DEVELOPMENT OF AN INSTRUMENT FOR AUTOMATIC SCHIZOPHRENIA DIAGNOSIS

BY

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DEDICATION

To my family(mother and sisters) for their patience, to my supervisor for his unflinching support and patience, and to God for the gift of knowledge, wisdom and choice.

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LIST OF ABBREVIATIONS

ASSR Auditory Steady State Response

CHR Clinical High Risk

CT Computerized Tomography

DSM Diagnostic and Statistical Manual of Mental Disorders

EEG Electroencephalogram

ERP Event Related Potential

FEP First Episode Psychosis

fMRI Functional Magnetic Resonance Imaging

fNIRS Functional Near Infrared Spectroscopy

GABA Gamma-Aminobutyric Acid

HC Healthy Control

ICD International Statistical Classification of Diseases and Related Health Problems

MMN Mismatch Negativity

MRI Magnetic Resonance Imaging

N100 100ms Negative Potential

P300 300ms Peak Potential

POC Point of Care

SNHL Sensorineural Hearing Loss

SSVEP Steady State Visually Evoked Potential

SZ Schizophrenia

ABSTRACT

Schizophrenia (SZ), a mental illness marked by hallucinations, disorganized speech, thoughts, and behavior, causing a distorted perspective of reality. There is no objective scientific tool for schizophrenia diagnosis. Psychosis-related schizophrenia is diagnosed using psychiatric nosology, which is based on the subjective assessment of qualified clinicians. The ability to detect and treat schizophrenia early (in the pre-psychotic stage, before conversion) has demonstrated that the onset of psychosis can be avoided. The lack of a non-psychosis dependent tool makes early treatment almost impossible. After first episode psychosis,treatment is more challenging, expensive, and occasionally lifelong, this makes the early, accurate, and definitive detection of schizophrenia a crucial issue that needs to be resolved. Through the use of features indicative of schizophrenic state that will be derived from the power spectral density, fuzzy-entropy, and mismatch-negativity (MMN) of scalp-acquired electroencephalography (EEG) signals, this project seeks to develop an instrument that accurately diagnoses schizophrenia in pre-psychotic and psychotic schizophrenia populations. These features will be passed to a features learner for learning and identification of schizophrenia characteristics. A point-of-care device

will hopefully be created in the future after the performance of this classifier has been evaluated with clinical populations.

CHAPTER ONE

INTRODUCTION

1.1 Background

Schizophrenia (SZ) is a brain disorder characterised by recurrent or continuous psychotic episodes (an altered view of reality) marked by auditory, visual, and delusional hallucinations, in addition to many other characteristics that are typical of SZ populations. Some other symptoms include consistent disorganised thinking, social withdrawal, decreased emotional expression and apathy. SZ is seen as an hetrogeneous syndrome and often referredto as a multitude of disease statesBakhshi and Chance (2015).

Statistics from 2011 indicate that there are 21 million people with SZ worldwide (about one of every 285). Data from the previous 50 years also demonstrates SZ's comparatively steady occurrence throughout time. SZ is diagnosed in men 1.4 times more frequently than in women, and it typically manifests in men earlier. Males typically experience psychosis at ages 20 to 28 and females typically experience it at ages 26 to 32. Before the age of 13 and between the ages of 40 and 60, early and late onsets of psychosis are possible. The average age of patients being treated for SZ in hospitals is from 25 to 35 years old. The Middle East and

East Asia have the highest populations of SZ worldwide, with the western and certain northern regions of Africa having the highest prevalence.

In its early phases, SZ is dormant and only gets worse with time. First Episode Psychosis (FEP) is the pivotal point in the epidemiology of a SZ case; in the prodromal phase (pre-psychosis), it is initially asymptomatic (without noticeable symptoms), and it is only diagnosed after the FEP, which often occurs in adolescence or young adulthood. Positive, negative, or cognitive symptoms are all categories used to describe SZ. The cognitive symptoms are seen following FEP during mental tasks like arithmetic problems or difficult essay readings. The cognitive symptoms are less evident compared to the positive and negative symptoms in typical day-to-day activities. It can be challenging to make a diagnosis of SZ before FEP because these symptoms are frequently transitory and dormant before FEP.

Positive signs of psychosis include delusions, hallucinations, disorganised speech and thinking, and other types of altered responses and behaviour. Only after psychosis are the positive symptoms visible. 80% of people with SZ experience hallucinations, which are largely related to auditory processes. The auditory hallucinations are a sign of a impaired auditory cortex (brain area responsible for auditory processes) functioning. The severity of hallucinations varies amongst individuals based on the number of sensory organs implicated and the degree of brain pathways linked to those sensory organs that are impaired. Passivity phenomenon, in which the patient feels that an outside force is influencing or controlling his or her thoughts and activities, is another helpful sign of SZ. Positive symptoms improve with treatment and lessen as the illness progresses.

Negative symptoms are impairments in regular emotional reactions or in other mental processes connected to feelings. Flat expressions or little emotion (blunt affect), poor speech (alogia), an inability to feel pleasure (asociality), a lack of desire to develop relationships (avolition), a lack of motivation, and apathy are some of the negative symptoms that have been discovered. Negative symptoms are rarely observed because they are indiscriminate and unique to each individual. Since they are tethered to human emotion, it is challenging to draw judgments about them only from their traits. Avolition and anhedonia are signs of a brain circuitry problem with reward processing which is associated with the prefrontal cortex of the brain. As a component of the brain's reward circuitry, the dorsal prefrontal cortex, brain signals from this region can shed light on how the reward circuitry differs in SZ populations and non SZ groups. Most SZ cases of negative symptoms are associated with apathy and are related to disrupted cognitive processing affecting memory and planning including goal directed-behaviour. Secondary negative symptoms are those that develop as a result of primary positive symptoms, antipsychotic drug side effects, substance use disorder, and social isolation, while primary negative symptoms are those that are innate to SZ. Compared to the original negative symptoms, the secondary negative symptoms are significantly more responsive to treatment. Negative symptoms are sometimes mistaken for hormonal fluctuations or stages of social disobedience, especially in adolescence, and are thus readily disregarded in day-to-day activities.

70% of people with SZ experience cognitive symptoms, which are more pronounced and recurrent in both early and late stages of the illness. The existence and severity of cognitive dysfunction are seen as greater indicators of functionality

than the presentation of core symptoms, despite the fact that they are not considered to be core symptoms of SZ. Cognitive deficiencies worsen during the initial psychotic episode, then recover to normal and stay largely stable throughout the disease. Social or non-social cognitive deficiencies are also possible. In populations with SZ, the following cognitive abilities are frequently accessed: verbal fluency, knowledge retention capacity, reasoning, problem-solving, processing speed, auditory perception, and visual perception. The most noticeable impairments are in verbal memory and attention, which all indicate damaged neural networks in the brain and altered brain function (reaction) to inputs. Cognitive impairment is also linked to episodic memory and visual backward masking. Antipsychotic medications have no effect on cognitive deficits; therapy is the preferred method of treatment.

Due to its difficult diagnosis, complex character, and concomitant post-psychotic behaviour symptomatic nature, which is mostly a combination of the behavioural symptoms of a significant class of mental diseases, SZ has been referred to as the heartland of psychiatry Goodwin and Geddes (2007). SZ has no precise boundary spreading its psychotic manifestations across that of other mental disorders and its exact causation is unknown, for this reason, SZ is seen as an interplay of different factors causing multiple mental disorders occurring simultaneously and this also makes it difficult to identify SZ cases even after FEP. It is also hypothesised that it results from a complex interaction between genetic and environmental risk factors that affect early brain development and the course of biological adaptation to experiences in life. Of all hypothesised causative factors of SZ, the genetic and environmental factors have been more prevalent in cases of SZ

and genetics hypothetically accounts for an estimated value of between 70% and 80% of SZ cases. However, Demis R. Combs (2011) show that most people with SZ have no family history of psychosis. Also results of candidate gene studies have generally failed to find consistent associations. The question of how SZ could be primarily genetically influenced, given that SZ populations have lower fertility rates remains a paradox. However, consistently, the gene-loci explained by genome-wide association studies explains only a small fraction of the variations in SZ. This reduces the confidence level in using genetic factors in prediction of SZ remission, epidemiology of SZ and identification of SZ risk population.

Genetic and environmental biomarkers of SZ have produced inconsistent results in multiple works, thus existing methods of identifying SZ require some level of active psychosis so as to take advantage of positive and negative symptoms and generates behavioural information for psychiatric evaluation based on some psychiatric criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Statistical Classification of Diseases and Related Health Problems (ICD). Very little empirical data such as Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) scan is used in identifying SZ and quality of psychiatric evaluation is subject to the experience and competence of the mental health official. Methods of treatment vary from patient to patient and after psychosis, is usually an individually tailored combination of talking therapy and medicine which is a very expensive process and mostly lifelong. SZ can be treated and managed if discovered early, before the onset of psychosis, but the pre-psychosis non salient nature of its symptoms make early identification, thus prevention difficult and the cost of treatment after FEP is high for the

average worker accounting for the cost of therapy, antipsychotics, electroconvulsive therapy, hospitalisation and other processes. In the use of psychiatric evaluation methods the need of psychosis indicates already active SZ which is a mental condition that is best prevented as its treatment can be lifelong and similar talking therapy and medicine can prevent transition into psychosis. For these reasons, there is the need to develop a standard empirical test for identification of SZ risk population and active SZ patients.

Research works done on identifying the pathophysiology of SZ have produced results which are not generic to a significant percentage of the SZ population with inconsistencies in results employing the same approach. This may be due to the comorbid nature of mental-disorders in SZ patients, the variations in genetic material behaviour among patients, the dynamism of brain networks among patients and so many other factors. Also the symptoms of SZ can only be utilised after FEP. Research has not been able to establish a specific cause of the comorbid nature of SZ and thus has not been able to establish a particular factor as the primary agent responsible for SZ. Seeking for answers at the cell/tissue level of organisation seems to be a longshot, therefore, can higher levels of human biological organisation (organ/system) provide early diagnostic methods of SZ risk populations and SZ patients. This brings us to the study of the neuronal, brain and cortical structures of the brain, their characteristics, functions and how SZ alters their behaviour.

Based on the fact that prodromal and post-psychotic stages of SZ are consistently accompanied by an evolution (degradation) of brain information processing in schizophrenic populations, perhaps in developing an empirical test for SZ

(characterising SZ patients and establishing links between genetic risk, brain biology, and other suspected factors), research should look beyond the symptoms and investigate the brain processes that result in these symptoms. As stated before, positive symptoms(hallucinations, delusions) indicate impaired auditory, visual and other sensory neural pathway functions in the brain, negative symptoms(apathy and social interaction) indicate impaired prefrontal cortex and other brain regions that act as seats of, or interact with emotional intelligence processing and also, cognitive symptoms indicate neural pathways responsible for cognitive functions are impaired some of which are found in the cerebral cortex and frontal cortex. Brain signals acquisition methods, such as the FEP, Functional Magnetic Resonance Imaging (fMRI), Functional Near Infrared Spectroscopy (fNIRS), are usually reflective of these changes. Research work done overtime has shown that some of these brain signal acquisition methods have given consistent results in discriminating between SZ patients, risk population and non-SZ population. Some research also shows some of these successfully predict remission from SZ and predict the path taken by SZ towards or away from remission. Among the stated methods we will describe and focus on the non-invasive Electroencephalogram (EEG).

1.1.1 Electroencephalography and Schizophtrenia

The non-invasive EEG is a method of acquiring electrical signals of the brain, which requires no surgical procedure. Signals from non-invasive EEG are used to study the brain, understand its cortical level of organisation, study changes

in cortical behaviour in response to events and in case of diseases and ailments. EEG systems are preferred in most research works because of the balance between cost and quality of signal acquired in terms of temporal and spatial resolution. EEG offers fine temporal resolution over spatial resolution, which is usually compensated for by the use of increased number of electrodes. In any study involving EEG signals, certain signal classes are monitored in the frequency domain and certain time-domain behaviour is monitored. In the frequency domain, interested frequencies of oscillations are usually the beta(12-30Hz) for activities of motion and gamma(30Hz and above) for cognitive functions. Study of time-domain changes are usually attached to response to stimulus events, visual, auditory or somatosensory. Some time domain signal behaviours include 300ms Peak Potential (P300), 100ms Negative Potential (N100), Mismatch Negativity (MMN) and many more. And in certain cases the time-frequency domain gives information, a typical example being the Steady State Visually Evoked Potential (SSVEP). EEG based methods of identification of SZ patients and prediction of path of SZ evolution has provided consistent and statistically significant results over the years, which show that increased study of the EEG signal classes in SZ and non SZ population will eventually lead to the development of a point of care, prognostic tool for SZ.

In light of the existence of auditory, visual and somatosensory hallucinations in SZ patients, impaired cognitive and social function, certain FEP signal classes that are indicative of the state of these functions have been found to be consistently altered in the SZ patients and risk population. One prominent class is the mismatch negativity which occurs in response to auditory and visual stimuli. The mismatch

negativity (MMN) is a component of the brain Event Related Potential (ERP) to an odd stimulus in a sequence of stimuli. The MMN signal occurs due to sudden change in parameters of the stimuli, such as frequency of sound within a standard time, time duration of signal of a standard frequency, sudden change in gradient of light intensity, etc. The MMN signal is consistently attenuated in SZ at risk populations and SZ patients. Another class of FEP signal is the Auditory Steady State Response (ASSR). ASSR is evoked using repeated sound stimuli presented at a high repetition rate and can be used to objectively estimate hearing sensitivity in individuals with normal hearing sensitivity and with various degrees and configurations of Sensorineural Hearing Loss (SNHL). SZ patients consistently show reduced ASSR power and phase locking to gamma range stimulation. Since FEP results are significantly consistent in SZ patients and risk population, how can they be used in developing a point of care prognostic measures for SZ.

1.1.2 Problem Description

In the quest of developing empirical methods of characterising SZ patients and discrimination SZ risk population from the non SZ populace, the medical and biological sciences seem to have hit a gridlock in seeking for pathological, environmental and genetic causes of SZ that consistently characterize SZ behaviour and its prognosis. In areas of genetics, inconsistencies have been found in the results of various research modalities. The comorbid nature of the SZ condition also makes it difficult to identify pathological causes of SZ and there exists

limitations on social methods of determining environmental factors and causes of SZ, as these social methods may not be empirical enough to reach a conclusion.

EEG methods of identifying SZ affected and risk population have provided more consistent results and has helped understand the ailment and develop various models that explained the ailment to an extent, one of such being the functional connectivity model which suggest reduced level of interaction between brain regions. The functional connectivity model has shown that people with SZ show both higher diversity at each brain region and lower variance in connectivity strength across the brain. This can be conceptualised as a randomization or de-differentiation of functional connectivity.

EEG methods have also suggested the use of auditory sensitive ERP's in identifying SZ affected and risk populations. As stated before, the MMN is a prominent ERP in FEP studies of SZ. The MMN is consistently attenuated in SZ populace and has some other ERP components that are concomitant to it and altered in SZ patients. One such ERP is the P3a. Auditory P3a response is a fronto-centrally maximal positive component elicited by infrequent, unpredictable stimuli in a stream of repeating sounds and peaking between 200 and 400 ms from the stimulus onset. P3a is reduced in FES SZ patients and is usually indicative of attention and working memory. The MMN is indicative of impaired auditory neural pathways, interpretation which can be due to deviation of attention patterns in the brain from the normal. Till date MMN is the most stable identified marker of SZ, its temporally stable and heritable.

A temporal-frequency domain feature of EEG whose behaviour is altered in SZ patients is the ASSR. ASSR demonstrates disturbances of neural synchrony and oscillations in SZ which affect a broad range of sensory and cognitive processes.These disturbances may account for a loss of neural integration and effective connectivity in the disorder. Interestingly, ASSR has provided consistent evidence for lower levels of organisation defects in SZ populations. ASSR may reflect disturbed interactions within Gamma-Aminobutyric Acid (GABA)ergic and glutamatergic circuits, particularly in the gamma range.

A persisting problem with use of EEG methods, in most cases MMN in discriminating SZ populace from the other populations is the existence of an overlap in results generated by EEG signal classes between these two populace. There is also the lack of definition of a specific threshold in case of ERPs and neural synchrony. The existence of this overlap and lack of a threshold in separating SZ populations and other populations has not allowed the development of a clinically acceptable EEG based point of care prognostic tool for SZ.

Most research works employing EEG signals focus on using one class of EEG signal such as the MMN, ASSR, etc. in discriminating between SZ populace and the others. And some others investigate the functional dysconnectivity model by making use of coherence and synchrony measures to describe spatial disconnectivity of brain regions for defined activities to be carried out.

The MMN has over time been the most stable marker for SZ but has a problem of overlap between the SZ populace and non-SZ populace, also it has no definite threshold of attenuation levels that can be used to discriminate between SZ

populations and other populations. Thus there is the need to investigate methods of improving the results of MMN by reducing or eliminating the overlap between SZ and other populations in the diagnostic results generated by MMN.

1.2 Problem Statement

SZ is a mental ailment mostly identified during psychosis through psychiatric nosology and one whose symptoms manifest as a parent class of other mental ailments. Early(pre-psychotic) detection and treatment of SZ has proved that transition into psychosis can be prevented. As diagnosis of SZ currently depends on symptoms of the psychotic phase, early treatment cannot be administered. Mental health diagnostics depend on the subjective evaluations of trained clinicians (albeit based on the considerable experience and judgement).There exists no objective scientific instrument to diagnose mental disorders, thus the need for psychosis. This means that in cases of schizophtrenia, the patient has to be exrtremely sick, before they can be identified as sick. Prevention is better than cure, as the financial, social and emotional expense of curative treatments are mostly expensive. Since SZ can be managed well in the pre-spychotic stage and such management usally prevents conversion to psychosis. This project aims to develop an instrument for early detection and diagnosis of SZ. Similar works have been done in the past but seem to have hit a standstill as there is a consistent exisint goverlap between the SZ and non SZ population in the results provided by these methods. These methods usually utilize one EEG signal class indicative of SZ state and mostly utilize MMN from EEG signals. This study will be conducted

to improve the accuracy and specificity of MMN as a marker for SZ by utilising a novel method of combining MMN computed features with other FEP modalities including ASSR and measures of connectivity and complexity such as fuzzy entropy. Then this project will evaluate the possibility of developing an objective, accurate and easy to administer test for SZ based on the study results.

1.3 Aims and Objectives

The aim of this project is to develop an instrument for improved diagnosis and management of SZ. Hopefully in the future, a Point of Care (POC) device for SZ based on this work will be created. Specific objectives of the project are to:

1. Consuct literature review on possible EEG features that can be used as markers for SZ diagnois.
2. Develop a signal processing pipeline for EEG signal classification towards SZ diagnosis.
3. Acquire EEG data from SZ patients and normal subjects.
4. Evaluate the accuracy of the system in diagnosing SZ.

1.4 Scope of Project

This study will focus on employing statistical, analytical and computer learning methods in understanding the distribution of MMN results across schizophrenic

and non-schizophrenic populations. This study will also investigate the best feature extraction, combination and computer learning methods to be employed in developing MMN and SZ classifiers. This study will correlate the results of the classifier with the type and severity of the SZ cases. This study will at no point seek to understand the neuronal, genetic or environmental workings that contribute to SZ. At no point will this study question the existing psychiatric evaluation methods or try to understand them. Being blind to the basis of psychiatric evaluation and nosology is important so as not to introduce any form of bias during data processing.

1.5 Outline of Thesis

While chapter two discusses the methods adopted by previous works with similar aim to this study and their results, chapter three will later on explain the methodolgy to be adopted for this work, explaining the reasons for the adopted methodology. Chapter four will at the end of this project present the results obtained and more on their interpretation in the discussion sub-section. Chapter five will at the end of this project draws conclusions from the results and suggests methods further works should use based on the results obtained and hallmarks achieved in this study.

CHAPTER TWO

LITERATURE REVIEW

2.1 Neuropathology and Brain anomalies of Schizophrenia

2.1.1 Neuropathological Findings Overtime

Most neuropathological findings in schizophrenia show that the identified neuropathological causes do not qualify for schizophrenia markers, due to their unique and dynamic evolution in patients and some due to incosistencies across the schizophrenia population.

> *The neuropathology of schizophrenia remains obscure despite the fact that many neuropathologists have investigated this area for over 100 years. While remarkable progress has been made in the neuropathological study of neurodegenerative diseases including Alzheimer's disease, progress in studying the neuropathological entity of schizophrenia has not kept pace; the phrase "schizophrenia is the graveyard of neuropathologists" has been stated in the field*

Iritani (2007)

At the neuronal level, the hypothesis of reduced neuropil as a neuropathology of schizophrenia has been mostly disproved as they have been shown to be associated more with age interactions. Rather a quantitative summary suggests that neuron density is increased in patients compared to controls.

Bakhshi and Chance (2015)

The hypothesis of reduced neuropil(a dense network of interwoven nerve fibres, their branches and synapses, together with glial filaments) is onw among many neuropathological findings in SZ that has been disproved, however, other findings have proved to be incosistent across SZ populations.

There is evidence of decreased inhibitory neurons in schizophrenia. This provides support for the involvement of inhibitory cortical circuits in the development and maintenance of schizophrenia.

Bakhshi and Chance (2015)

Post-mortem neuropathologial abnormalities have been found in almost all areas of the brain, but there are more reports describing the temporal lobe(auditory) and frontal lobe(language, expression,cognition) compared to those describing other areas of the brain.

Iritani (2007)

Thus the prominence of neuropathological anomalies in the temporal and frontal lobe could explain why auditory hallucinations and cognitive deficienceis is prominent in SZ patients, but these anomalies vary across patients.

> *Computer imaging studies using statistical analysis and immunohistological techniques has led to post-mortem neuropathological examination of the brains of schizophrenia patients, over the last 20 years it is clear that schizophrenia is not a pure functional disease without organic factors.*
>
> Iritani (2007)

> *Most neuropathological abnormalities are rationally explained by the hypothesis of a neurodevelopmental disorder in schizophrenia.*
>
> Iritani (2007)

> *Studies over time have shown that the neuropathological picture of schizophrenia is not static but changes over time, and indicates that age and length of illness are relevant variables in any analysis..*
>
> Bakhshi and Chance (2015)

SZ being views as a neurodevelopmental disorder suggests changes in its root mechanisms overtime, but consistent behavioural readouts in its patients. This shows that SZ might need to be studied at higher levels of organization ti develop diagnostic tools for the ailment. The eveolution of SZ pathology thus suggests that:

A single, fixed pathological description may no longer be expected to reflect the complex nature of changes in development, adult plasticity and ageing in schizophrenia studies.

Bakhshi and Chance (2015)

2.1.2 Consistent Brain Anomalies Overtime

Certain anomalies of the brain are however consistent with the schizophrenic population and have withstood the test of time. Overtime the following findings have remained consistent:

Imaging studies reveal certain differences in schizophrenia including larger ventricles, decreased grey matter, smaller hippocampus, decreased asymmetry and altered gyrification, in schizophrenia pathology.

Bakhshi and Chance (2015)

Certain regional and functional anomalies have been consistent in the brain over years of research despite the evolving nature of SZ, one of such is:

The frontal and temporal lobes and their thalamic relays appear particularly affected in schizophrenia and there exists evidence for significant asymmetries. These regions are consistently affected in patients having neurodegenerative cognitive impairment.

Halliday (2001)

> *Differences in volumes of various forebrain subregions have been reported, but with less consistent results, the lack of consistency being a hallmark of schizophrenia pathology.*
>
> Bakhshi and Chance (2015)

So therefore,

> *Schizophrenia may involve a spectrum of brain network changes that are only unified in the extent to which there are all deviations from the healthy equilibrium.*
>
> Bakhshi and Chance (2015)

This suggests that empirical diagnosis of schizophrenia may only take place at higher levels of organiztion in the brain. So there is the question of how genetics contribute to schizophrenia and how does schizophrenia affects the brain structure at the functional level of organization?

2.2 The Role of Genetics in Schizophrenia

> *There exists multi-factorial genetic heritability in schizophrenia, for which studies have provided evidence of diversity of involved phenotype in patients.*
>
> Bakhshi and Chance (2015)

Recent molecular biology studies have reported some putative genes, some of which may have the function of neurodevelopment or making neuronal networks.

Iritani (2007)

Structurally compromised cellular phenotypes have yet to be definitively identified in schizophrenia and the relationship between any neurochemical and structural abnormalities remain unclear. This is largely due to the subtle changes that take place in these components and their diffuse nature.

Halliday (2001)

The several identified gene loci in schizophrenia leave many questions unanswered including the therapeutic significance of these gene loci in schizophrenia.

Harrison (2015)

There exist more unidentified gene loci which may result from rare variants, gene-gene and gene-environment interactions. The biological significance of these gene loci remains unclear and may possess more therapeutic information.

Harrison (2015)

The identification of genes and loci, though a triumph, is merely the start of a long process towards meaningful biological understanding, let alone better treatment of the disorder.

Harrison (2015)

Genetic studies have consistently suggested a genetic overlap of schizophrenia with bipolar disorder and neurodevelopmental disorders such as autism.

Van Winkel et al. (2010)

Genomic wide association studies are identifying novel common and rare genetic variants associated with psychotic disorder such as schizophrenia.

Van Winkel et al. (2010)

Associations between common and uncommon genetic variants and schizophrenia, though statistical facts, are not necessarily indexes of causal pathways.

Henriksen et al. (2017)

Many of the discovered genetic associations in schizophrenia cases are in fact non-specific to schizophrenia but indicative of a genetic vulnerability to several mental disorders.

Henriksen et al. (2017)

Genetic discoveries in schizophrenia come with the sobering realisation that the genetic basis of schizophrenia is more complex in many ways than had generally been anticipated.

Harrison (2015)

Therre has always been and will always be genetic discoveries in relation to SZ, but the variations in discovery across populations and the amoun of understanding of these discoveries limits the use of genes in developing diagnostics tools for SZ.

2.3 Cortical Organization in Schizophrenia

Genetics and neuropathology might be complex, but engineers and the natural existence of abstractions and pyramidal flow in structures is always to the rescue.

> *There exists structural brain abnormalities of developmental origin and neuropsychological deficits in schizophrenia.*
>
> Raggi et al. (2022)

> *There is increasing evidence that altered cortical oscillatory activity may be associated with neuropsychiatric disorders such as schizophrenia, that involve dysfunctional cognition and behavior.*
>
> Uhlhaas et al. (2008)

> *Schizophrenia is associated with abnormal cortical oscillatory activity in a wide range of frequencies with disturbed large-scale synchronization of oscillations. These are consistently associated with core cognitive dysfunctions and symptoms of disorder suggesting a causal relation.*

Uhlhaas et al. (2008)

The neurodevelopmental hypothesis of schizophrenia is consistent with the involvement and possible dysfunction of neural oscillations in early development of cortical circuits and with delayed manifestation of the disorder in late adolescence.

Uhlhaas et al. (2008)

Among known cortical behaviours, some are more prominent among certain populations of SZ patients, some of which are the Clinical High Risk (CHR), FEP and among non FEP such as the Healthy Control (HC).

There is consistently widespread smaller cortical volume among CHR schizophrenia patients compared with healthy control subjects, particularly among the younger group.

Chung et al. (2019)

There exists similar cortical changes in CHR who later go into psychosis or remit from schizophrenia.

Chung et al. (2019)

Some altered function in SZ patients are reflected prominently in certain corticla regions. We discuss some of those consistent across previous works here.

Poor premorbid functioning in childhood is associated with smaller surface area in orbitofrontal, lateral frontal, rostral anterior cingulate, precuneus and temporal regions.

Chung et al. (2019)

There exists an association between decreased dorsolateral prefrontal cortex activity and connectivity and a task-related neural network in schizophrenia patients.

Yoon et al. (2008)

There may exist imbalance across multiple regions of the neocortex in imaging studies of schizophrenia patients.

Rolls (2021)

Short term treatments are associated with prefrontal cortical thinning in schizophrenia patients and treatment is associated with better cognitive control and increased prefrontal functional activity.

Lesh et al. (2015)

The whole brain volume tends to correlate with the measures of general intelligence as well as with a range of specific cognitive functions in control and female schizophrenia patients.

Antonova et al. (2004)

Inhibitory signalling in the prefrontal cortex cortex is required for gamma oscillatory activity and working memory function; and disturbances in this signalling contribute to altered gamma oscillations and working memory changes in schizophrenia.

Rolls (2021)

Archicortical but not paleocortical, prefrontal cortex tends to associate with the measures of executive function.

Antonova et al. (2004)

Temporal lobe, hippocampus, and parahippocampal gyrus correlates with cognitive abilities such as performance speed and accuracy, memory and executive function, verbal endowment and abstraction/categorization, some of which are specific to schizophrenia.

Antonova et al. (2004)

The consistent behaviour of cortical regions with brain functions significantly impaired in schizophrenia indicate the ability of cortical level brain data in developing diagnostic and prognostic tools for schizophrenia.

2.4 Electroencephalogram and Schizophrenia

Various brain electroencephalogram signals are indicative of cortical activity and significant change in brain state in response to stimuli. This signal classes can detect deviations of cortical activities from the normal. The correlation of cortical activty with degrading cognitive function in schizophrenic populations can be monitored using certain electroencephalogram signal class and can be used to understand the prognosis of schizophrenia and get insight into diagnostics of the

condition. We discuss some of this signals below and state finding s consistent from review of past works found in MMN and ASSR.

N100 EEG component which is a negative peak for auditory stimuli in response to infrequent deviant auditory stimuli and 150ms for visual stimuli is consistently reduced among schizophrenia patients and first degree relatives. It is also associated with severity of symptoms in healthy, clinical high risk patients and psychotic children. There occurs deficiency in N100 suppression during self generated speech in schizophrenia patients and first degree relatives, alsoduring vocalization in clinical high risk patients relative to healthy control subjects.

Hamilton et al. (2020)

The P50 EEG component is elicited during sensory gatind paradigm in response to pairs of auditory stimuli separated by 500ms interstimulus interval,larger at first stimulus(S1) and suppressed at second stimulus(S2) which reflects gating out of irrelevant information. Deficiency in gating in terms of ratio of S2 to S1 has been consistently shown in schizophrenia patients.

Hamilton et al. (2020)

Repetition positivity is an EEG component elicited by standards that increase with successive standard repetitions, they are consistent with strengthening of standard memory trace and are associated with prediction that such standard will reoccur. There exist deficiency

in clinical high risk patients of schizophrenia for earliest appearing standards and more prominently for late appearing standards within local sequences of repeating standards following each deviant.

Hamilton et al. (2020)

EEG P300 component is elicited in the process of choice/decisions making on stimuli requiring response(P3a subcomponent) and those requiring no response(P3b subcomponent). P3a and P3b have consistently been reduced in schizophrenia patients and first degree relatives. P300 amplitude reduction may reflect genetic risk for schizophrenia. The P300 in some research works have predicted future psychosis onset time, differentiated converters and non-converters, predicted clinically high risk patients remission, predicted improvement in negative and general psychopathology symptoms and has been shown to be linked to some neuronal activity and hormones. The P300 has been localised to the temporo-parietal junction with amplitude deficiency potentially implicating compromise of these regions in those at greater risk.

Hamilton et al. (2020)

The mismatch negativity occurs in response to violations of a rule established by a sequence of sensory stimuli.

Demis R. Combs (2011)

MMN generators have been localised to the auditory cortex and frontal cortex and its generation has been mapped to the theta frequency band in man.

Alho (1995)

MMN can distinguish future remitters from non-remitters and predict later functional recovery and has been shown to predict shorter time to conversion among clinical high risk patients of schizophrenia.

Hamilton et al. (2020)

There exists resting state EEG abnormalities in schizophrenia patients including increased delta, theta power and reduced alpha power.

Boutros et al. (2008)

EEG spectral abnormalities which predict psychosis conversion including increased delta, theta power alone or in combination with symptom severity and decreased alpha peak frequency have been identified.

Gschwandtner et al. (2009)

Schizophrenia is associated with gamma band abnormalities(30-80)Hz implicated in sensory registration, cross-modal sensory integration and higher order cognitive functions.

Uhlhaas and Singer (2010)

Gamma auditory steady state response(ASSR) are the most replicated gamma oscillation abnormalities in schizophrenia.

Hamilton et al. (2020)

There is evidence for reduced alpha event-related desynchronization in schizophrenia patients and clinical high risk patients relative to healthy control subjects.

Koh et al. (2011)

2.4.1 Mismatch Negativity in Schizophrenia

Mismatch Negativity is a negative component of the event-related response in an EEG signal, elicited by any perceptible change in some repetitive aspect of an auditory stimulation (e.g., stimulus pitch, stimulus duration).

Goodwin and Geddes (2007)

The mismatch negativity (MMN) is a brain response to violations of a rule, established by a sequence of sensory stimuli (typically in the auditory domain)

Demis R. Combs (2011)

MMN is elicited following a deviation in any sound characteristic, amplitude, frequency, intensity, duration, location.

Demis R. Combs (2011)

There exists some ERP components whose characteristics are consistent with schizophrenia that exist simultaneously with MMN.

de Tommaso et al. (2020)

The P3a component occurs 250-280ms post-stimulus alongside MMN.

Comerchero and Polich (1999)

The P3a is associated with activity related to engagements of attention, shift in attention and novelty processing.

Friedman et al. (2001)Polich (2007)

P3a has been found to be consistently impaired in schizophrenia and like MMN is a strongly automatic process.

Grillon et al. (1990)Jahshan et al. (2012)Koshiyama et al. (2022)

Impaired early auditory processing is a well characterised finding in schizophrenia that is theorised to contribute to clinical symptoms.

Kim et al. (2020)

Auditory mismatch negativity is consistently impaired in schizophrenia as well as in bipolar disorder with psychotic features, though to a lesser extent in bipolar disorder.

Raggi et al. (2022)

Auditory mismatch negativity shows the involvement of the N-methyl-D-aspartate receptor in the pathophysiology of both bipolar disorder and schizophrenia.

Raggi et al. (2022)

Auditory mismatch negativity may be considered as a correlate of a common psychopathology of schizophrenia and bipolar spectrum illnesses.

Raggi et al. (2022)

Duration deviant MMN might be more sensitive to schizophrenia than frequency deviant MMN among first episode patients.

Umbricht and Krljes (2005)

MMN can be sourced for near the primary auditory cortex, in the hemisphere contralateral to the ear of stimulation and the frontal region mainly involving the right hemisphere.

Raggi et al. (2022)

MMN is quantified by subtracting the evoked response to the standard tone from the corresponding response to the deviant stimulus.

Ferri et al. (2003)

MMN is more evident on the frontal sites and on the mastoids due to dipole inversion.

Alho et al. (1986)

MMN is considered as a highly reproducible neurophysiological marker.

Javitt (2000)Umbricht and Krljes (2005)

MMN has been shown to follow a progressive course, with reduced MMN amplitude associated with a loss of grey matter in the left superior temporal gyrus.

Salisbury et al. (2007)

There exists significant associations between MMN and psychotic symptoms.

Hall et al. (2007)

Most works on mismatch negativity show that they are consistent biomarkers in characterising schizophrenia.

2.4.2 Auditory Steady State Response in Schizophrenia

Most of the studies that show abnormalities of gamma oscillations in the scalp-recorded EEG of schizophrenics and thus hypothesise their reflection neural circuit abnormalities has come from studies of ASSRs in which simple auditory stimulus such as clicks are delivered at rapid rates and entrain the EEG at the stimulation frequency.

Spencer et al. (2008)

Chronic schizophrenics show a gamma ASSR deficit with reduced power and phase-locking of ASSRs in the gamma band but not at lower frequencies compared with healthy individuals and seems to be most pronounced for 40Hz stimulation.

Hong et al. (2004)

ASSR deficit has also been reported in early onset psychosis suggesting that it might be a manifestation of a neural circuit disorder (or set of disorders) that is shared by psychosis in general.

Wilson et al. (2008)

ASSR deficit has been reported consistently as being consistent with grey matter volume loss, which is a consistent change in brain structure of schizophrenics.

Salisbury et al. (2007)

Some of the neural circuitry abnormalities underlying the gamma ASSR deficit might be common to psychosis in general, whereas others might be specific to particular disorders.

Spencer et al. (2008)

ASSR evoked power at 40Hz is reduced in schizophrenics compared to healthy control subjects.

Spencer et al. (2008)

20Hz ASSR does not differ between groups, but phase-locking and evoked power of the 40Hz harmonic of the 20Hz ASSR are reduced in both SZ and affective disorder patients. Phase-locking of this 40Hz harmonic was correlated with total positive symptoms in SZ.

Spencer et al. (2008)

The gamma ASSR deficit is present at first hospitalisation for both schizophrenia and affective disorder but shows a left hemisphere bias in first hospitalised SZ.

Spencer et al. (2008)

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