field of neuropsychiatry, the mechanisms and developmental nature of schizophrenia are recurring themes (Tandon, Keshavan, & Nasrallah, 2008). A considerable effort has been made to further understand the neurological underpinnings of the disease, and to better solidify an all-encompassing etiological model. Similarly, PTB has received significant attention from researchers but focusing more prominently on outcome measures and associated psychiatric and neuroanatomical risks. Both disorders have characteristics that make them unique: schizophrenia is most commonly diagnosed as the result of neuropsychological testing of a large array of heterogeneous symptoms and features (Davis et al., 2016; McGrath, 2008; Takahasi, 2013). Whereas currently, PTB is understood from a clearer observational level: an infant is born within a time frame deemed premature. This distinction means that research prioritises different directional goals, for schizophrenia a large amount of research focuses on identifying risk factors and premorbid symptoms that may increase the likelihood of transitioning to the disease. Conversely, for PTB the main goals focus on understanding risks as a result of this event, and uncovering preventative measures that may reduce the likelihood of future complications, both behaviourally and cognitively (Daamen et al., 2015).

As modern medicine continues to overcome previously fatal medical complications, an increasing number of brain injured PTB patients are surviving into adulthood (Nosarti et al., 2002). The problem is that this territory is mostly uncharted for prognosis and treatment procedures and consequently, it is important to cultivate an informed understanding of the events that transpire and possible outcomes for PTB adolescents and adults. That way, treatment opportunities can be more optimally sought, and the hope is that eventually, preventative measures can be more strongly facilitated. Similarly, the understanding and efficacy of treatment for schizophrenia has surpassed the expectations of many (Kane et al., 2012), but ultimately lacks consistent preventative measures due to its heterogeneous nature. Theoretically, PTB can be used as a proxy to examine the developmental underpinnings of schizophrenia, if a relationship between the two conditions can be established, this can benefit both research fields. Better understanding the early biological constraints that can lead to schizophrenia transition could help develop reliable biomarkers and solidify a reliable high-risk criterion.

This thesis aims to examine both schizophrenia and PTB grey matter (GM) of similar aged adults in an attempt to uncover structurally distinct regions that may be indicative of shared neurological deficits and comorbidity. Through the incorporation of machine learning techniques,

the hope is to establish models that are both consistent with literature, and are applicable to each respective sample and to see if generated pattern signatures are predictive of either sample. Through this analysis, if successful, perhaps a model of disease prevention could be conceived that relates to a relationship between PTB and schizophrenia and to highlight the most important features to focus on in the future to limit or at the least predict progression likelihood to schizophrenia.

It is important to introduce the relevant literature for the two disorders and to give sufficient rationale for the experimental design. Therefore, the introduction has been broken into chapters that establish the current definitions and theories surrounding PTB and schizophrenia using a combination of experimental and review-style publications, culminating in intuitive hypotheses that were developed as a result of this literature review. A chapter has also been dedicated to the machine learning approaches that were employed and the rationale behind choosing these techniques.

Chapter 1 - Preterm Birth

PTB is defined as an obstetric complication in which a child is born before 37 weeks gestational age (Machado, Passini, & Machado, 2014). It is often subject to perinatal complications such as reduced birth weight, hemorrhage (typically ventricular; Dyet at al., 2006), preeclampsia/eclampsia (Dalman et al., 1999), as well as cognitive and developmental complications and even coincides with frequency of hospitalisation (Moster et al., 2008; Nosarti et al., 2012; Selling et al., 2008). Whilst a singular etiological cause is unknown, there are common maternal conditions that may cause a child to be born prematurely, including: infection, preeclampsia, high blood pressure, diabetes, and malnutrition (Cannon et al., 2002). There are also other social factors that can influence PTB such as: smoking, drug-use, stress, age, and alcohol (Behrman & Butler, 2007b). PTB is commonly associated with a variety of psychiatric, cognitive, and behavioural consequences (Botting et al., 1998; Johnson & Marlow, 2001). Examples include: poorer educational success, developmental learning impairments, learning attention and social-emotional control issues, significant decline in IQ, and motor/cognitive function deficits (Aarnoudse-Moens et al., 2009; Botting, 1998; Hille et al., 2007; Saigal et al., 2008). It is theorised that many of the most prevalent problems caused by PTB are related to physical brain alterations as a result of disruption of normal cerebral development (Nosarti et al., 2008).

Some of the prominent examples of disruptive development include: decreased maturation of oligodendrocyte precursors, disrupted programming of cortical connectivity, delayed grey-white matter differentiation, and global/local decreases in cortical and deep GM development (Batalle et al., 2017). The subsequent developmental delay has been strongly linked with neurological complications such as intra/periventricular hemorrhagic infarctions, and a variety of frank lesions (Dyet et al., 2006; Saigal et al., 2008). PTB has also been reliably demonstrated to cause brain volume alterations even into adulthood - particularly in areas such as temporal, frontal, and occipital lobes (Nosarti et al., 2008, 2014). Regions such as the hippocampus, caudate nucleus, fusiform gyrus, putamen, insula, thalamus and cingulate gyrus have garnered attention for being reduced in PTB teenagers compared to controls (Nosarti et al., 2002, 2008, 2014).

PTB is routinely associated with reductions in adult GMV, including subcortical and medial temporal regions (Karolis et al., 2016). Furthermore, the basal ganglia has been demonstrated to have significant reductions in PTB compared to controls (Loh et al., 2017). Incidentally, increases in frontal GMV have been found in PTB patients (Nosarti et al., 2008). This finding led to the suggestion that frontal regions are more resilient to any trauma of PTB and associated obstetrical complications. Karolis and colleagues (2016) indicated that due to a compensatory mechanism, lower gestational age may have an association with higher maturation index than controls. The authors claim that whilst PTB adults were found to have global reduction of GM, this was not evenly distributed. There was notably less GMV in the temporal regions, and larger relative GMV in the fronto-striatal and lateral parieto-temporal regions. One possible compensatory mechanism may be an incorrectly tuned process of “hyper-pruning” which refines interneuron connectivity (Gogtay et al., 2004; as cited in Nosarti et al., 2014). Modern theories of brain maturation explain that GMV decreases linearly with age, particularly in the frontal cortex (Gogtay et al., 2004; Peters, 2006; Sowell et al., 2003). This occurs due to the much later myelination and synaptic pruning that the frontal cortex encounters (*see Chapter 3 - Grey Matter*). Consequently, if a disruption to important glial precursors delays the processes of myelination, the frontal cortex could potentially be shown as enlarged.

PTB has already been linked to numerous childhood onset disorders such as cerebral palsy, mental retardation, autism spectrum disorder, and even epilepsy (Johnson & Marlow, 2001;Moster et al., 2008; Saigal et al., 2008). This evidence demonstrates an intuitive link between prematurity and future neuropsychological deficits and a whole cohort of research has been dedicated to evaluating obstetrical complications and their significant associates for over fifty years (Cannon, Jones, & Murray, 2001). For example, Barker’s Hypothesis (Calkins &

Devaskar, 2011; De Boo & Harding, 2006) is widely considered a pioneering approach to the fetal origins of adult disease and stipulates that early development has a profound influence on future adult disease. Indeed, Barker demonstrated an association between low birth weight (a common outcome of PTB) and coronary artery disease (Barker, 2004) as well as other physical deficits such as hypertension and obesity. Barker's work serves as proof of concept for the aforementioned research and lends support to the suggestion that PTB may have a relationship with psychiatric illnesses such as schizophrenia.

In summary, maternal and social factors can lead to an increased risk of PTB. When a child is born prematurely, there are a whole host of neurodevelopmental complications as a result, including the delay of important precursor neurons, glial cells, and brain hemorrhaging. This delay has been associated with many neuroanatomical abnormalities, such as reduction of GMV as well as enlarged ventricles. These deficits lead to a risk of lowered cognitive ability and IQ and to a variety of potential psychiatric disorders.

Chapter 2 - Schizophrenia

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) defines schizophrenia as an abnormality in at least one of the five following domains: hallucinations, delusions, negative symptoms (e.g. blunted affect), disorganised motor behaviours, and speech. Both behavioural and cognitive disturbances are typical of schizophrenia, including issues with sleep, mood, depersonalisation, and a growing list of other physical symptoms and features. Schizophrenia is a rare disorder, affecting between 0.3-1% of the population (Os & Kapur et al., 2009; Kessler et al., 2005; Wu et al., 2006). Neurologically, schizophrenia is associated with several specific deficits; reductions in frontal, temporal, striatal, and limbic GM, as well as distinctive enlargement of lateral ventricles (Dazzen et al., 2015; Fornito et al., 2009; Gur et al., 2000). Enlargements have also been noted in the putamen, with evidence suggesting this is related to increased neuroleptic medications (Wright, Woodruff, & Murray, 2000). Across a cohort of studies, a distributed network of regions have been identified within these larger domains that are widely and consistently reported as having reduced GM for patients with schizophrenia when compared to controls. These include: bilateral insular cortex, cingulate gyrus, the caudate nucleus, the middle frontal gyrus, fusiform gyrus, and the thalamus (Crespo-Facorror, et al., 2000; Fornito et al., 2009; Glahn et al., 2008).

Developmental research into schizophrenia is exploratory and it is difficult to uncover a singular mechanism that can account for the wide-spread deterioration in brain anatomy (Maynard, Sikich, Lieberman, LaMantia, 2001; Rapoport, Giedd, & Gogtay, 2012). Risk factor models are essential tools for researchers to determine likelihood of transition to psychosis as well as to better understand patient histories. According to the World Health Organisation (Barbato, 2016), risk factors for schizophrenia can be grouped into three categories: sociodemographic, predisposing factors, and precipitating factors (Cooper, 1978; as cited in Barbato, 2016). Indeed, a large amount of literature agrees on broad factors such as Socioeconomic status (SeS), urban living, occupational stress, and obstetric care as significant risk factors for schizophrenia (Laurens et al., 2015; Murray, Bhavsar, Tripoli, & Howes, 2017). Pathogenetically, schizophrenia is strongly linked to genetic risk factors such as heritability which is a predominant feature for diagnosing high-risk status (Gejman, Sanders, & Duan, 2010). Furthermore, the Neurodevelopmental Hypothesis of Schizophrenia (NDHS, Fatemi & Folsom, 2009) explains how schizophrenia is related to brain lesions that were caused by genetic and environmental factors that influenced the maturational development of the brain. Therefore, based on the understanding that obstetric complications typically precede brain lesions, it would follow that PTB fits the criteria of a schizophrenia risk factor.

A "two-hit" model, first coined by Keshaven et al., (1999) proposed that there are two critical events that drive the development of schizophrenia. First, a congenital brain disruption, obstetrical complication, or genetic factor introduces a susceptibility to a "second hit" (thought to occur around adolescence or early adulthood), often theorised to involve some form of aberrant synaptic pruning (Murray et al., 2017) which ultimately leads to the onset of schizophrenia. As it currently stands, most schizophrenia researchers would agree on the following course of events as a textbook example (although not definitive) of disease progression:

1. Obstetric complications, genetic, or some other congenital disruption of normal prenatal neurodevelopment causes early complications.
2. Resulting complications include (but not limited to): periventricular hemorrhage, preeclampsia, frank lesions, axonal development disruption, decrease or delay of GM/white matter (WM) proliferation, enlarged ventricles, and cortical mass reduction (Cannon, Jones, & Murray, 2002; Dalman et al., 1999)
3. Resulting social trajectory: lowered IQ, cognitive and behavioural deficits, learning and attentional issues, increased risk of psychiatric hospitalisation, drug usage, isolation/asociality (Murray et al., 2017) - at risk for developing psychosis.

4. Leading to disrupted neuronal circuits during adolescence (second hit), including aberrant synaptic pruning and leading to psychiatric symptoms.

In summary, researchers working in the field of developmental schizophrenia aim to uncover an etiological model that characterises the circumstances leading to a diagnosis. It would appear that some genetic component or prenatal event is indicative of disease proliferation and serves as a decisive risk factor for progression, but that social, environmental, and behavioural events are mediating stressors to this progressive risk. This suggests that obstetrical complications, such as PTB, are of paramount importance when exploring the risk factors for schizophrenia. It is now essential to explore the direct association between these two disorders in order to emphasise the rationale for this project.

Chapter 3 - Evidence of Relationship Between PTB and Schizophrenia

Evidence suggests that PTB is a risk factor of schizophrenia and psychosis (Jones et al., 1998; Maki et al., 2005; Nosarti et al., 2012,2014; Van et al., 2016). Schizophrenia has been found to be significantly more common for PTB patients at an odds ratio of ~2.5 (Ichiiki et al., 2000; Kunugi et al., 2001). PTB has been shown to be significantly associated with increased risk of psychiatric hospitalisation in adulthood with 2.5 times increased odds of having nonaffective psychosis if born below 32 weeks gestational age (Nosarti et al., 2012). Other obstetric complications such as birthweight have also been shown to impact psychiatric symptom prevalence (up to 46% over controls; Indredavil et al., 2004). Studies have shown that general prenatal underdevelopment is prevalent in patients with schizophrenia, most prominently low birth weight (Indredavil et al., 2004; Kunugi et al., 2001) and a further significant trend was found between schizophrenia and very low birth weight (Abel et al., 2010). The Murray-Lewis Obstetric Complications Scale is a clinical estimate of the degree of obstetric problems a participant has encountered in infancy. Using this metric it has been shown that At Risk Mental State (ARMS) patients had significantly higher obstetric complications than controls (Ballon et al., 2008). A further review has also identified three obstetric groups that are said to be associated with increased risk of schizophrenia (Cannon et al., 2002):

1. Complications of pregnancy (bleeding, diabetes, preeclampsia).

2. Abnormal fetal growth & development (low birth weight, congenital malformation).
3. Complications of delivery (uterine atony, asphyxia, emergency c-section).

Jones and colleagues (1998) assessed a large scale population cohort and found that of the patients who had survived severe perinatal brain damage (*n* = 125), 4.8% had developed schizophrenia. Furthermore, the model of risk factors for schizophrenia (Murray et al., 2017) claims that aberrant development in the prenatal stages in conjunction with environmental factors including obstetric complications (such as PTB) and further lifestyle influences such as drug usage and urban living can culminate in increased risk of progression to the disease. Whilst very heterogeneous, factors such as abnormal dopamine expression (Brisch et al., 2014), the enlargement of ventricles (Bakhshi & Chance, 2015; Fatemi et al., 2009; Murray & Lewis, 1987), and reduction of cortical GM (Fornito et al., 2009) are consistently demonstrated for both PTB and schizophrenia.

Clinically, both PTB and schizophrenia are often reported as having reduced Intelligence Quotient (IQ, Aylward, 1984; Kendler et al., 2015; Gu et al., 2017), executive functioning (Orellana & Slachevsky, 2013; Taylor & Clark, 2016), working memory (Anderson & Doyle, 2003; Van Snellenberg et al., 2016; Woodward et al., 2005), and many other instances of shared cognitive impairment (Carter et al., 2010; Guarini et al, 2010; Rommel et al., 2017; Stephane et al., 2007). It has even been demonstrated that being born before 32 weeks GA increased the risk of other psychiatric disorders such as eating disorders, alcoholism, and drug dependency (Nosarti et al., 2014).

Dopamine

It is well established that dopamine expression plays an essential role for PTB infants, in that it helps moderate blood pressure, boost production of cerebrospinal fluid (CBF), and increase mean arterial pressure (Vesoulis et al., 2016; Wong et al., 2008). One theory is that prematurity causes the dopamine regulatory system to become hyper-responsive to stress (Murray et al., 2017). This is a particularly important concept as stress is a notable risk factor in adolescence for schizophrenia (Gomes & Grace, 2017). This relationship is further exemplified when considering the basal ganglia network. Within the basal ganglia is the substantia nigra, that houses dopaminergic neurons which routinely synthesise dopamine (Bjorklund & Dunnett, 2007). Both

disorders are associated with reduced GM in the basal ganglia (Loh et al., 2017; Perez-Costas, Melendez-Ferro, & Roberts, 2010). The overall implication is that early disruptions to structural development can lead to a reduction in the basal ganglia network GM, thus mediating the consistency of dopamine expression, which can later lead to risks of psychosis or other mental illnesses. This is consistent with research that has demonstrated how perinatal brain injuries can lead to adult dopamine dysfunction (Froudist-Walsh et al., 2017).

Ventricles

The neurodevelopmental damage that can occur as a result of PTB is strongly associated with germinal matrix hemorrhage, peri/intraventricular hemorrhage, and periventricular leukomalacia (PVL, Keshavan, Kennedy, & Murray, 2004). The complications of PVL relate to necrosis, whereby developing axons and oligodendrocytes die thus delaying myelination processes. Murray and Lewis (1987) postulated that PTB periventricular hemorrhage and subsequent ventricle dilation may be indicative of a comorbidity to disorders such as schizophrenia, remarking that issues may remain dormant until triggered during adolescent development (The two-hit hypothesis; Davis et al., 2016). Murray and Lewis argue that it is not unheard of for obstetric complications to have a latent period to their sequelae, citing examples from epilepsy and dyskinesias.

Despite over 30 years of study, very little concrete evidence demonstrates the biological etiology of ventricular enlargement in schizophrenia (Sayo, Jennings, & Van Horn, 2012). Whilst scarce, some evidence suggests that it may be related to thalamic shrinking, notably in the striatum and insular cortex (Gaser, Nenadic, Buchsbaum, Hazlett, & Buchsbaum, 2004). These authors imply that ventricle enlargement is associated with regionally specific reductions of brain parenchyma. For example, the main body of the lateral ventricle is directly adjacent to the thalamus. This would suggest that ventricular enlargement is related to GM disruptions and perhaps a consequence of proximal lesions to structures surrounding them.

Undeniably, both schizophrenia and PTB patients develop enlarged ventricles, although an important distinction is that earlier stages of schizophrenia do not typically present with this symptom (Berger et al., 2017), whereas morphological changes have been shown even as infants for PTB patients (Nosarti, 2002; Paquette et al., 2017). Ultimately, there appears to be no general consensus as to the true prognostic outcome of brain ventricular dilation.

Grey-Matter

Normal GM development follows a pattern that is anatomically non-linear, and includes growth spurts in cortical GM which are notable during childhood and adolescence (Gogtay & Thompson, 2010). GM is shown to reduce significantly during early adulthood which is referred to as the post-pubertal loss. Frontal, parietal, and temporal lobes follow a reversed U-shape trajectory peaking at around 11 years old for frontal lobe but ranging up to 14 years old for the temporal lobe and then decreasing with age until early adulthood (19-20). This indicates that there is a heterogeneity to cortical development, suggesting caution should be taken when interpreting results and particular attention given to the age range of samples. Nonetheless, even within healthy development, the reduction of GM exceeds current models of synaptic-pruning, and suggest an involvement of intra-cortical myelination (Paus, 2005). Therefore, a combination of the proliferation of progenitor myelination cells and degree of synaptic pruning are sufficient to explain the mechanisms of GM development in a healthy functioning brain. Importantly, GM reduction is highly associated with a vast assortment of diseases, developmental disorders, and environmental events (such as alcoholism, Yang et al., 2016) making GM images ideal for analysing a potential relationship between PTB and schizophrenia.

There is still debate as to the mechanisms behind GMV reduction in schizophrenia due to two different streams of research: one emphasising the role of developmental and obstetric insults and how these may contribute to a delay in GM maturation (Cannon, Jones, & Murray, 2002; Dalman et al., 1999), and the other demonstrating the effects of medication in reducing brain tissue matter (Ho et al., 2011; as cited in Zhang et al., 2016). However, longitudinal work has examined the differences between UHR patients that transitioned versus those who did not and found significant differences in GMV (Pantelis et al., 2003). Participants were considered clinically indistinguishable before transition and reductions in the prefrontal, insular, temporal cortex, the basal ganglia and the bilateral cingulate cortex were therefore considered measures of transition. This solidifies the argument that schizophrenia is often reliant on a prior biological event, and although disease progression may enhance or accentuate structural insults, it is unlikely to originate from this.

Analyses have typically examined both PTB and schizophrenia GM images in comparison to control groups both cortically and subcortically. The majority of research that attempts to establish a relationship does so on the basis of literature that follows these protocols, the consequence of this is that research examining both groups directly is scarce. A major benefit of the current thesis is the ability to directly explore patient populations from both groups, independently (versus their own respective control groups), and directly; applying GM signatures

across conditions using well controlled and carefully age-matched groups and utilising machine learning techniques.

Chapter 4 - Machine Learning

Over the past decade, the utilisation of supervised machine learning (ML) has grown in neuropsychiatric and neuroimaging MVPA communities and has become one of the most prominent statistical tools for promoting individual level characterisation ahead of group (Orru et al., 2012). One of the key goals for ML in clinical science is to provide tools that can benefit both doctors and patients to improve patient outcomes, such as the application of biological signatures to determine suitable treatments and diagnostics. In neuroimaging fields, ML algorithms aim to perform a feature selection that will generate anatomical prognostic biomarkers or "signatures" that represent the learning that has occurred across decision boundaries using datasets (Leger et al., 2017). A critical aspect of ML is the ability to infer generalisability (how well a model for a group performs for a separate individual) across a variety of data types (Dwyer et al., 2018). Moreover, multivariate methods such as supervised ML have the advantage of uncovering more subtle spatial distributions that univariate approaches may not detect and incorporating these distributions into classification models. Support Vector Machine (SVM) is a common supervised ML method for classifying data by attempting to maximise a hyperplane dimensional boundary between classes. As the name suggests, SVM utilises support vectors in order to generate a hyperplane boundary. In brief, support vectors refer to the inner products of observation which means the closest data points to the boundary between classes (James, Witten, Hastie, & Tibsharani, 2013). If a linear decision surface is not applicable, a surface is generated by expanding feature space via the application of specific kernels to accommodate multidimensional classes of data.

In principle, an SVM learns by determining the optimal algorithm model through a "training" phase that uses data to calculate the optimised discrimination based on prior information (supervised learning). Followed by a "testing" phase where these newly formed algorithmic models are tested by attempting to predict the correct class boundary of new data. Conceptually, the procedure of generating models in one sample and directly applying it to another is considered the gold standard of translational science (Cannon et al., as cited in Dwyer et al., 2018). ML methods, however, have the additional benefit of being able to iteratively

resample learning algorithms and thus enhance generalisation by a process known as cross-validation (CV).

CV is a procedure by which samples are split into training and testing and iteratively resampled using different partitions as testing set (Filzmoser et al., 2009; Orru et al., 2012). CV is considered one of the most robust forms of resampling due to its reliable partitioning of training and testing data, and in many instances, increases the ecological validity of the analysis due to simulating a clinical setting where the model may be applied to a new individual (Dwyer et al., 2018). Different CV procedures exist for separating the folds of training and testing data, these include: leave-one-out and k-fold CV. However, these particular methods have been reported as potentially susceptible to overfitting when using held-out datasets for feature selection (Koutsouleris et al., 2016). Nonetheless, one of the most reliable approaches is the repeated nested CV (Dwyer et al., 2018; Filzmoser et al., 2009). In this approach an inner (CV1) and outer (CV2) loop are generated which serve to further separate the data partitions. Both partitions are split into folds of training and testing sets (size is often user specified) and parameter tuning occurs based on execution of CV1 partition resampling. The output from CV1 is a result of hyperparameters from the CV2 training set, which then loops through CV2 using this output and its performance is iteratively evaluated for generalisation error. These permutations are conducted randomly within sets, and the CV loops for each permutation.

Typically, SVM data are reconstructed through a process known as feature extraction, which transforms neuroimaging data (3D) into vector matrices (2D) and sets each cell to a value representing the corresponding voxel intensity (Orru et al., 2012). This can be applied to both structural and functional datasets and is integral to GMV analyses. The resultant models can then be recompiled upon completion to look at voxel probability maps of reliable contributions to an averaged SVM hyperplane on a brain map. These maps are useful for illustrating structural regions that were critical in defining support vectors and therefore are reliable estimates of differences between groups. Once the SVM model is complete, the trained models can be applied to external, out-of-sample CV (OOCV) data to further strengthen claims of generalisability or even to examine potential relationships between independent groups. Often OOCV is taken as an independent group for a validation sample from the main patient group (Cabral et al., 2016) and applied later as unseen data. OOCV is a critical application for this thesis and will be required for the application of schizophrenia and PTB GMV images onto each SVM model respectively. This thesis utilises a cross-over approach, first requiring the creation of SVM models for both schizophrenia and PTB versus control groups in order to generate signature patterns that contributed to discrimination, and then applying these models using OOCV to the opposing

external dataset. As of yet, no paper has employed such a cross-over style of analysis and one of the major benefits of this approach is the robust generalisability claims that may be inferred from results. Utilising repeated nested CV, the hope is to avoid any unintentional information leakage between training and testing sets (Dwyer et al., 2018), and to further prevent transference of information between the two studied groups via OOCV.

Within the field of MVPA, many neuropsychiatric conditions have demonstrated significant differentiation from controls using neuroimaging datasets and utilising SVMs (Fu & Costafreda, 2013; Kambeitz et al., 2015). Critically, GMV is the measure of choice for a variety of SVMs used in neuroimaging studies to look at both psychiatric illnesses and neurodegenerative disorders such as: mild cognitive impairment (Orru et al., 2012), Alzheimer's disease (Kloppel et al., 2008), and multiple sclerosis (Bendfeldt et al., 2012). Furthermore, GMV has been shown to be up to 88.9% accurate for predicting antidepressant medication response using SVM (Costafreda et al., 2009). SVM has also been successfully implemented to look at the transition likelihood of at-risk for psychosis patients (Koutsouleris et al., 2009), which was further complemented by a follow up analysis 4 years later and examined GMV to predict transition to psychosis with an accuracy of ~82% (Koutsouleris et al., 2012). Orru and colleagues (2012) posited that this reinforced the importance of GMV disruptions due to their tendency to diffuse ubiquitously across the brain. Schizophrenia can also been accurately classified compared to controls (Kambeitz et al., 2015) despite the aforementioned heterogeneity and large network of neuroanatomy that is involved.

Importantly, SVM techniques have been used to successfully classify PTB adolescents compared to controls with a high degree of accuracy (Chu, Lagercrantz, Forssberg, & Nagy, 2015). Experimenters employed a linear SVM to GMV using two different methods: firstly between PTB and controls and secondly using OOCV on a subsection of patient images that were tested as independent unseen data. Correct accuracy was around 90% for both methods and researchers claim that the high accuracy of classification SVMs may eventually lead to non-invasive predictions of prognostic outcome of PTB patients using such classification parameters. An effect was also demonstrated in post-hoc investigation that participants with more severe obstetric complications had a further mean distance from decision boundary compared with controls. As of yet, no experiment has used SVM to compare schizophrenia to PTB groups or applied a cross-over OOCV approach between two disorders.

Chapter 5 - Aims & Hypotheses

The aims of this thesis were firstly to apply age matching protocols to both PTB and schizophrenia datasets and additional control subjects. This was based on the fact that developmental processes are time sensitive, especially with the addition of a transitional progression during young adulthood that could significantly vary neuroanatomy. It was crucial to examine groups that had similar age ranges, but also had similar matching control groups due to the normal brain aging effects that may influence results. The next aim was to generate SVM signatures for both groups utilising their respective controls. The reasoning behind this was twofold: firstly to confirm that the datasets were consistent with prior research, and secondly in order to generate signatures that could be used for the cross-over analysis. The final aim of this thesis was to apply these generated signatures using a cross-over OOCV in order to evaluate whether there is an uncovered relationship between the two conditions that would match the cohort of reviewed literature. The experiment was designed based on an informed assumption that there is a likely relationship between the adult brains of PTB and patients with schizophrenia. Based on the assortment of presented literature the hypotheses are presented thus:

1. Classification patterns associated with PTB will uncover enlargements in the frontal cortex and and reductions of both cortical and subcortical GM when compared with age-matched controls. More specifically, PTB will present with significantly reduced GMV in hippocampus, caudate nucleus, fusiform gyrus, basal ganglia, and thalamus. Enlargements of GMV will be noted for PTB in the frontal regions, particularly the frontal middle and frontal superior gyri and lateral ventricles.
2. Classification patterns associated with schizophrenia will uncover enlargement in the putamen and lateral ventricles and reductions of GMV in the frontal, temporal, striatal, and limbic regions when compared with age-matched controls. More specifically, schizophrenia will present with reductions of GMV in the insular cortex, cingulate gyrus, the caudate nucleus, the middle frontal gyrus, fusiform gyrus, basal ganglia, and the thalamus. Enlargements of GMV will be noted for the schizophrenia group in the putamen/pallidum and lateral ventricles.
3. Accuracy, specificity, and sensitivity metrics from SVM analysis will perform at a manner consistent with research on neurological disorders showing between 58-

100% accuracy (Bisenius et al., 2017) for both OOCV analyses. PTB GM images will be an effective classifier for schizophrenia GM and vice versa. With the implication that the two disorders share a large pattern of structural similarity that is significantly different from control groups.

Methods

PTB sample

Participants

101 adults born with Very Low Birthweight (VLBW) and low Gestational Age (GA, *m* = 30.5) were demographically matched to 102 term born controls from a sample obtained from the Bavarian Longitudinal Study (BLS; Wolke & Meyer, 1999) - henceforth referred to as the Bayerisch Entwicklungsstudie (BEST) dataset. Participants were part of a geographically defined cohort who partook in a follow up assessment 26 years after an initial examination which included MRI scanning and tests of obstetric complications (Intensity of Neonatal Treatment Index (INTI)) as well as cognitive tests. GA estimations were based on maternal reports of menstrual period at the time. All infants that were born between the months of January 1985 and March 1986 in south Bavaria who, within 10 days of being born, required access to the neonatal care centres in seventeen children's hospitals were included. Eligibility sample follow ups have been previously explained (Gutbrod et al., 2000). The dataset has been previously used to show cognitive status and pre-reading skill deficits in 6-year-olds (Wolke & Meyer, 1999), attentional problems in adulthood (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2016), reduction of cholinergic basal forebrain integrity (Grothe et al., 2017), and decline in other cognitive attributes: working memory, visual attention, and non-verbal IQ (Bauml et al., 2015; Daamen et al., 2015; Finke et al., 2014). Participant information has been previously described and was adapted from prior research (e.g., Daamen et al., 2015; Wolke & Meyer, 1999).

Data acquisition

The MRI data were acquired at two site locations, one in Munich at the Department of Neuroradiology, Technische Universität Munchen, Germany, and one in Bonn at the Department of Radiology, University Hospital Bonn, Germany. Scans were collected using a Philips Achieva 3T

TX system (Achieva, Philips, the Netherlands) and utilised an 8-channel *SENSE* head coil. However, a scanner upgrade occurred during data collection and meant that acquisition was switched onto a Philips Ingenia 3T system, also utilising an 8-channel *SENSE* head coil after seventeen participants. This led to a situation where 4 separate scanners had been used for image acquisition. Scanner effects were later controlled for (See *Methods - Scanner Effects*) as scanner type was recorded as a covariate of no interest. Across all scanners, sequence parameters were kept as similar as feasibly possible. Previous studies have performed signal to noise ratio tests on the scanners and found no significant differences (Bäuml et al., 2014). The original data acquisition included both functional and anatomical scans, but for the purposes of this thesis only the anatomical scans were utilised. A high-resolution T1-weighted 3D-MPRAGE sequence (TI = 1300ms, TR = 7.7ms, TE = 3.9ms, flip angle = 15°, 180 sagittal slices, FOV = 256 x 256 x 180 mm, reconstruction matrix = 256 x 256, reconstructed voxel size = 1 x 1 x 1 mm^3) was collected (previously described in Bäuml et al., 2014).

Schizophrenia sample

Participants

158 schizophrenia patients were assessed at the Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich (henceforth referred to as MUC sample). Structured Clinical Interviews (SCID-I/-II) were collected along with medical record data including psychotropic medication usage by highly skilled and experienced clinical psychiatrists in the department. PANSS (see Chapter 2 – Schizophrenia) scores were utilised to determine patient symptom levels. Participant exclusion criteria has been previously described (Dwyer et al., 2018).

366 control subjects were also collected as part of this MUC sample and were required for prior validation studies and have also been previously described. Age range was between 18-65 and exclusion criteria is available elsewhere (see Dwyer et al., 2018 for brief summary). Critically, patients with head trauma, and family psychiatric history were excluded. This dataset has been previously used to examine the acceleration of brain aging in schizophrenia (Koutsouleris et al., 2014) and as an external validation sample for brain subtyping and the generation of effective discriminative signatures for schizophrenia (Dwyer et al., 2018).

Data acquisition

The MRI data were acquired in Munich, at the Department of Radiology, Ludwig-Maximilian-Universität, Germany. Scans were collected using a 1.5T SIEMENS Magnetom Trio scanner and a high-resolution T1-weighted 3D-MPRAGE sequence (TE = 4.9ms, TR = 11.6ms, 126 continuous axial slices (1.5mm thick), FOV = 512x512x126, voxel size = 0.45x0.45x1.5mm) was collected. This information has been previously described (Dwyer et al., 2018; Koutsouleris et al., 2014).

Scanner Effects

One critical step was to minimise any MRI scanner differences between datasets that may occur and influence results. This problem is particularly important for SVM analyses due to the tendency to uncover more subtle spatial distributions. Differences in resolution and other sequence parameters described above would undoubtedly be more prominently integrated into algorithms to determine hyperplane boundaries than relevant anatomical distributions. Consequently, three methods were conceived to address this concern, these included: a mean subtraction method, a regression method and a Principal Components Analysis (PCA) method. The performance of the PCA method was found to be the most reliable based on histograms of BEST and MUC control groups and was therefore utilised for this thesis (the other methods are described in the supplementary material). It was important to account for differences in scanner type both across (MUC & BEST) and between (BEST) groups. Utilising the PCA method initially across group, voxel-level intensity matrices were developed using the output from NeuroMiner (see *Methods - Multivariate Pattern Classification Analysis*). A PCA was then conducted on these data to identify components that are correlated with scanner, and subsequently remove these from a reduced version of the data. Following this, the newly calculated matrices were reconstructed into brain images. During this PCA a dimensionality reduction toolbox DrTools (developed by Deng Cai, 2006) was applied using a cut-off identification threshold [0.3]. This reduction was deemed suitable for the MUC group as scanner-type had not been initially controlled for. However for the BEST sample, an effective method was chosen to account for the differences between the four different scanners. Simply, the entire MUC sample was iteratively compared to groups from the separate scanners and then compiled into a full reduced BEST dataset. This way each individual site could be compared to the MUC site without any intersite interference. A final comparison was performed on control groups using histograms to see whether voxel-level intensity matrices were still normally distributed and whether they matched more efficiently than uncorrected images and found the approach to be successful.

Age Matching

One of the most important aspects for this thesis was applying reliable and effective age matching protocols. Based on the concepts outlined in the introduction, both PTB and schizophrenia involve the linear progression of neuroanatomical states in relation to age. Furthermore, the inclusion of control groups presents an additional obstacle to overcome due to the heterogeneity of brain structural development that occurs even into young adulthood in a healthy brain. Within the initial overall samples, the MUC group had a much older mean age (*m* = 32.2) than the BEST group (*m* = 26.8), and also had a far larger age range (18-65 vs 25-26 respectively). This disparity is damaging to a thesis that incorporates developmental concepts and aims to examine a relationship between neuroanatomical patterns across two patient groups. Ideally, groups would be as similar as possible for age range to minimise normal developmental digression as well as to strengthen claims of generalizability by refining the specificity of results.

In an attempt to minimise differences between the two samples, participants were matched for age and sex using a MATLAB script (see *Appendix 1*) which reduced comparative *p* values to greater than 0.8. Firstly, due to the large disparity between sample sizes, it was important to perform age/sex matching for the MUC sample individually (schizophrenia group vs controls). This initially lead to 158 patients and 158 controls, however, upon post-hoc inspection of histograms, it was determined that the balance of age range was too spread, compared to the range for the BEST sample. Therefore a further MATLAB script (see *Appendix 1*) was implemented to reduce the range in order for the two groups to have a closer similarity beyond the average. This culminated in 102 patients and 102 controls with a tighter age range (20-35) whilst still matching across groups for age/sex (see *Figure 1*).

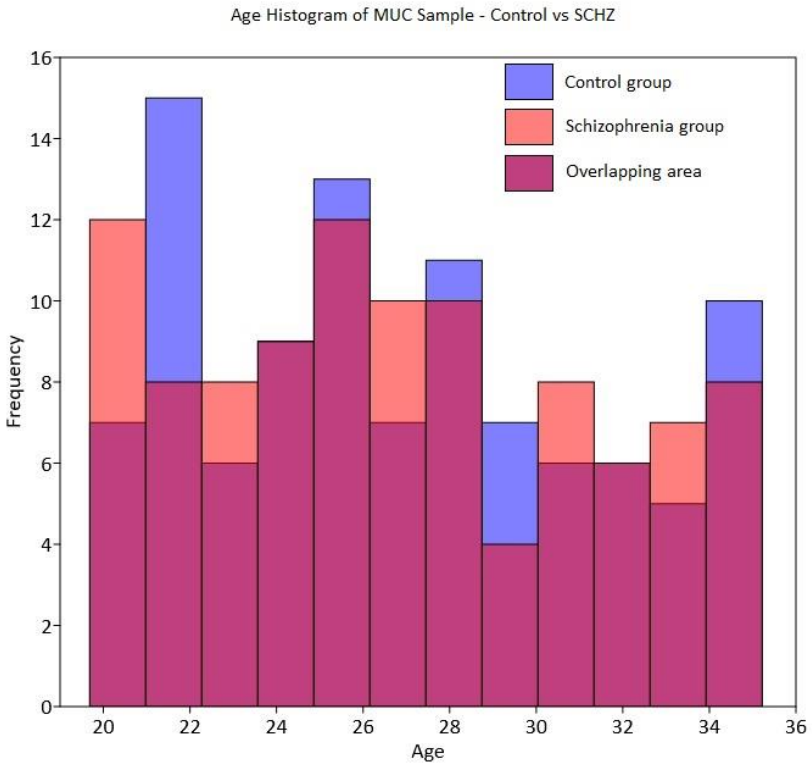

Figure 1: Age histogram demonstrating the variance between MUC healthy controls (*orange*) and schizophrenia group (*blue*). It is evident from manual inspection that the compatibility is strong and the overlap (*purple*) successful.

Upon completion of this, the MUC sample could now be applied to the BEST sample using the same age matching script. With this more conservative age range, ages between the two samples (BEST and MUC) could be plotted to estimate how successful the overall method had been in generating data that are reliable and ensuring that the covariates would not diminish any effect sizes.

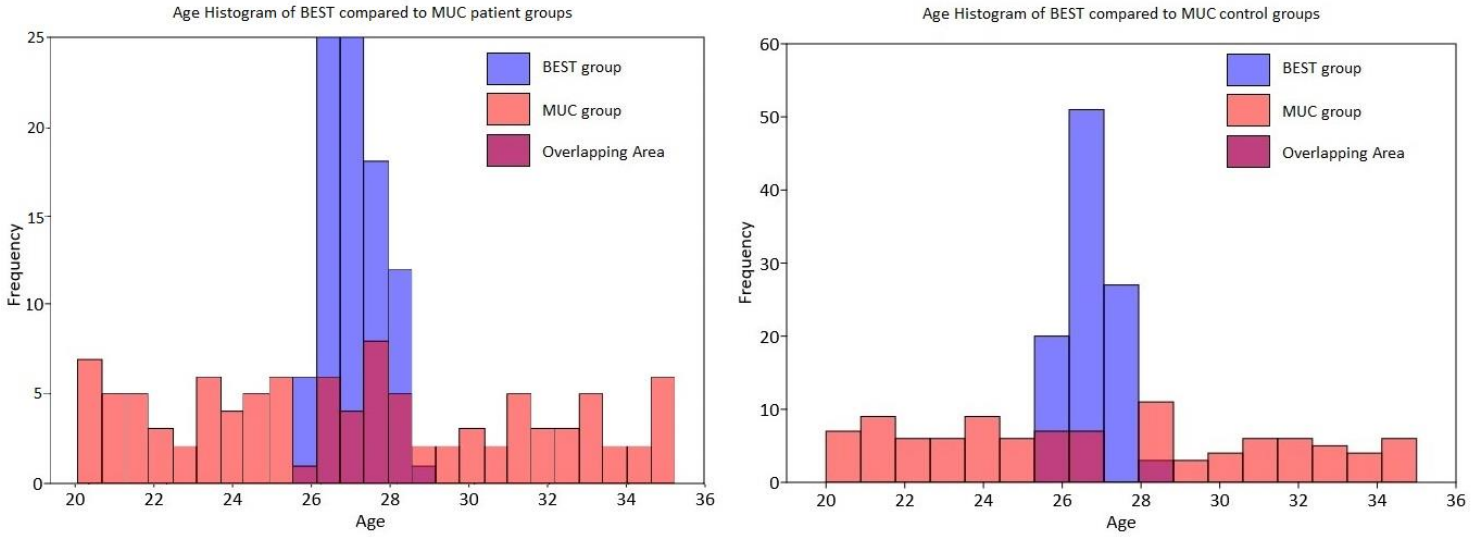

Figure 2: Histograms of patients (*left*) and healthy controls (*right*) for age demonstrating the overlap between the two samples. BEST (*blue*) and MUC (*orange*) frequencies at each age are shown as well as the overlap between them (*purple*).

Figure 2 demonstrates the difficulty in matching the two groups. Whilst it was deemed important to maximize the overlap between age groups, this was done along with the desire to maximize the participant number. The solution was to strike a balance and be more liberal with the MUC sample age-range in an attempt to have the script algorithm match the participants with a more suitable specificity. Coincidentally, when restructuring the age-range for the MUC patient group, the total participants was reduced to exactly 102 making the algorithm obsolete for this group. An experiment was performed later into testing to determine whether extremely tight age matching (MUC sample between 25-27) would have an impact, the results did not significantly differ (see supplementary material).

Quality Control

Both the BEST and MUC samples were rigorously quality checked to ensure that all GM images were consistent and of testing quality. PRONIA (https://www.pronia.eu/) research centre protocols were adhered to for the sake of and ease of replication. Initially, this required all GMVs (i.e. “mwp1” files) to be processed through Computational Anatomy Toolbox 12 (CAT12) Homogeneity testing which produces a correlation matrix of all volumes (see *Figure 3*). This

procedure averages correlation values and generates a homogeneity value for the sample (see CAT12 manual; Gaser & Kurth, 2017). There is also the option to display the weakest correlation subset (largest deviation) of the overall sample.

Initial homogeneity testing revealed several participants in both the BEST and MUC samples that were ultimately excluded (for a full list of quality control excluded participants see *Appendix 2*). After removal of unreadable or corrupted GMVs, CAT12 Homogeneity was rerun and the results can be seen on *Figure 3.* The majority of images were of very high homogeneity and unlikely to contain artifacts or brain warping technical problems. However, even after this second iteration of CAT12 Homogeneity testing, the outputs still displayed lower quality outliers that would require further inspection.

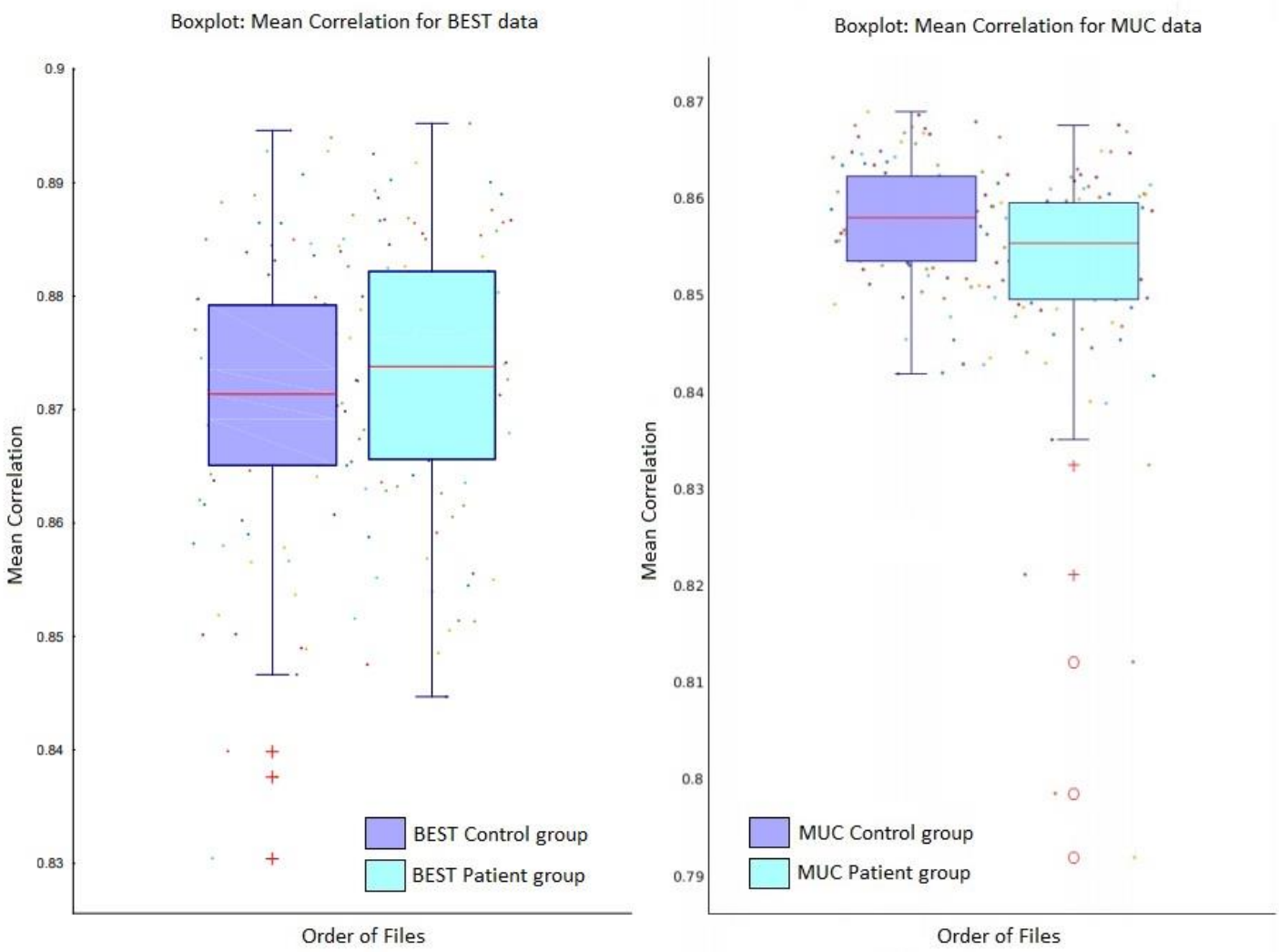

Figure 3: CAT12 Homogeneity testing outputs. The BEST sample (*left*) shows the healthy controls (*purple*) and the PTB patients (*blue*) mean correlation box plot. The MUC sample (*right*) shows the healthy controls (*purple*) and the SCZ patients (*blue*) mean correlation box plot. Red markers below are images that CAT12 deemed worthy of inspection as potential unusable or unreadable outliers.

The next quality control step required a manual inspection of every GM image. The researcher (having received MRI quality control training) inspected the images individually making note of any inconsistencies or irregularities that were observed. Special attention was drawn to the CAT12 outlier images which were ultimately accepted as valid images. According to the CAT12 manual (Gaser & Kurth., 2017) the homogeneity testing should be used purely as a guideline for further inspection and not as a tool for image rejection. Therefore, the following manual protocol was followed: images were loaded into Statistical Parametric Mapping 12 (SPM12, Penny et al., 2011) display software and inspected across X, Y, and Z coordinates through the whole brain space. Particular emphasis was placed on locating image tears, common artifacts, and anatomical irregularities, and the researcher used their experience and intuition to flag any images that required further inspection or should be excluded. Based on these protocols, the outlier images were deemed suitable to continue analysis.

Procedure

Voxel Based Morphometry (VBM)

The main goal of VBM is to identify differences in local composition of brain tissue while managing to mediate any differences caused by anatomy or position (Mecheilli, Price, Friston, Ashburner, 2005). During this experiment, both the BEST and MUC group were preprocessed using CAT12 in preparation for VBM analysis. This met the following standards and requirements: structural image volumes were segmented into corresponding issue probability maps using a standardised MNI template in stereotaxic space. Following this, the transformed maps were utilised to perform DARTEL normalisation using the generated forward deformation fields. The finalised images ("mwp1") are modulated, segmented, GMVs. CAT12 manual recommends to not smooth at this stage due to the likelihood of removing anatomical specificity and resolution (Gaser & Kurth, 2017).

For analysis, two-sample Threshold Free Cluster Enhancement (TFCE) tests were conducted using an International Consortium for Brain Mapping (ICBM) masking template image. Total Intracranial Volume (TIV), age, and sex were implemented as covariates and two separate contrasts were evaluated (control > patient, and control < patient). TFCE is designed to resolve issues of cluster thresholding and spatial pre-smoothing that are common in standard *t*-tests and are ultimately arbitrary. This is accomplished by taking the raw statistic image and producing an output where the values represent cluster-like local spatial support (see Smith & Nichols, 2009).

The VBM tests were performed for two reasons: to return reliable estimates of anatomical specificity between patients and control groups (of both samples) and to provide a rough projection for expected results of the SVM. This could be utilised as a sanity check for ensuring the pattern classification algorithms were running correctly.

Multivariate Pattern Classification Analysis (MVPA)

The in-house pattern recognition software package NeuroMiner (http://www.pronia.eu/neurominer) was used to set up the SVM analyses. Operating through MATLAB (2015b), NeuroMiner aims to implement a fully automated machine learning pipeline and construct predictive neuroanatomical features using high-dimensional GM maps. Furthermore, it aims to apply this pipeline in a manner that helps it to develop learned decision rules using these available features to help with prediction. In the case of this experiment, the initial usage of NeuroMiner was to generate predictive maps of GM volumes for PTB and controls using the BEST sample, and to generate further predictive maps of GM volumes for schizophrenia and controls using the MUC sample. To setup an analysis, NeuroMiner requires Total Intracranial Volume (TIV) to be set as an adjusted global measure. This means that the software will proportionally scale subject features to that global measure. Furthermore, a space-defining image mask is applied to reslice volumes to a reliable resolution.

Utilising repeated, nested CV involved splitting partitions into two CV schemes: inner (CV1) and outer (CV2). The preprocessing steps mentioned below are applied to the CV1 cycle and generalisation error is computed only on the CV2 testing cycle - this way training and testing data can be isolated from each other and minimises the effects of information leakage. On the inner cycle (CV1) permutations were set to the maximum available value in NeuroMiner, so there were a total of 10 folds with 10 permutations making 10 x 10 = 100 training and testing sets. For the outer cycle (CV2) 1 permutation was computed 1 x 10 = 10 training and testing sets, making a total of 10 x 100 = 1000 samples.

SVM Preprocessing

Further to the CAT12 preprocessing that images undergo as part of the VBM analysis, NeuroMiner has a built in preprocessing feature which is required to minimize variability and improve effect sizes, reducing cross-dimensionality and outlier effects. NeuroMiner testing defaults were used for the majority of analyses and applied to the inner (CV1) cycle. Firstly, a

pruning algorithm was implemented, excluding non-informative columns from any matrices (e.g. NaN). Following this, smoothing was conducted using a Gaussian 8mm Full Width at Half Maximum kernel via the Spatial OP Wizard. Next, the data were corrected for any nuisance variables, in this case both age and sex covariates were regressed out. A PCA feature reduction was implemented at this stage operating at 0.8 dimensionality. Finally, data were scaled featurewise independently to [0, 1] via a zero-out mechanism. The machine-learning algorithmic criterion was set to accuracy (sum(expected=predicted*100/negative accuracy & precision) due to the balanced sample sizes and because specificity and sensitivity did not require direct balancing. The machine learning algorithm was set to LIBSVM 3.1.2 with instance weighting support, this was based on standard options within the Library for SVM toolbox (LIBSVM, Chang & Lin, 2010). The kernel type was set to Linear in order to find the maximum-margin hyperplane that divides groups across multidimensional space.

Output of the SVM provides Grand Mean Results, amongst which is a volume representing the amount of times that the median value has been greater or less than the 95% confidence interval ("Prob95CL_GrM"). This delineates a classification pattern associated with the two groups, and once paired with the classification accuracy values, gives a clear demonstration of the predictive power of the analysis across an individual. In addition to this, the classifier provides measures of performance: *sensitivity*, *specificity,* and *balanced accuracy*. *Sensitivity* is a metric used to demonstrate true-positive values, for the purposes of this thesis this will mean that participants were classified as control subjects. *Specificity* is a metric used to demonstrate true-negatives, for this thesis this refers to classifying as patient (PTB, schizophrenia). *Balanced Accuracy* is the total accuracy of classification between both groups compared to the supervised learning parameters that were implemented and is useful for determining the overall success of a model.

Out-of-Sample-Cross-Validation (OOCV)

Upon finalising the classification results for both sets of data (BEST & MUC), the trained models were used to predict targets in a separate dataset using OOCV. Using a cross-over analysis of both pattern signatures, the CV2 data folds are utilised as the testing set. Meaning the BEST classification signatures were applied to an independent set (in this case MUC) and vise-versa. The initial analysis is locked because the external validation is reliant on the trained models being isolated from the OOCV data. Both patient and control groups were added as OOCV samples and separately re-sampled using their own TIV global values. Age and sex were entered as covariates

to regress out. Subsequently, OOCV parameters were applied, including ensemble settings: aggregate all based learners into one big ensemble, and model retraining mode: as defined for CV model training. Mean effects were tested using no adjustment and mean adjustment using mean function and found no differences between either testing procedure. Identical CV2 partitions were used for the analysis (1 x 10).

Results

BEST Sample

Chi-squared tests of independence were performed comparing PTB and control groups and found no significant differences for sex (χ^2 (1) = .004, p = 9.52) or socioeconomic status (SES χ^2 (2) = .423, p = .809). Furthermore, participants did not differ in terms of age (t = -1.131, p = .216). However, there were marked significant differences in key distinguishing factors; PTB patients were found to be born with significantly lower birth weights, at a significantly lower GA and were found to have lower scores of full-scale, verbal, and performance IQ (see table 1). PTB patients had high Duration of Neonatal Care (DNTI) and Intensity of Neonatal Care (INTI) scores, indicating worse obstetric complications upon birth which has been suggested to reflect developmental clinical outcomes (Aluvaala et al., 2017), this information was unavailable for control patients, but an assumption was made that their scores would be drastically lower considering their neonatal hospitalisation time was significantly lower than PTB patients indicating a decreased necessity for treatment.

Table 1: Demographic and covariate information for BEST sample:

	PTB	Controls	Comparison Values
N	101	102	
Sex, *male/female*	58/43	59/43	χ^2 (1) = .004
Age, *years* (*SD*)	26.8 (0.6)	26.7 (0.7)	t = -1.131
Gestational Age, *weeks* (*SD*)	30.52 (2.1)**	39.75 (1.06)	t = -39.252
Birth Weight, g (*SD*)	1318.27 (312.5)**	3405.77 (420.4)	t = -40.120
Maternal Age (*SD*)	29.32 (4.8)	29.36 (5.2)	t = -.066
DNTI (*SD*)	53.94 (29.4)	-	
INTI (*SD*)	11.57 (3.8)	-	
Hospital duration, *days* (*SD*)	72.83 (27.1)**	6.67 (2.4)	t = 24.606
SES	29/44/28	33/44/25	χ^2 (2) = .423
Full-scale IQ (*SD*)	94.32 (12.6)**	102.8 (12.1)	t = -4.785
Verbal IQ (*SD*)	99.24 (13.7)**	106.25 (14.5)	t = -3.472
Performance IQ (*SD*)	89.66 (13.7)**	98.54 (10.6)	t = -5.151

* Significantly different from control at p < 0.01

**Significantly different from control at p < 0.001

DNTI = Duration of Neonatal Treatment, INTI = Intensity of Neonatal Treatment (combination of clinical and neurological scores) - 0 denotes best, 18 denotes worst state), SES = Socioeconomic Status (at birth)

Voxel Based Morphometry

Using a TFCE in order to strengthen the VBM, a two-sample *TFCE test* of segmented GM images demonstrated significant GM reductions for PTB patients compared to controls in some key areas (see *Figure 4*), including the subcortical regions of the bilateral thalamus, fusiform gyrus, precuneus, and frontal pole. There was also a significant GM reduction of the middle temporal gyrus (Brodmann's area 21), premotor cortex, and lateral occipital cortex both posterior and anterior (See table 2). These measures were tightly extent thresholded to 150 voxel clusters and Family Wise Error (FWE) corrected as many smaller, potentially false positive areas appeared in the outcome. No significant effects were found for PTB > control contrasts when the rigorous thresholding techniques were included, although many small (significant but uncorrected) cortical clusters were found in post-hoc exploration with less strict measures employed.

It is clear from this analysis that there are key regions, particularly in the area surrounding the basal ganglia, that are significantly distinct between healthy controls and PTB patients, most notably areas with reduced GM in PTB.

Table 2: Threshold Free Cluster Enhancement (TFCE) results (BEST sample)

Region	Cluster Size	*TFCE* value	x	y	z	FWE corrected *p*
Thalamus (R)	62440	8759.18	14	-30	9	0.020
Middle Temporal Gyrus (R)	5961	9118.61	62	-9	-14	0.020
Premotor Cortex, BA6 (R)	3262	1178.59	-26	-78	-52	0.020
Lateral Occipital Cortex (L)	712	1056.35	-30	-74	24	0.020
Fusiform Gyrus (R)	688	1900.16	45	-40	-20	0.020
Frontal Pole (R)	349	911.02	24	64	9	0.020
Precuneus (L)	155	885.18	-12	-40	48	0.020
Lateral Occipital Cortex (L)	206	769.49	-45	-75	18	0.020

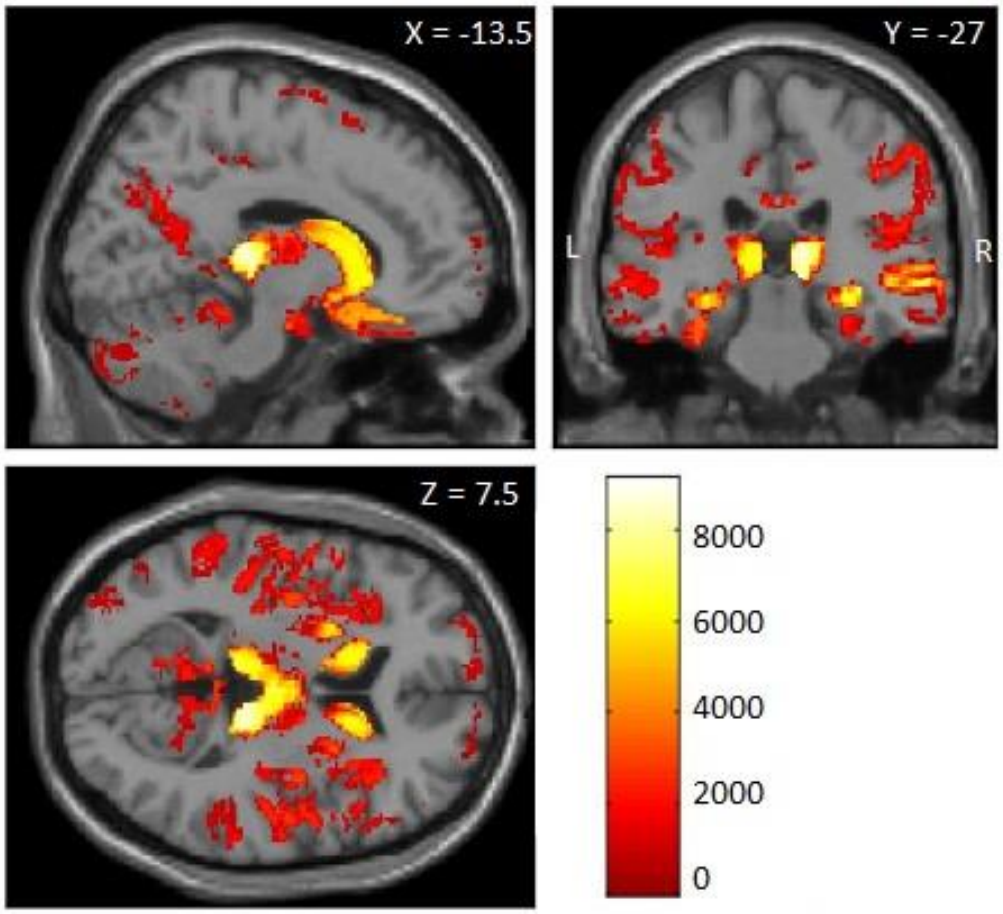

Figure 4: (for MNI coordinates, see *Table 2*). Results of a TFCE analysis for BEST sample. Contrast represents areas where controls > PTB. Most prominent subcortical areas include the right thalamus, lateral occipital, fusiform gyrus, frontal pole, and precuneus. The cortical region of the right middle temporal gyrus was also significant. Note: areas such as the bilateral caudate appear to be strongly represented, they were not included in the table due to their absence from SPM12 output. This may be due to how TFCE performs cluster grouping.

SVM Classification Analysis

BEST Interpretation

As demonstrated in table 3, the classification performance of PTB versus controls found metrics of Balanced Accuracy (BAC, 86.2%), sensitivity (93.1%), and specificity (79.2%) to be very reliable. In this experiment a high sensitivity would mean that controls were rarely categorised as PTB, and a high specificity means that PTB were rarely categorised as controls. Generally, a BAC of around 80% is considered as robust enough to publish in high impact journals in psychiatry (Dwyer et al., 2018; Kambeitz et al., 2015)

The most prominently affected areas of discriminative signature (see *Figure 5)* showed

reduced GM for PTB patients compared to controls in the basal ganglia complex nuclei: neo-striatum, bilateral putamen, caudate gyrus, and hippocampus. There was also reduction in the thalamus, as well as the cortical region of the medial temporal gyrus. An additional premotor cortex reduction was also uncovered via the SVM. There also appears to be an increase in GM volume of bilateral frontal, parietal and occipital regions, as well as extending across medial regions such as the corpus callosum and bilateral cingulate gyrus. This was particularly apparent around the medial longitudinal fissure, illustrated clearly in Figure 5 multislice images.

Table 3: The statistical Neurominer output of the SVM trained on PTB patients and controls VBM images demonstrating the Binary Classifiers after training supervised classifiers.

Performance	
TP	95
TN	80
Sensitivity	93.1%
Specificity	79.2%
Balanced Accuracy	86.2%
Positive Predictive Value	81.9%
Negative Predictive Value	92%
False Positive Rate	20.8
Positive Likelihood Ratio	4.5
Negative Likelihood Ratio	0.1

Abbreviations: GMV (Grey Matter Volume), TP (true-positive), TN (true-negative)

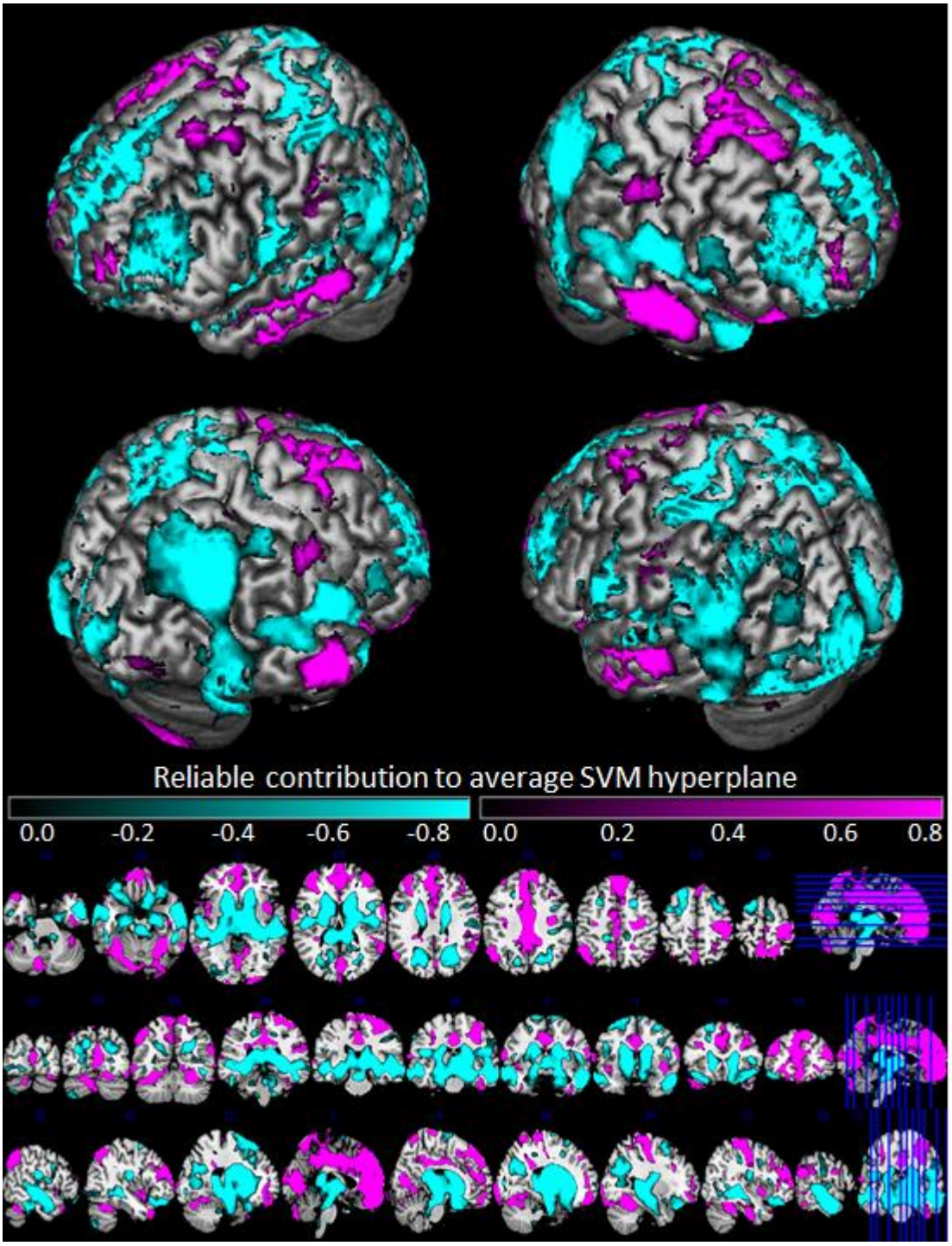

Figure 5: 3D renders and multislice of SVM signatures of cortical surface (Voxel Probability Map - VPM). *Cyan* represents areas of reduced GMV in PTB patients, purple represents enlarged GMV in PTB patients. Notably reduced areas include the middle temporal lobe and premotor cortex. Cortical areas around the frontal, and bilateral parieto-occipital lobes show notable enlargement especially in and around the medial longitudinal fissure. Presented onto a single subject MNI template using MRIcron software package rendering tools.

MUC Sample

Chi-squared tests of independence were performed comparing schizophrenia and control groups and found no significant differences for sex (77 male, χ^2 (1) = 0, p = 1) or handedness (χ^2 (2) = 2.464, p = .292). Furthermore, participants had been matched via MATLAB scripting for age (m = 26.86, t = -0, p = 1). However, the schizophrenia group were found to be significantly lower in years of education (t = 6.783, p < 0.001) and higher in body mass index (BMI, t = -2.515, p = 0.013). The schizophrenia sample was also tested using some typical clinical measures outlined by the DSM-V as precautionary for schizophrenia severity, these included: number of hospitalisations, positive and negative symptom scale (PANSS) score, and medication dosage (normalised across type to an equivalent Chlorpromazine score). The schizophrenia sample was made up of First Episode Psychosis (FEP) patients (n = 42) and Chronic patients (n = 54) and for the sake of further clarity, the clinical variables were compared for these subgroups (see supplementary material).

Table 4: Demographic and covariate information for MUC sample:

	Original MUC			Age Matched		
	SCZ	Control	Comparison Values	SCZ	Control	Comparison
N	158	366		102	102	
Age	30.84(9.9)	33.65(11.2)**	t = 2.717, p = .007	26.86(4.5)	26.86(4.5)	t = 0, p = 1
Handedness	14(13.7%)	47(12.8%)	χ^2 (2) = 1.819, p =	8.8(8.6%)	15.5(15.2%)	χ^2 (2) = 2.464, p =
Gender	117/41	182/184**	χ^2 (1) = 26.649, p >	77/25	77/25	χ^2 (1) = 0, p = 1
Education (years)	10.6(2.1)	12.15(1.2)**	t = 10.801, p < 0.001	10.73(2.1)	12.31(1.1)**	t = 6.783, p <
BMI	24.28(4.4)	23.26(3.3)**	t = -2.949, p = 0.003	23.95(4.3)	22.64(3.0)**	t = -2.515, p =
Clinical Variables						
Age at 1st	25.5(8.0)	-		24.1(5.0)	-	
Duration of	4.46(7.0)	-		2.69(3.5)	-	
Number of	1.94(2.1)	-			-	
PANSS - positive	11.85(8.0)	-		11.89(8.3)	-	
PANSS - negative	15.2(9.7)	-		14.62(9.7)	-	
PANSS - general	25.58(16.1)	-		25.9(17.3)	-	
Medication dose	346.3(373.4)	-		332.1(330.1)	-	

* Significantly different from control at p < 0.01

**Significantly different from control at p < 0.001

BMI = Body Mass Index, PANSS = Positive and Negative Syndrome Scale, CPZ = chlorpromazine (antipsychotic medication)

Voxel Based Morphometry

Two-sample *TFCE tests* of segmented GM images for the age-matched sample (not distinguishing between schizophrenia sub-groups) found reliable significant differences of

subcortical and cortical GM between SCZ and HC (see *Figure 6*). These areas included the following subcortical regions: olfactory bulb, fusiform gyrus, and hippocampus. Cortical regions included: premotor/supplementary motor area, superior and inferior temporal gyrus, inferior occipital gyrus, bilateral primary visual area, frontal middle gyrus, and superior frontal gyrus. Other areas including large portions of the basal ganglia thalamic network were also clearly noted. Measures were more liberally extent thresholded than the BEST sample at 45 voxel clusters and were FWE corrected using the same protocols. It may be fair to suggest that the orbital part of inferior frontal gyrus cluster overlaps with the cingulate cortex making this area relevant. The significantly reduced GM is all well represented in literature as having a relevance to schizophrenia.

Table 5: Threshold Free Cluster Enhancement (TFCE) results (age-matched MUC sample). Cluster thresholded at 45, FWE corrected.

Region	Cluster Size	*TFCE*	x	y	z	*P* value FWE
Prefrontal - *olfactory bulb* BA11 (L)	622304	1964.56	-10	26	-21	*p < 0.001*
Premotor/Supplementary Motor	543	634.67	27	-3	46	*p < 0.001*
Fusiform Gyrus (R)	492	575.57	48	-56	-6	*p < 0.001*
Superior Temporal Gyrus	166	525.84	-51	-56	21	*p < 0.001*
Inferior Occipital Gyrus	160	618.86	52	-68	-3	*p < 0.001*
Primary Visual (R)	152	522.00	16	-92	0	*p < 0.001*
Inferior Temporal Gyrus (R)	90	482.86	50	-16	-33	*p < 0.001*
Superior Frontal Gyrus (R)	77	499.79	6	32	56	*p < 0.001*
Frontal Middle Gyrus (L)	57	587.73	-42	34	32	*p < 0.001*
Primary Visual (L)	51	530.79	-2	-93	6	*p < 0.001*
Hippocampus (R)	45	528.84	28	-8	-20	*p < 0.001*

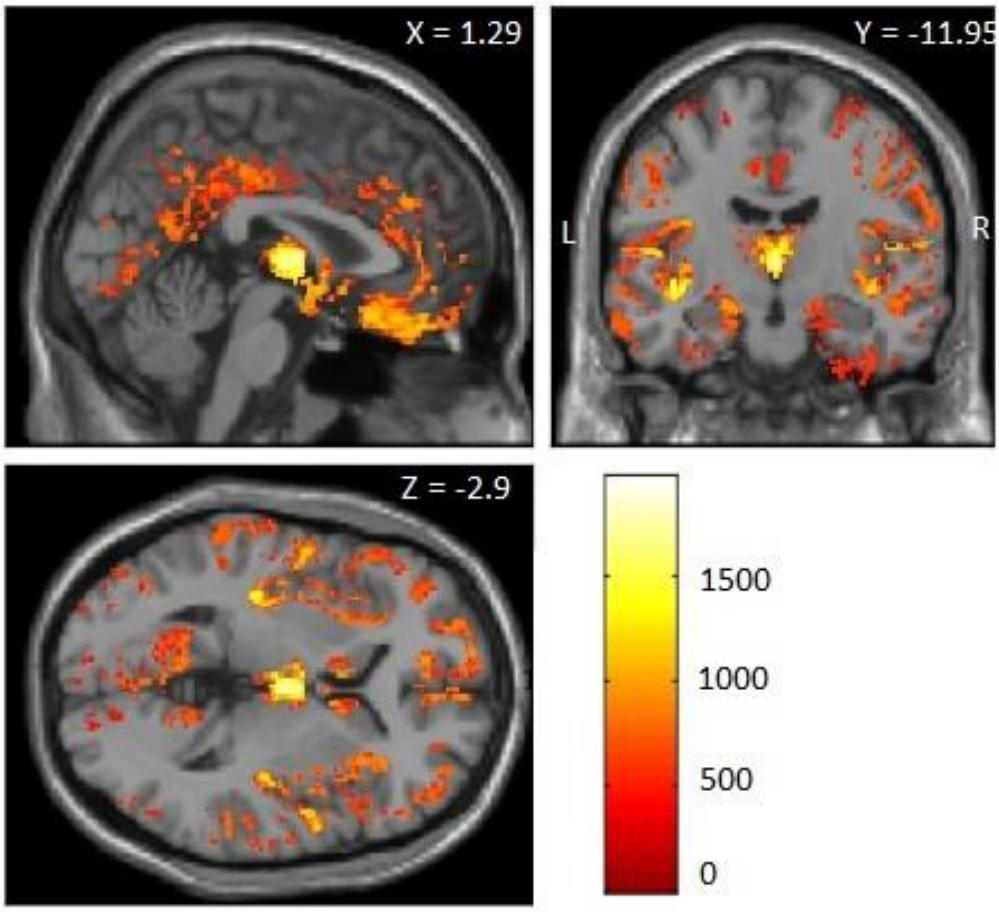

Figure 6: (for MNI coordinates, see t*able 5*). Results of a TFCE analysis for MUC sample. Contrast represents areas where controls > SCZ. This represents the results of the TFCE analysis FWE corrected. Subcortical regions matched those of *table 5* although slightly different cluster sizes are noticeable and the cortical STG region was no longer found to be significant.

SVM Classification Analysis

MUC Interpretation

As demonstrated in table 6, the classification performance of schizophrenia versus controls found metrics of BAC (67.6%), sensitivity (68.6%), and specificity (66.7%) to be moderately reliable and in-line with other neurological illness studies (see Discussion). In this experiment a high sensitivity would mean that controls were rarely classified as schizophrenia patients. A high specificity would mean that schizophrenia patients were rarely classified as controls.

SVM results demonstrated that a wide variety of areas were utilised for the classification of schizophrenia sample from controls. The schizophrenia group were found to have reduced GM

in several cortical regions, these included: the frontal lobe, with the rectus, medial frontal orbital, superior frontal orbital, and olfactory bulb being most prominently represented. The bilateral temporal gyrus was almost globally smaller for schizophrenia, especially on the left. The occipital lobe was also reduced, with areas such as the calcarine sulcus, cuneus, lingual, and lateral occipital gyrus showing distinguishable results. In terms of subcortical regions, the bilateral precuneus was smaller for patients with schizophrenia, as well as the cingulate gyrus (bilaterally), thalamus, bilateral para-hippocampus, and rolandic operculum. Discriminative signatures were also noted for control groups showing larger GM in the cerebellum. The schizophrenia sample was found to have a larger bilateral globus pallidus, frontal superior medial cortex, supplementary motor area / paracentral lobule, and lateral ventricles.

Table 6: The statistical Neurominer output of the SVM trained on schizophrenia patients and controls VBM images demonstrating the Binary Classifiers after training supervised classifiers.

Performance	
TP	70
TN	68
Sensitivity	68.6%
Specificity	66.7%
Balanced Accuracy	67.6%
Positive Predictive Value	67.3%
Negative Predictive Value	68.0%
False Positive Rate	33.3
Positive Likelihood Ratio	2.1
Negative Likelihood Ratio	0.5

Abbreviations: GMV (Grey Matter Volume),

TP (true-positive), TN (true-negative)

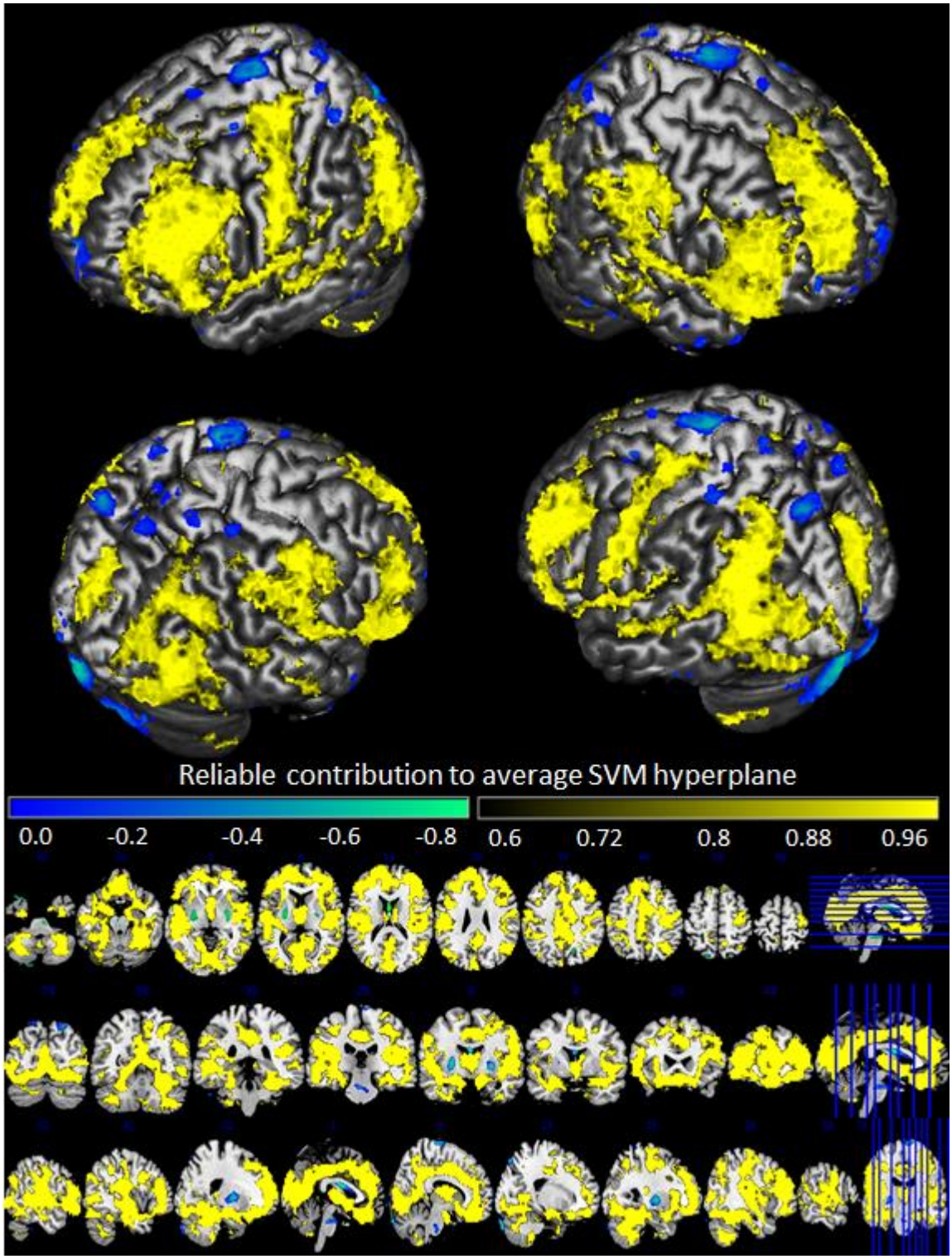

Figure 7: 3D renders and multislice of SVM signatures of cortical surface (Voxel Probability Map - VPM). *Yellow* represents areas of reduced GMV in patients with schizophrenia, *blue* represents enlarged GMV in patients with schizophrenia. Notably reduced areas include the frontal lobe, bilateral temporal gyrus, postcentral gyrus (L), superior motor area, as well as subcortical regions: cingulate gyrus, inferior caudate, thalamus, bilateral para-hippocampus, and precuneus. Areas of enlarged GMV for schizophrenia group included: pallidum (putamen), paracentral lobule, frontal middle lobe, postcentral gyrus, and lateral ventricles. Presented onto a single subject MNI template using MRIcron software package rendering tools.

Qualitative Images

Before the cross-over OOCV was performed for either sample, the initial SVM signatures were overlaid to give an indication of anatomical relationships between the two conditions (see *figure 8*). This demonstrated that the two signatures had mostly different overall voxel probability maps and suggested that the OOCV may not generate significant results. At this stage, this qualitative result is rudimentary and not statistically driven and only serves as a representation of a potential relationship. The two groups were initially applied to separate control groups which could be relevant, meaning when a direct comparison is performed, results may differ. Only small overlaps were found in the subcortical regions of the basal-ganglia and central subcortical areas.

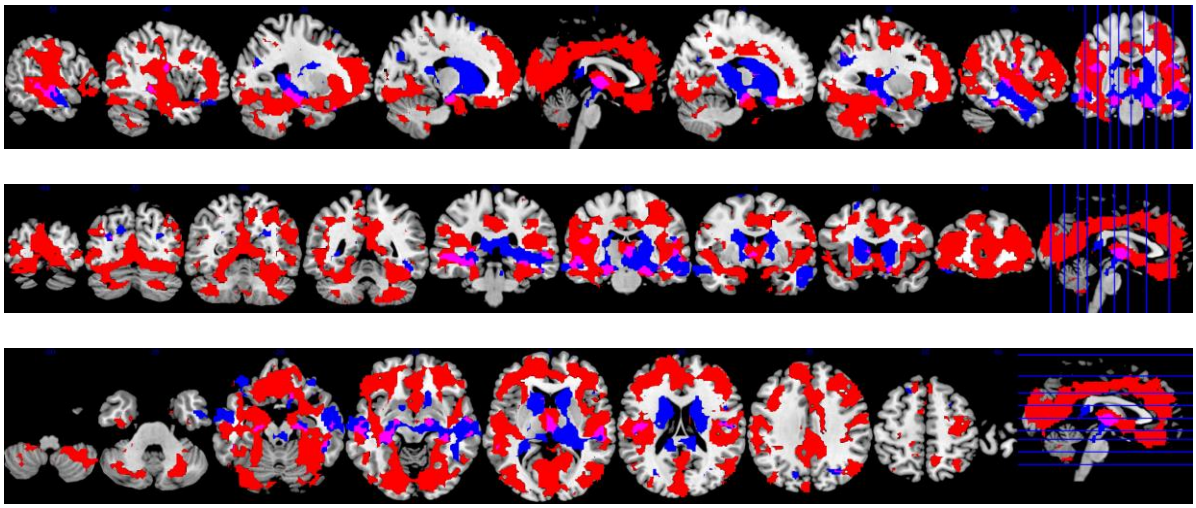

Figure 8: MUC SVM signature (*red*) showing reduced GMV for schizophrenia group compared with controls overlaid onto BEST SVM signature (*blue*) showing reduced GMV for PTB group compared to controls. Additive areas are shown for overlapping regions of signature (*purple*), indicating very low similarities for cross-over analysis.

OOCV Cross-over analyses

BEST and MUC OOCV analyses

The first stage of the OOCV cross-over analysis applied the MUC group as unseen data to the BEST signatures. The goal was to classify the schizophrenia group as patients by utilizing the PTB signatures developed in the initial SVMs. *Figure 9* demonstrates that the SVM OOCV for the MUC sample applied to the BEST did not yield significant results. It would appear that both the schizophrenia group and controls were classified as comparable to the BEST control group only. In

fact, only 13.9% of schizophrenia group images were categorised as patients using the BEST pattern signatures. BAC (50.6%) scored at chance level, *sensitivity* scored highly (87.3%) as both groups were registered as controls, and *specificity* was low (13.9%). Notably high was the false positive rate (86.1%) which indicates that there is a high likelihood of misidentifying schizophrenia patients as controls, rather than as patients while using the BEST signatures (see *table 7*).

Cross Validation Results

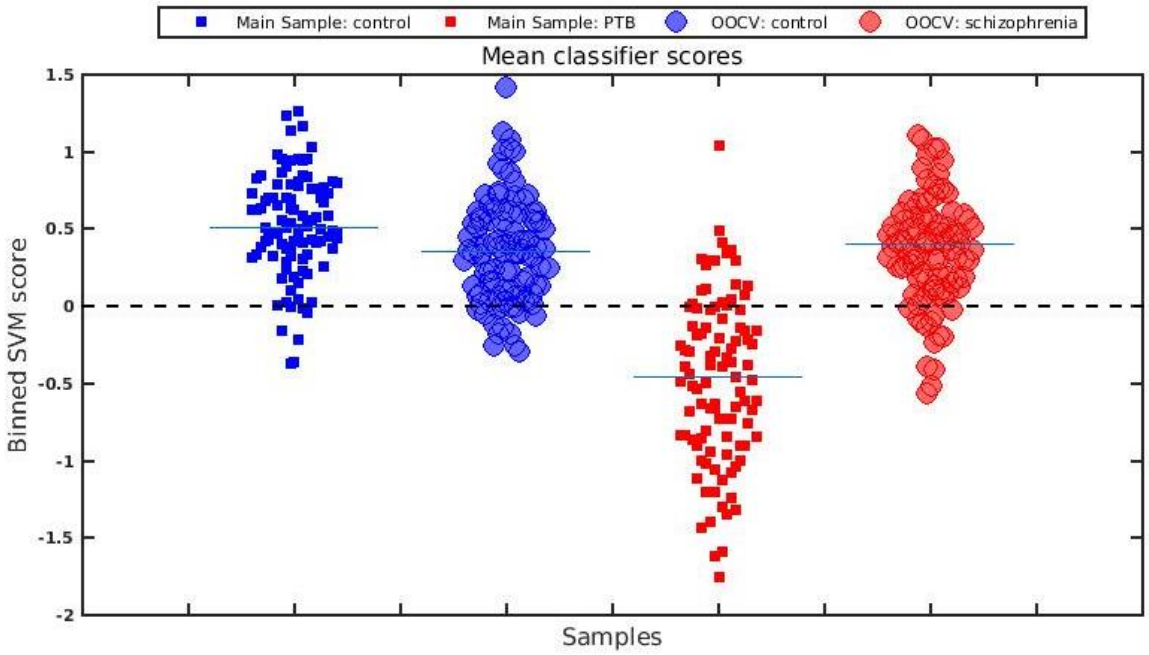

Figure 9: SVM scores for OOCV MUC group - applied PCA correction to account for scanner effects. The smaller squares shapes are the BEST sample cross-validation scores and the larger circles are the OOCV MUC group. In both cases *blue* are control groups and *red* are patients. Meaning ideally blue would match to blue and red would match to red.

The second stage of the cross-over analysis performed an OOCV SVM using the BEST group as unseen data to the MUC signatures, attempting to classify PTB individuals as patients. As illustrated in *figure 10* the OOCV of the BEST sample being applied to the MUC signatures was also unsuccessful at differentiating between patient and control groups. However, the signatures were more sporadic than in the OOCV for the MUC sample. In this case, 32.7% of PTB patients were classified with schizophrenia, although 37.3% of controls were also matched with the schizophrenia group. As before, BAC (47.7%) fell at chance level, indicating that PTB patients were not able to be classified as patients based on the MUC signature patterns. Sensitivity (62.7%) and Specificity (32.7%) were also poor, and a large false positive rate (67.3%) demonstrates a high

likelihood of misclassifying PTB patients as control while utilising the MUC signatures (see *table 7*).

Cross Validation Results

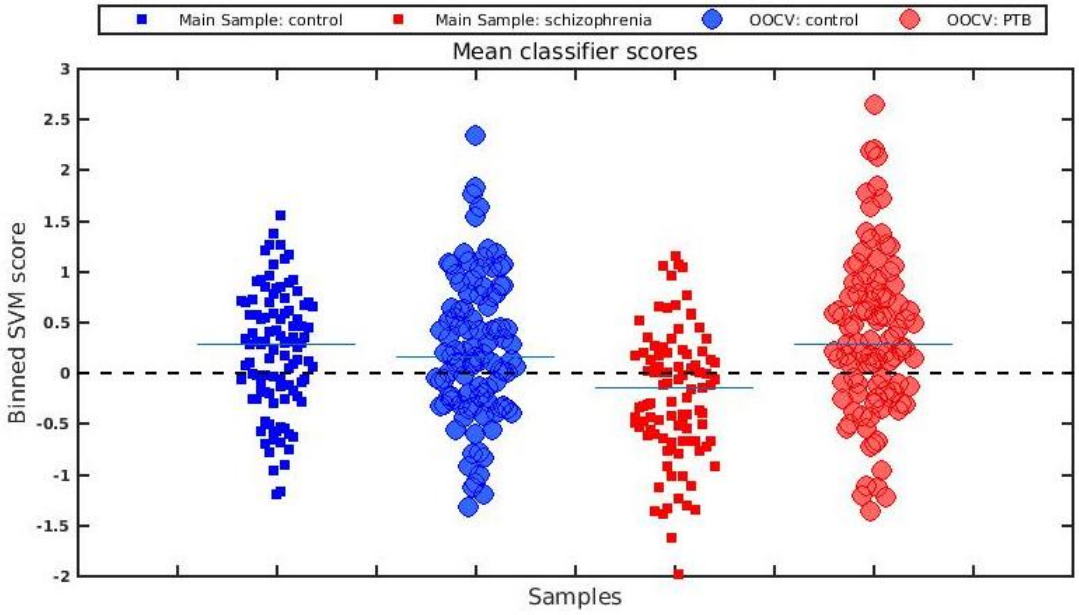

Figure 10: SVM scores for OOCV BEST group - applied PCA correction to account for scanner effects. The smaller square shapes are the MUC sample cross-validation scores and the larger circles are the OOCV BEST group. In both cases *blue* are control groups and *red* are patients

Table 7: The statistical Neurominer output performance scores of the OOCV SVM analyses. This includes MUC applied: PTB patients and controls with the OOCV MUC group having the signature applied to it. BEST applied: schizophrenia patients and controls with the OOCV BEST group having the signature applied to it.

Performance	MUC Applied	BEST Applied
TP	89	64
TN	14	33
Sensitivity	87.3%	62.7%
Specificity	13.9%	32.7%
Balanced Accuracy	50.6%	47.7%
Positive Predictive Value	50.6%	48.5%
Negative Predictive Value	51.9%	46.5%
False Positive Rate	86.1	67.3
Positive Likelihood Ratio	1.0	0.9
Negative Likelihood Ratio	0.9	1.1

Subgroup Analyses

Despite the unsuccessful initial OOCV, several follow up OOCV analyses were conducted in order to try and identify subgroups within PTB and schizophrenia that could be more suitably classified. The rationale was that perhaps more strictly defined groups, such as the previously

discussed FEP and chronic patients (see supplementary material for demographics) could be more successfully classified into a patient group with the applied signatures. For example, FEP patients are usually found to have less overall substantial GM alterations, whilst chronic patients typically present with more cortical GM reductions (Ellison-Wright et al., 2008). Furthermore, FEP patients present with higher scores in the PANSS, and sharper cognitive decline, often attributed to lack of treatment at this stage (Del Bello, Menculini, Moretti, & Tortorella, 2016). Therefore, an OOCV was conducted to see if either FEP or chronic group would be more strongly defined as PTB/control. The results of this found no discernible differences between the two groups (see *figure 11a*) which were both classified similarly to the BEST controls. Accuracy (45.7%), Sensitivity (98.3%), and Specificity (6.2%), all scored poorly, indicating that the majority of the patient group had been classified incorrectly. With a very high false positive rate (93.8%), it would appear that almost all patients would be misclassified as controls. The goal was to find a clearer separation between the two samples, with the one group being classified more over the boundary of PTB. An analysis was also performed to see whether the loose age-matching protocols may have influenced the subsequent results. Subgroups were split once again for FEP and chronic patients, but now applying a stringent age matching (25-27) protocol. Theoretically, due to the robust nature of an SVM OOCV, a very small sample can still provide statistically reliable results. However, no significant classification scores were demonstrated for the more conservative approach (this analysis is in the supplementary material).

To further examine the hyperplane signatures that the initial analysis had generated, a number of other subgroup OOCV analyses were attempted to see if some grouping of patients were perhaps more suited or more prominently classified as patient. It was critical that these subgroups were created based on informed reasoning to avoid data fishing. Furthermore, these categories were limited by the availability of demographic data. Therefore three subcategories for each analysis were chosen to examine, these included (for MUC applied to BEST): number of hospitalisations, duration of illness, and PANSS total scores, and included (for BEST applied to MUC): birthweight, DNTI score, and duration of hospitalisation.

Subgroups within MUC dataset

The following three results were based on subgroups of the schizophrenia sample without the control group. Firstly an OOCV was performed looking at number of psychiatric hospitalisations for patients with schizophrenia. Research has suggested that number and length of hospitalisation can differ depending on the severity and associated symptoms of schizophrenia

(Henigsberg & Folnegovic-Smalc, 2002) indicating that the number could be indicative of anatomical alterations. The groups were determined by splitting the sample at the mean difference, this left 34 low vs 68 high from the total of the dataset (*n* = 102) in each condition. Results demonstrated BAC (48%) at chance level, indicating that this subgroup was not differentiable to a degree that was compatible with the BEST signatures. *Sensitivity* (82.4%) was high as the majority of patients were classified as controls. *Specificity* (13.6%) showed that only a small subset were classified as patients and a high false positive rate (86.4%) was also found (*See figure 11b & table 8*).

Next, duration of illness was tested in a similar style and based on similar intuitive reasoning. Research has long suggested that schizophrenia is degenerative both cognitively and neuroanatomically, particularly in cortical GM (Vita et al., 2012). This group was split via the duration of Illness (in years) once again based on a mean difference leaving 35 low vs 69 high from the schizophrenia sample. As illustrated in *figure 11c* this OOCV was also unsuccessful for classifying a patient group using the BEST signatures. BAC (51.2%) was again at chance level, *sensitivity* (96.7%) was very high, meaning a large majority of participants were classified as controls and there was a high false positive rate (80.0%) once again showing a low level of general accuracy (see *table 8*). At this stage it is unclear why the sensitivity was so much higher for this subgroup considering the same schizophrenia group was being applied as unseen data.

The final subgroup created from the MUC sample was based on PANSS total scores. The split was determined via literature and general consensus suggesting 58 is a good cut-off for moderately ill participants (Leucht et al., 2005). Generally FEP patients present with higher PANSS scores compared to chronic patients generally thought to relate to treatment and patients acclimatising to their situation. 68 patients fell below the cut-off of 58 total PANSS score, meaning that 34 patients had scores between moderate and severe. *Figure 11d* shows that PANSS score failed to subgroup patients effectively into a group that could be classified as patient. BAC (52.1%) scores fell at chance, *sensitivity* (87.9%) and *specificity* (16.4%) were consistent with the other subgroups and ultimately cement the fact that the BEST signature was unable to successfully classify the MUC group regardless of stringent methods employed.

Table 8: The statistical Neurominer output performance scores of the OOCV MUC-subgroup SVM analyses. This table includes: FEP vs chronic, number of hospitalisations, duration of illness, and PANSS total score performance metrics as OOCV samples being tested as unseen data on the BEST signatures.

Performance	FEP vs Chronic	Hospitalisation	Duration of Illness	PANSS scores
TP	59	28	29	29
TN	5	9	4	11
Sensitivity	98.3%	82.4%	96.7%	87.9%
Specificity	6.2%	13.6%	5.7%	16.4%
Balanced Accuracy	52.3%	48.0%	51.2%	52.1%
Positive Predictive Value	44.0%	32.9%	30.5%	34.1%
Negative Predictive Value	83.3%	60.0%	80.0%	73..3%
False Positive Rate	93.8	86.4	94.3	83.6
Positive Likelihood Ratio	1.0	1.0	1.0	1.1
Negative Likelihood Ratio	0.3	1.3	0.6	0.7

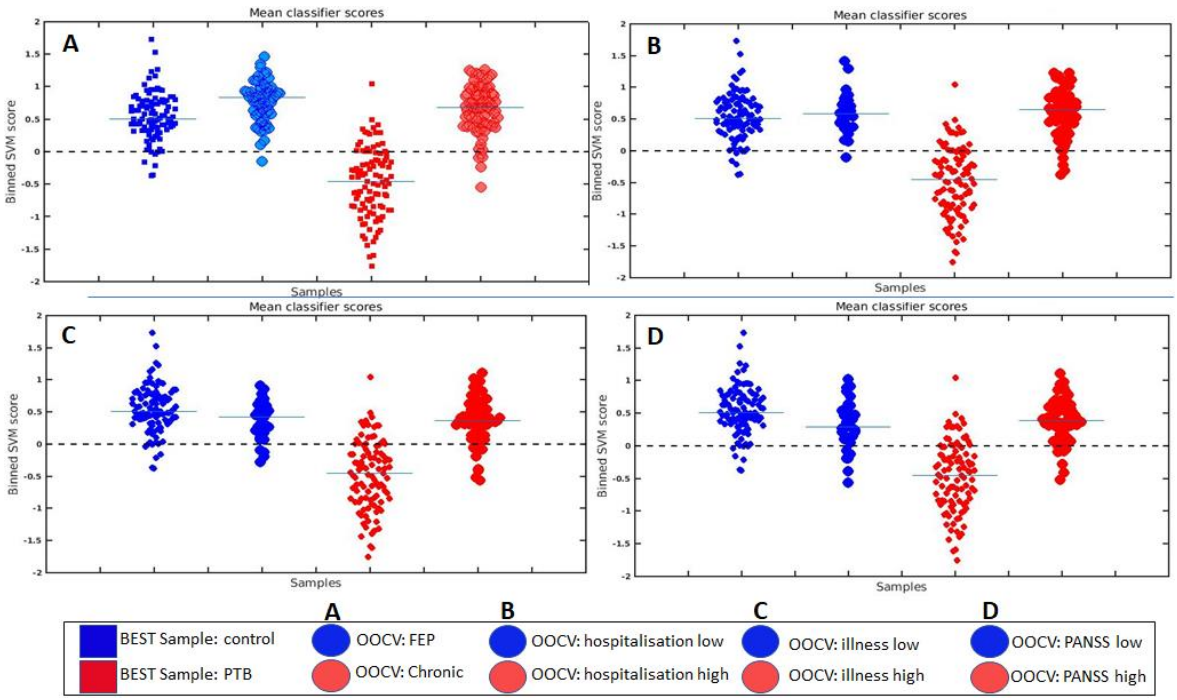

Figure 11: SVM scores for the OOCV MUC subgroups applied to BEST sample. (A) shows the mean classification scores for the FEP vs chronic subgroups with binned SVM scores. (B) shows the mean classification scores for the number of hospitalisation subgroups with binned SVM scores. (C) shows the mean classification scores for the duration of illness subgroups with binned SVM scores. (D) shows the mean classification scores for the PANSS total scores with binned SVM scores.

Subgroups within BEST dataset

The following three results were based on subgroups of the PTB sample without the control group. Firstly, birthweight (BW) was used as a subgroup to threshold participants.

Generally a weight of 1500g is considered VLBW - and a weight of 1000g is considered extremely low (Aarnoudse-Moens et al., 2009). For this experiment a mid-way cut-off was used and was determined by mean values for the pre-classified PTB group. Therefore, low BW was patients below 1300g (*n* = 45) and high BW was above 1301g (*n* = 56). It is recognised that for this experiment the opposite classification should be expected - whereby low is worse health-wise than high unlike in many of the other subgroups. Results from *figure 12*a demonstrate that BW was not a successful discriminator for classifying as patient using the MUC signatures. BAC (49.9%) was at chance level, *sensitivity* (67.3%) and *specificity* (32.6%) were less spread than for the MUC subgroups but this simply matches the initial OOCV analyses as should be expected (see *table 9*).

The next analysis focused on the duration of neonatal care (DNTI) that PTB patients had received. DNTI was used as in order to specify a level of severity between groups. As much research focuses on hypoxia, hemorrhage and other neonatal events it was predicted that DNTI would be a useful metric for emphasising early obstetric complications. Low DNTI (*n* = 47) was set via mean comparison of the BEST sample and yielded a DNTI score of 53 and below. High DNTI (*n* = 54) was set as 54 and above - with the general assumption being that higher DNTI would constitute higher severity of complications. *Figure 12b* demonstrates that this analysis was also unsuccessful for classifying the PTB group as patients using the MUC signature. BAC (47%) was around chance level, *sensitivity* (63.8%) and *specificity* (30.2%) were very similar to the results for BW and the initial OOCV indicating that this subgroup had not made a successful distinction.

The final subgroup that was examined was based on the duration of hospitalisation at birth. This analysis was chosen based on the intuitive likelihood that there is a linear relationship between severity of symptoms and the level of intervention that was required at early stages of development. In this care low duration of hospitalisation (*n* = 60) was set to less than 70 days based on the means for the PTB group. Thus, high duration (*n* = 41) of was set to 71 days and higher. *Figure 12c* shows that this final analysis was unsuccessful in finding a discriminative subgroup that could be associated as patient when the MUC signature was applied. BAC (49.2%) fell at chance level, *sensitivity* (66.7%) and *specificity* (31.7%) were also very similar to the prior analyses indicating that no easily discernible subgroup can be successfully classified based on the available groups using either anatomical signature in this cross-over analysis.

Table 9: The statistical Neurominer output performance scores of the OOCV BEST-subgroup SVM analyses. This table includes: birthweight, Duration of Neonatal care (DNTI), and duration of hospitalisation performance scores as OOCV samples being tested as unseen data on the MUC signatures.

Performance	Birthweight	Duration of Neonatal Care	Hosptial Duration
TP	37	30	40
TN	15	16	13
Sensitivity	67.3%	63.8%	66.7%
Specificity	32.6%	30.2%	31.7%
Balanced Accuracy	49.9%	47.0%	49.2%
Positive Predictive Value	54.4%	44.8%	58.8%
Negative Predictive Value	45.5%	48.5%	39.4%
False Positive Rate	67.4	69.8	68.3
Positive Likelihood Ratio	1.0	0.9	1.0
Negative Likelihood Ratio	1.0	1.2	1.1

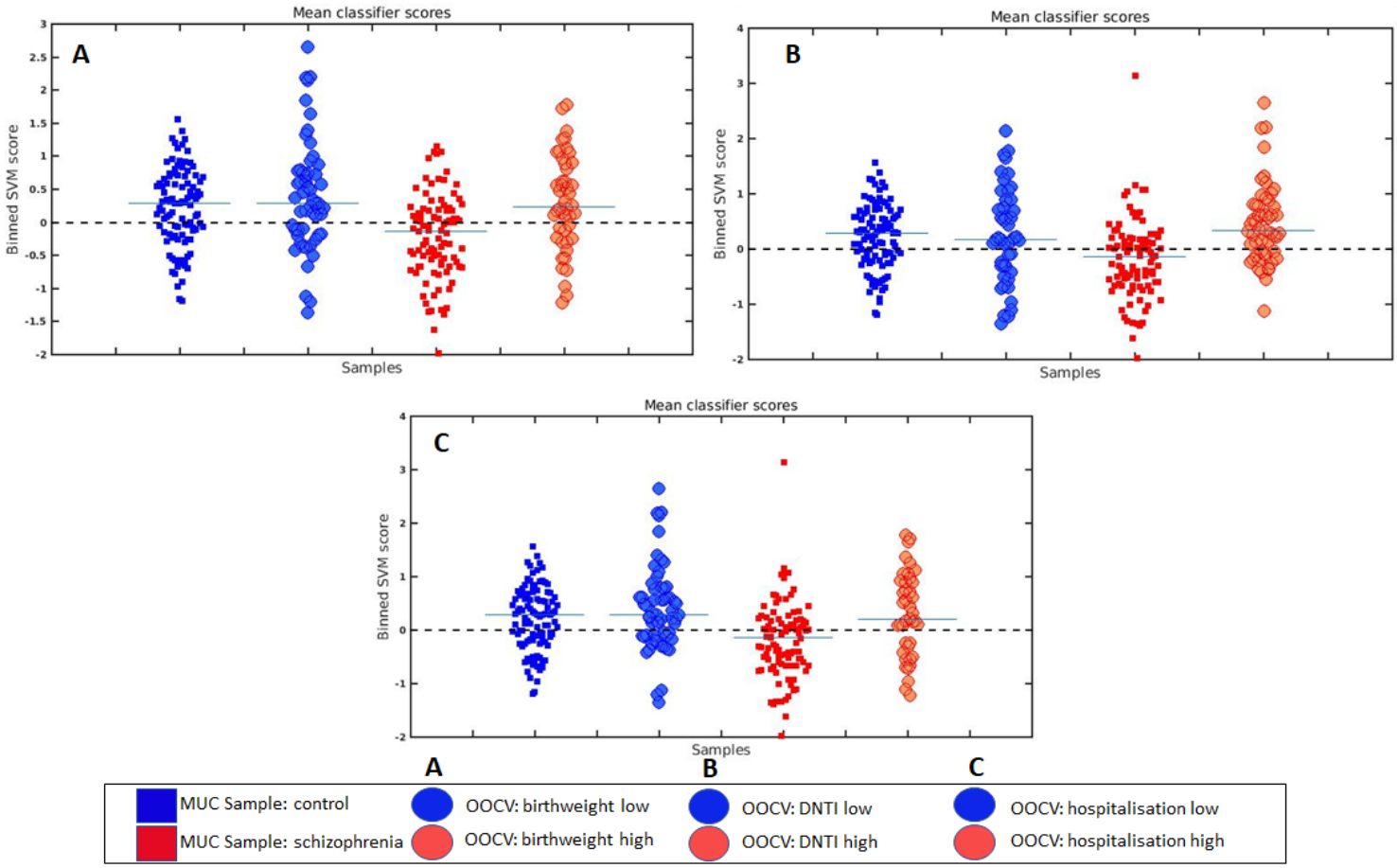

Figure 12: SVM scores for the OOC BEST-subgroups applied to the MUC sample. (A) shows the mean classification scores for BW subgroups with binned SVM scores. (B) shows the mean classification scores for the DNTI subgroups with binned SVM scores. (C) shows the mean classification scores for the duration of hospitalisation subgroups with binned SVM scores.

General Discussion

This thesis set out to examine three hypotheses based on contemporary literature in the field of neuropsychiatry and development. The first two hypotheses were grounded in a back-catalogue of established research and aimed to complement the results of numerous studies using a cross-over analysis while adhering to strict age-matching protocols in order to minimise developmental variance. The following segment will be structured first looking at the initial SVM analyses for both BEST and MUC, before discussing the cross-over OOCV and associated subgroup analyses, finally both limitations and future directions will be considered.

BEST Discussion

The results of the BEST SVM appear in-line with contemporary literature (Karolis et al., 2016; Loh et al., 2017). Accuracy for SVM classification of PTB to control was around 86% which is consistent with contemporary literature for PTB (Chu et al., 2015) and within the boundaries of SVM neurological disorder studies which ranged between 58-100% (Bisenius et al., 2017). Large subcortical networks of reduced GMV were found for the PTB group compared to control, including: basal ganglia network, thalamus, putamen, caudate, and hippocampus. GMV reduction was also noted in cortical regions, such as: medial temporal lobe, and premotor cortex. Finally, GMV enlargement was found for the PTB group compared to control in: bilateral frontal, parietal, cingulate and occipital regions, particularly along the longitudinal fissure and in areas not directly measured including the corpus callosum and lateral ventricles. Importantly, the majority of the GMV reductions reported as significant in the TFCE were in accordance with the SVM analysis. Indeed, basal ganglia regions (particularly the thalamus), the middle temporal gyrus, and premotor cortex were all well represented in both analyses. The TFCE analysis failed to uncover significant enlargements in GMV for the schizophrenia group, but the majority of subcortical results were consistent, this may be demonstrating the resilience and better spatial classification abilities of SVM. VBM analyses are not at the calibre of ML approaches in terms of handling large datasets partially due to their tendency to focus on regions of interest (ROIs) and in general have lower predictive power due to a lack of generalisability. Nonetheless, the results of the TFCE were consistent with literature and served as a valid sanity check for the reliability of claims being made.

The initial BEST hypothesis was mostly consistent with the results of this thesis, including

the enlargements across the cortex although these were more widespread than was originally considered. An interpretation was formulated based on the results of the BEST analysis in an attempt to examine the mechanisms that may be at work in the underlying developmental processes of PTB. This interpretation is grounded in evidence surrounding early neurodevelopment and suggests an intuitive link between the obstetric complication of PTB and a disruption of various important growth events that occur both prenatally and neonatally. Firstly, PTB is associated with a disruption in the completion of key developmental events that would otherwise occur late into the 3rd trimester at regions including the temporal lobe, thalamus, caudate nucleus, and putamen (Nosarti et al., 2014). These events include: subplate neurons and cell migration from subventricular zone, proliferation of premyelinating oligodendrocytes, as well as other microglia production (Volpe, 2009; as cited in Nosarti et al., 2014). This leaves the subcortical regions particularly vulnerable to direct trauma as the result of obstetric complications due in part to lowered myelination and less early structural consolidation.

The adult brain contains a large amount of oligodendrocyte progenitor cells (OPC), particularly in the hippocampus and the cortical regions (Bergles et al., 1997; Ong et al., 1999). OPC are the precursor to both astrocytes and oligodendrocytes and thus are important for insulating axons and many other critical functions. In a healthy brain, processes such as myelination and synaptic pruning are demonstrated to drive a frontal and parietal lobe GM reduction at the latest stages of brain maturation (Sowell et al., 2003). This process, first noted in postmortem studies, continues into a person's 30s and coincides with increased synaptic pruning during adolescence (Gogtay et al., 2004). The fact that the present results are suggesting a trend in the opposite direction (enlargement of frontal and parietal GM) leads to a conclusion that less pruning and myelination are occuring which is consistent with prior research on the matter (Sowell et al., 1999). The implication of this is that through early trauma, these developmental processes may become disrupted and thus, cause a delay in neural-maturation causing the frontal regions to remain enlarged, even with subcortical reductions.

Regardless of the mechanisms that lead to this position, the contribution of the premotor cortex has yet to be explained. Evidence has suggested a strong relationship between the basal ganglia and premotor cortex for 3 decades (Leisman, Braun-Benjamin, & Melillo, 2014; Marsden, 1987). The basal ganglia network has a direct association with the premotor cortex (Leisman et al., 2014) through the caudate gyrus, putamen, and thalamus. This is via the cortico-striatal dopaminergic pathway which, incidentally, is theorised to directly contribute to schizophrenia development (Haber et al., 2016, see Introduction - Chapter 3). A dysconnectivity of dopaminergic pathways between the basal ganglia and premotor cortex could explain the reduction of GM. A

direct circuitry exists connecting the motor cortices and the basal ganglia network that is integral to voluntary motor functions (Nambu, 2004). Furthermore, it has been theorised through DTI imaging that relative anisotropy is limited in the white matter of PTB infants leading to underdeveloped fibre tracts and may be indicative of poorer connectivity between basal ganglia and cortical regions including the premotor cortex, again suggesting a reduction in GM (Huppi et al., 1998).

Some regions were more strongly utilised for classification than was anticipated, such as the medial longitudinal fissure, corpus callosum, and full length of the cingulate gyrus. Post-hoc research did suggest that the corpus callosum is abnormal for lower GA into adolescence (Narberhaus et al., 2007), indeed, PTB has a drastic thickening of the corpus callosum - up to 13% compared to controls (Allin, Nosarti, & Narberhaus, 2007). Allin and colleagues had not anticipated this result and suggested several explanations for it. They argue that corpus callosum development in PTB patients may manifest differently from controls. The growth could be a plastic reaction to compensate for environmental demands (Fields, 2005; as cited in Allin et al., 2007). Another possible explanation is that an enlarged corpus callosum may be indicative of a neuroplastic response to a brain that is drastically *underconnected* and trying to compensate via the preservation of functionality and consequently, optimising existing connections. Finding literature in support of an enlarged cingulate gyrus and medial longitudinal fissure proved more difficult. It may be that the disruption of the frontal regions is shared by the anterior longitudinal fissure, and could potentially extend more ventrally into the deep GM of the cingulate gyrus. Furthermore, the mechanisms described by Allin et al (2007) are not necessarily unique to the corpus callosum and could be extended to involve more rostral areas.

To summarise, the results of the BEST SVM were consistent with the literature in identifying key GM structures that can be used to effectively classify PTB patients compared with controls. A neurodevelopmental interpretation attempted to expand on the mechanisms that may be at work, this included an evaluation of events and expanded on concepts such as the poorer growth of key subcortical regions and their developmental roles for reduction of GMV. The involvement of the premotor cortex was discussed in relation to the basal ganglia, which is prominently featured. Finally, unexpected results were discussed, such as the enlargement of the corpus callosum, with potential explanations provided relating to plastic catch-up mechanisms.

MUC Discussion

The results of the MUC SVM were also in-line with contemporary literature (Dazzen et al., 2015; Fornito et al., 2009 ; Gur et al., 2000). Accuracy for SVM classification of the schizophrenia group to control was around 68% which is consistent with neurological disorder study accuracy ranges (Bisenius et al., 2017). Discriminative signatures for the MUC SVM found reductions of GM for the schizophrenia group in frontal, temporal, limbic, and occipital regions. More specifically, the frontal lobe found reductions in the rectus, frontal medial orbital, superior frontal gyrus, inferior frontal lobe, and olfactory bulb regions. The temporal lobe found reductions in the inferior, middle, and superior temporal gyri, temporal pole, and fusiform gyrus. Further reductions were noted in the superior motor area and the postcentral gyrus. Subcortical regions of GM reduction included: The cingulate gyrus (global), the inferior caudate, para-hippocampus, thalamus, and precuneus. GM enlargements were found for the schizophrenia group in the pallidum (putamen), anterior caudate, paracentral lobule, frontal mIddle lobe, and lateral ventricles. Results of the TFCE were consistent in some areas, notably surrounding the inferior prefrontal region around brodmann's area 11 and olfactory bulb, fusiform gyrus, and prominent reductions in and surrounding the basal ganglia network. As with the BEST analysis, the TFCE results were reliable, but did not directly replicated the SVM, most notably, there were no significant enlargements for the TFCE analysis. As explained above, this was likely because of lower predictive power and the more robust nature of ML approaches. It should also be emphasised that the TFCE analyses for both groups were strongly FWE corrected, and included a low boundary voxel thresholding. Nonetheless, some key distinctive areas were consistent between TFCE and SVM analyses including: olfactory bulb, fusiform gyrus, temporal gyrus, inferior occipital gyrus, and superior frontal gyrus.

The MUC hypothesis was consistent with the results of this thesis, with one minor concession; the insular cortex was not noted in SVM or TFCE analyses as being significantly different between the schizophrenia group and controls. The majority of contemporary literature would agree that the most consistently affected brain regions for schizophrenia are: the forebrain, hindbrain, and limbic system, with much research emphasising the specific involvement of the temporal lobe, and specialised limbic regions (cingulate, amygdala, hippocampus, para-hippocampus). In particular, research has demonstrated decreased GM for frontal and temporal regions (Gur et al., 2000; Job et al., 2005) and widespread global reduction of GM has been shown of up to 3% (Vita et al., 2015). Alterations have been consistently found in the medial temporal, and prefrontal cortical areas (Dazzan et al., 2015) as well as anterior cingulate, para-hippocampal gyrus, middle frontal gyrus and the thalamus (Crow et al., 2013; Glahn et al., 2008). Likewise, an enlargement of the lateral ventricles is a consistent finding of

schizophrenia research (Bakhshi & Chance, 2015) which has been correlated to reductions in areas such as the temporal lobe, para-hippocampus and fusiform gyrus volumes (Chance et al., 2003; as cited in Bakhshi et al., 2015).

Frontal, limbic and basal ganglia regions are routinely associated with the symptoms of schizophrenia. Executive function, decision-making, and ordered thoughts are cognitive functions that are often impaired in patients with schizophrenia, this is primarily attributed to the prefrontal cortex (Yang & Raine et al., 2009). It has been theorised that the functional connectivity between limbic and frontal regions is impaired in patients suffering from schizophrenia (Vai et al.., 2015) resulting in a reduced ability to adequately process emotional stimuli and thoughts. Moreover, patients suffering with schizophrenia perform significantly worse than controls for smell tests and a deficit in olfactory volume has been demonstrated (Nguyen et al., 2011). The results of this SVM are consistent with schizophrenia research, but the mechanisms at work are still disputed.

The developmental interpretation of PTB in the *BEST discussion* may also be applicable here. Within schizophrenia research, the main causes of global GM reductions, basal ganglia network disruptions, and subsequent dopamine dysconnectivity are yet to be truly understood. Early damage to pre-myelinating oligodendrocyte precursors as well as to other important developmental resources may disrupt the later development of key subcortical domains and in-turn weaken neurotransmitter synthesis (Loh et al., 2017) and structural development. The disruption of basal ganglia development would likely relate to a dopamine regulation dysfunction and subsequently, could be indicative of the later progression into schizophrenia. Following the disease progression example outlined in Chapter 2, it can be extrapolated that these earlier disruptions can lead to a decline in cognitive and social functioning, which as discussed, are often risk factors for transition into psychosis. As highlighted, GMV reductions are prolific in studies of PTB neuroanatomy (Cannon et al., 2002) which leaves the neuronal circuitry particularly vulnerable to insult. A lower social trajectory may involve many negative behaviours (drug usage, isolation, aggression, etc.) which is perhaps a critical point for divergence of developmental processes.

Some prominently featured areas were not anticipated, such as the enlargement of supplementary motor areas and caudate gyrus for schizophrenia patients compared to controls. Post-hoc research of evidence linking the supplementary motor cortex to schizophrenia has existed for over 15 years (Schroder, Wenz, Schad, Baudendistel, & Knopp, 1995), moreover, the clear involvement of the basal ganglia in these results should serve as evidence that there would be likely effects on the motor cortices as explained in the BEST discussion. Evidence has also

suggested that FEP patients often present with enlargements of the caudate gyrus, with the suggestion that it is indicative of the plasticity of the dopaminergic systems (Chakos et al., 1994; Emsley et al., 2015).

To summarise, much like the results of the BEST SVM, the MUC SVM was able to develop anatomical signatures of structural GM disruptions that were consistent with literature for patients with schizophrenia compared with controls. Furthermore, clinical features associated with these anatomical disruptions were discussed, in particular the basal ganglia and frontal cortex in relation to cognitive decline and behavioural issues. The PTB interpretation was also reviewed here to demonstrate the potential involvement of early obstetric complications to schizophrenia GM disruptions.

OOCV Cross-over Discussion

The results of the OOCV SVM were not in-line with contemporary literature that indicated a theoretical relationship between neuroanatomical structures of schizophrenia and PTB (Nosarti et al., 2014). The third and perhaps most crucial hypothesis was, therefore, not consistent with the results of this thesis. Based on the results of the OOCV it would appear that despite having similar disruptive anatomical patterns in theory - PTB and schizophrenia were not effective at classifying each others condition. Accuracy values fell at chance level for both MUC applied (50.6%) and BEST applied (47.7%) cross-over OOCV analyses, indicating that patients were classified as controls just as reliably as patients.

The reasons for this result extend beyond simple conjecture and may become more salient with further investigation. However, one of the simplest explanations is that the schizophrenia classification patterns, whilst distinct, were far less differentiable (between patient and control) than the PTB group. The BAC results for the initial PTB and schizophrenia analyses (86.2% & 67.8% respectively) are a clear illustration of this. The fact that in the initial BEST SVM it was far more successful in classifying patients from controls implies that the condition is more anatomically severe than schizophrenia (at least in early adulthood), a claim that is further highlighted when looking at VBM and TFCE results (particularly TFCE values). The cortical structures were one of the largest hurdles the classification algorithm could not overcome. As illustrated in the qualitative analysis, the frontal regions GM for PTB were clearly shown to be enlarged in this thesis and much effort has been placed on justifying this observation. However, almost the exact opposite result was found in the schizophrenia sample, with the frontal regions

GM being almost entirely reduced. This would perhaps indicate some negative correlation that could still be useful for classification purposes. But, the subcortical regions were shown almost exclusively to be reduced across both samples.

This result was unexpected, and motivated the subgroup analyses that were performed as a result. These analyses were primarily investigative and aimed to test a subset of theories (see Results - subgroup analysis) that may have explained the lack of successful classification. The results of the subgroup analyses showed a failure to differentiate between PTB and schizophrenia groups even when applying more strict demographically suited filters. The accuracy of the FEP and chronic OOCV (45.7%) scored at chance level, the MUC subgroups applied to the BEST sample found low accuracy levels for hospitalisation (37%), duration of illness (33%), and PANSS total scores (40%). The accuracy for the BEST subgroups applied to the MUC sample also found low accuracy scores for birthweight (40%), DNTI (46%), and hospitalisation (52.5%). The lack of success in OOCV would appear to indicate that the two groups were not distinct enough to differentiate using the generated signatures of the other group. Alternatively, it could indicate that PTB and schizophrenia do not share distinctive neuroanatomical patterns and are incomparable at least within the specific age range that was utilised.

Extrapolating from the NDHS (Fatemi & Folsom, 2009), perhaps the initial course of events for both groups follows a structurally related pattern initially, but that a second environmental or behavioural event leads to the development of schizophrenia at which point a divergence occurs anatomically between the two due conditions due the subsequent effects of psychosis. Therefore, it may be instructive to examine a group who have not yet transitioned to schizophrenia, such as UHR groups, to get a clearer indication of whether a divergent mechanism is at work. Indeed, research has suggested that there are GM disruptions even in patients classified as UHR (Tognin et al., 2014) and it is well documented that transition to psychosis is accompanied with progressive GM reductions and alterations (Takahashi et al., 2009). Consequently, transitioned patients may exhibit a large array of differences from those who had the initial vulnerability but never transitioned.

Limitations

The scanner differences between BEST and MUC were a difficult issue to solve, which was further complicated by the use of multiple scanners in the BEST sample across two different locations. Generally speaking scanners follow their own unique protocols and are difficult to match. In particular, the BEST sample scans were conducted on a 3T scanner and the MUC sample

were conducted on a 1.5T scanning system. Therefore, some anatomical specificity may be lost in the MUC sample due to the reduced operational resolution. Even after controlling for this using the PCA approach (see *Methods*) it is possible that some valuable information may have been removed. Nonetheless, based on the fact that the two control groups (BEST and MUC) were closely matched after this approach, it was deemed successful.

Another issue was age matching. As discussed in *Methods* there was a forced trade-off between age-variance and sample size that was difficult to account for. However, during OOCV it was possible to apply smaller group sizes to test more strict age-matched samples. Results of which can be seen in the Supplementary material. These tests garnered no additional significant results and served to confirm that tighter age matching would not have drastically altered results in the initial SVMs.

One further limitation is logistical and stemmed from the fact that these datasets were not originally collected to be compared. Therefore, no clinical variables exist to see any direct correlation between PTB and schizophrenia. There are loosely comparable clinical values that can be compared such as number of hospitalisations and duration of illness which were utilised in this manner, but no psychosis metric for BEST or obstetrical complications metric for MUC. As discussed above, subgroups were formulated to attempt to account for this, but it must be acknowledged that this limitation does serve to confound any potential implications of this thesis.

Finally it should be mentioned that the primary images used for this analysis were GM and results that indicate an inclusion any non GM areas, such as the lateral ventricles do so on the basis of the SVM grand mean results. The empty space in lieu of CSF or WM was undoubtedly considered important in classification of vectors and for the generation of a sufficient hyperplane in the SVM. This does, however, mean that ventricle results should be taken with care as empty space is not a direct replacement for the anatomical specificity of the actual ventricles.

Future Directions

One of the best ways to determine whether hypothesis three should be rejected is to perform a similar analysis but instead of using FEP and chronic schizophrenia patients, use UHR (Fusar-Poli et al., 2013) patients. The major benefit of using these participants is that they have not yet transitioned and have not been subject to the progressive effects of psychosis (Takahashi et al., 2009). Following the NDHS, the implication is that eventual transition to schizophrenia includes obstetrical complications and some grouping of additional trauma or environmental

events (Murray et al., 2017). UHR participants are usually categorised based on a comprehensive list of trait and state functioning criteria (Clark et al., 2016) and research has demonstrated that UHR patients have typically received some level of childhood trauma (Kraan et al., 2015). Furthermore, as mentioned earlier, GM volumes are disrupted for UHR patients but not as severely as fully transitioned patients (Tognin et al., 2014). Perhaps these documented GMV disruptions are more compatible with the PTB group based on the idea that transition may involve a divergence in compensatory mechanisms due to the strong progressive effects of schizophrenia and the associated treatments. Indeed, evidence suggests that around one third of UHR participants transition within a three year period (Yung, Phillips, & McGorry, 2004) so clinically, if PTB signatures could be implemented at this stage, it may serve as an additional predictive biomarker for identifying likelihood of transition.

As mentioned earlier, the cortical regions were found to be strongly contrasted in SVM results for BEST and MUC. However, the subcortical regions did follow a more homogeneous pattern. Therefore, a region-of-interest (ROI) style analysis of more subcortical regions, particularly the basal ganglia may be worth exploring. Masking out cortical regions and seeing the extent to which PTB and schizophrenia signatures match up in deep GM may give valuable information about the development and etiology of the disorders. Theoretically, if subcortical regions did match, this could be indicative of the neurological divergence at the point of compensatory mechanism. Earlier it was posited that the enlargement in GMV of PTB patients may be related to a plastic catch-up mechanism designed to strengthen the connections that are still available (Allin et al., 2007). Perhaps a divergence occurs at the point in which this mechanism is usually initiated, this may even coincide with the concept of the 2-hit model (Keshaven et al., 1999) and occur some time in adolescence or as the result of early childhood trauma. This could be indicative of differences at a hereditary or genetic level. Fundamentally, this avenue would be interesting in-of-itself as a further exploratory experiment and to ascertain whether there is any merit to the claims of this thesis.

Finally, functional data and and *in vivo* examination of the dysfunction of dopamine and how this may be related across the two conditions should be explored. It has been remarked that the underdevelopment of the basal ganglia and subsequent disruptions to motor areas may be indicative of incorrectly functioning dopamine systems. It is well documented that PTB infants that are treated with low dose dopamine have better functional outcome due to the benefits for CSF development and regulation of blood pressure (Vesoulis et al., 2016). As discussed in Chapter 3 - *Dopamine*, there is an established link between dopamine dysfunction and susceptibility to stress (Murray et at., 2017) which is particularly crucial when considering that stress is a risk

factor for schizophrenia (Gomes & Grace, 2017). Moreover, schizophrenia has been directly associated with dopamine dysfunction (Brisch et al., 2014) making a potential developmental catalyst likely. If a similar pattern of dopamine dysfunction can be established between the two conditions it could strengthen motivations for a comorbidity between PTB and schizophrenia.

Conclusion

In summary, this thesis explored PTB and schizophrenia and aimed to evaluate the relationship in a quantitative way incorporating SVM and nested CV techniques. A cross-over analysis was performed by applying the signatures of the PTB sample onto an OOCV of the schizophrenia group and vise-versa. The results demonstrated that PTB and schizophrenia are not suitable classifiers of each other. This result was unexpected as the majority of contemporary research and theories indicated that PTB and schizophrenia were likely to share comorbidity. The initial rationale for this paper was to emphasise this relationship in order to highlight PTB as a potential biomarker and risk factor for schizophrenia and thus validating an inclusion in schizophrenia etiological models. However, the results run contrary to the literature and suggest that other, more subtle mechanisms may be at work - such as a diversion of compensatory hyper-pruning. A developmental interpretation was formulated based on the results that detailed the biological events that may accompany GMV disruptions, this included the interrupted creation of OPC and potentially dysfunctional dopaminergic synthesis and distribution. It is therefore essential to do further exploratory experiments, involving participants less influenced by progression of schizophrenia (e.g. UHR), and perhaps examine more specific ROIs that could yield informative results.

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Appendix 1

Age Matching

Adding the age matching script (nk_MatchOne2One) path and executing it on the data

```
% Applying age  *cut-off* " filter (Optional, simply comment out to exclude)


age = (hc_covartab.AGE);

hc_covartab = hc_covartab((age > 19 & age < 36), :);

age = (pat_covartab.Age);

pat_covartab = pat_covartab((age > 19 & age < 36), :);


% preparation variables for age_matching
prepHC = [hc_covartab.AGE,hc_covartab.SEX];
prepPAT = [pat_covartab.Age,pat_covartab.Sex];
prepSUB = [hc_covartab.ID];


% Age matching and generating table of matched health controls with subject
% labels, age, and sex
[~, subjectsHC,agesexHC] = nk_MatchOne2One(prepHC,prepPAT,prepSUB);
subjectsHC = cellstr(subjectsHC);
age_matched_HC = table(subjectsHC,agesexHC(:,1),agesexHC(:,2));
age_matched_HC.Properties.VariableNames{2} = 'Age';
age_matched_HC.Properties.VariableNames{3} = 'Sex';

% Reapplying the age match to entire demographic sample

[FINAL_HC,~] = nk_MatchID(hc_covartab.ID,hc_covartab,age_matched_HC.subjectsHC,age_matched_HC);

% creation of file tables ready for analysis and saving them to a mat file

FINAL_PAT = pat_covartab;

cd(scriptDir)
save age_matched_MUCsample FINAL_HC FINAL_PAT
```

Appendix 2

Creating the demographic tables

Folder with demographics/covariates

```
cd /volume/BEST_classify/Data/Scripted_Data;
addpath /volume/BEST_classify/Data/Scripted_Data;
addpath /volume/BEST_classify/Data/Scripted_Data/Raw_Demographics;
addpath /opt/NM/NeuroMiner_Release/;


dirname = ['processed-',datestr(now, 'dd-mmm-yyyy_HH')];
scriptDir = strcat('/volume/BEST_classify/Data/Scripted_Data/',dirname);
mkdir(scriptDir);

% the following participants had no Nifti files present after preprocessing
% due to errors or were ruled out during CAT12 Homogeneity testing so will be excluded from the analysis
exclusion_data = {'basis1_328','basis1_414','basis1_421','basis1_424','basis1_426',
    'basis1_456','basis1_429','basis1_460','basis1_467','basis1_500','basis1_476',
    'basis1_166','basis1_498','basis1_504','basis1_442','dfg_4','basis1_443','basis1_499'}';

[~,~,hc_covar] = xlsread('CONTROL_DATABASE.xlsx');
[~,~,pat_covar] = xlsread('PATIENT_DATABASE.xlsx');

% turn these into compatible tables
hdata = hc_covar(2:end,:);
hheader = hc_covar(1,:);
hc_covartab = cell2table(hdata);
hc_covartab.Properties.VariableNames = hheader;

pdata = pat_covar(2:end,:);
pheader = pat_covar(1,:);
pat_covartab = cell2table(pdata);
pat_covartab.Properties.VariableNames = pheader;

clear hdata hheader pdata pheader pat_covar hc_covar;

% removing the excluded data

[hc_covartab,~] = nk_MatchID(hc_covartab.ID,hc_covartab,exclusion_data,exclusion_data,'src_not_dst');
[pat_covartab,~] = nk_MatchID(pat_covartab.ID,pat_covartab,exclusion_data,exclusion_data,'src_not_dst');
```

Supplementary Material

Two methods were considered for fixing scanner effects before the PCA approach was decided upon. The first method, known as *mean subtraction* required age matched control groups which should theoretically be structurally similar. Meaning that any mean differences between them are the result of scanner differences. Therefore, mean differences were calculated for each voxel and subtracted from the total scans. Images were then recompiled with the mean subtracts applied.

Method 1: simple site control through mean subtraction using controls

```
load /volume/BEST_classify/AnalysisOOCV/Images_Without_TIV/BEST/nm_no_TIV.mat
s1_ctrls = NM.Y{1}(NM.label==1,:);% reference the controls in an NM structurs (if == does not work use strmatch)
s1 = NM.Y{1};
s1_cases = NM.cases;
badcoordsBEST = NM.badcoords{1};

clear NM
load /volume/BEST_classify/AnalysisOOCV/Images_Without_TIV/MUC/nm_no_TIV.mat
s2_ctrls = NM.Y{1}(NM.label==1,:); % reference controls from s2 in NM structure
s2 = NM.Y{1}; % get all subjects from sample 2
s2_cases = NM.cases;

% Calc mean difference for each voxel
mY_s1 = mean(s1_ctrls);
mY_s2 = mean(s2_ctrls);
m_diff_image = mY_s1 - mY_s2;



% Subtract the mean difference from all the NM scans
aY_s2 = bsxfun(@minus,s2,m_diff_image); % where "a" is adjusted
aY_s1 = bsxfun(@minus,s1,m_diff_image);


% Save the mean difference map and view it

brainmask = '/volume/BEST_classify/TEMPLATES/p0ICBM-Template_bmask-improved_vox3-3-3.img'; % The mask used
badcoords = NM.badcoords{1};
filename = sprintf('MUC_DIFF_MAP_UPDATED_%s',datestr(now, 'dd-mmm-yyyy-HH-MM-SS'));
nk_WriteVol(m_diff_image', filename, 2, brainmask, badcoords',0,'gt');

cd /volume/BEST_classify/AnalysisOOCV/Images_Without_TIV

for i=1:size(aY_s1,1)

    direc = 'Diffmap_Method1/BEST';
    fname = sprintf('%s/%s',direc,s1_cases{i});
    nk_WriteVol(aY_s1(i,:)',fname,2,brainmask,badcoordsBEST',0,'gt');

end

for i=1:size(aY_s2,1)

    direc = 'Diffmap_Method1/MUC';
    fname = sprintf('%s/%s',direc,s2_cases{i});
    nk_WriteVol(aY_s2(i,:)',fname,2,brainmask,badcoords',0,'gt');

end
```

The second method involved regressiong out the scanner effects using a linear regression. This included taking the control group voxel matrices for both sample (BEST and MUC). Performing partial correlations analysis on these samples using a Neurominer script to generate beta values. Then performing a further partial correlations analysis on the full sample using the created beta values.

Method 2: control of site by regressing it out

```
% The idea of this is that you can regress out the site effects using
% regression

Y_ctrls = [s1_ctrls;s2_ctrls]; % Enter matrix of control images from both samples


A = [ones(102,1)];
B = [zeros(102,1)];
ctrl_site_vec = vertcat(A,B); % Vectors of control images
clear A B


% Get the betas from the controls in INPUT PASS 1 (INp1)
INp1.TrCovars = ctrl_site_vec; % works when there is beta included
INp1.nointercept = 1;
INp1.beta = [];
INp1.revertflag = [];

[cY_ctrls, INp1] = nk_PartialCorrelationsObj(Y_ctrls,INp1);

% Apply to the full samples

Y_all = [s1;s2]; % enter all subjects

A = [ones(203,1)];
B = [zeros(203,1)];
all_site_vec = vertcat(A,B); % enter site vector for all subjects
clear A B

INp2.TsCovars = all_site_vec; % works when there is beta included
INp2.nointercept = 1;
INp2.beta = INp1.beta;
INp2.revertflag = [];

[cY_all, INp2] = nk_PartialCorrelationsObj(Y_all,INp2); % This is the corrected data

cY_all_s1 = cY_all(1:203,:);
cY_all_s2 = cY_all(204:406,:);

cd /volume/BEST_classify/AnalysisOOCV/Images_Without_TIV/
for i=1:size(cY_all_s1,1)

    direc = '/Diffmap_Method2/BEST';
    fname = sprintf('%s/%s',direc,s1_cases{i});
    nk_WriteVol(cY_all_s1((i),:)', fname, 2, brainmask, badcoordsBEST',0,'gt');

end

for i=1:size(cY_all_s2,1)

    direc = '/Diffmap_Method2/MUC';
    fname = sprintf('%s/%s',direc,s2_cases{i});
    nk_WriteVol(cY_all_s2((i),:)', fname, 2, brainmask, badcoords',0,'gt');

end

clear fname
```

Table 10: Demographic and covariate information for MUC FEP and Chronic subgroup sample:

	First Episode	Chronic	Comparison Values
N	42	54	
Age	26.57(4.5)	27(4.6)	t = -.479, p = .663
Age at 1st psychotic symptom	26.13(4.6)	22.41(4.7)**	t = 4.009, p < 0.001
Duration of Illness (*years*)	0.42(0.8)	4.6(3.8)**	t = -7.231, < 0.001
Number of hospitalisations	1.17(0.7)	2.2(1.8)**	t = -3.598, p = 0.001
PANSS - positive symptom score	13.7(8.5)	10.51(8.1)	t = 1.858, p = .066
PANSS - negative symptom score	12.95(10.2)	15.93(9.2)	t = -1.496, p = .138
PANSS - total symptom score	50.91(35.3)	53.84(28.3)	t = -.451, p = .653
BMI	23.24(4.8)	24.5(4.8)	t = -1.469, p = .145
School	11.28(1.8)	10.4(2.0)	t = 2.336, p = .022

As can be seen in the table 10; SCZ subgroups did not differ in age (t = -.479, p = .663) but were significantly different for age of 1st psychotic symptom (t = 4.009, p > 0.001), duration of illness in years (t = -7.231, p = > 0.001), and number of hospitalisations (t = -3.598, p = 0.001). Importantly, the two groups did not differ for PANSS scores, suggesting their schizophrenic symptoms (at the time of testing) were comparable.

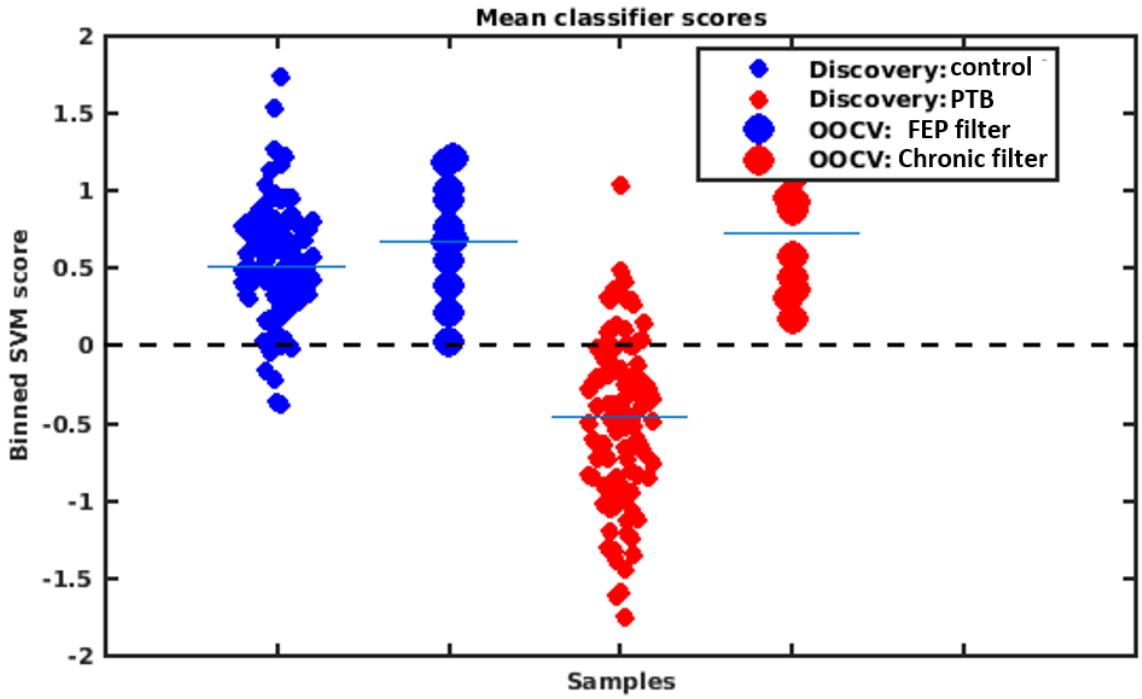

Figure 13: Stringent age match protocols applied to MUC sample which was then applied as OOCV to the BEST SVM. Main sample SVM for the BEST controls (*blue diamonds)*, BEST PTB group (*red diamonds*). OOCV group FEP (*n* = 10, *blue circles*) and chronic (*n* = 12, *red circles*).

Classification performance metrics did not differ from the other groups indicating that more strict age matching (between 25-27 to match the BEST groups range of 26-26) would not have improved OOCV results.

Table 11 (right): *demonstrating the performance scores of the stringent age matched group SVM classification as OOCV onto BEST data*

Performance	Score
TP	85
TN	13
Accuracy	51.6%
Sensitivity	86.3%
Specificity	14.9%
Balanced Accuracy	50.6%
Positive Predictive Value	49.6%
Negative Predictive Value	52.9%
False Positive Rate	85.3
Positive Likelihood Ratio	1.1
Negative Likelihood Ratio	0.8

Declaration of autonomy

I hereby confirm that I did the present work by myself and that I have used no other sources/ references than those mentioned in the reference list. I did not submit this thesis to another university examination office and the present study is/ studies are not yet published.

_____

Date, Signature