Evaluation of Retinal Nerve Fiber Layer, Macula Thickness and Visual Evoked Potential in Schizophrenia Patients

DR SARAH SATHYAPRIYA A/P TAMILARSAN

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (OPHTHALMOLOGY)

SCHOOL OF MEDICAL SCIENCES
UNIVERSITI SAINS MALAYSIA
2022

DISCLAIMER

I hereby clarify that the work in this dissertation is my own except for quotations, some figures, and summaries which have been duly acknowledged. I declare that I have no financial interest in the instruments and the computer software used in this study.

…….

(Dr. Sarah Sathyapriya A/P Tamilarsan)

P-UM0129/18

Date: 23rd November 2022

ACKNOWLEDGEMENT

First and foremost, I am thankful to God for the good health and well-being that were necessary to complete this book.

I wish to express my greatest appreciation and gratitude to my supervisor, Professor Dr. Wan Hazabbah Wan Hitam, senior lecturer and consultant ophthalmologist in the Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, for his continuous support and guidance throughout the study.

I am also thankful to my co-supervisors, Dr Juanarita Jaafar, Ophthalmologist, Hospital Sultanah Bahiyah, and Professor Madya Dr Asrenee Ab Razak, Department of Psychiatry, School of Medical Sciences, Universiti Sains Malaysia for their great support in conducting this study. Apart from that, I would also like to take this opportunity to express my appreciation to all lecturers in the Department of Ophthalmology, technicians, support staffs, and all my ophthalmology peers and colleagues for their constant support and willingness to help with the completion of this dissertation. In addition, I would like to extend my gratitude to all the patients for their involvement.

Finally, I would like to record my sense of indebtedness towards my family, especially to my parents, parents-in-law, husband Dr Emmanuel Jairaj Moses, and my adorable son Jude for their love, endless support, encouragement, and sacrifices. This master journey accomplishment would not have been possible without them.

ABSTRAK (BAHASA MELAYU)

Latar Belakang

Skizofrenia merupakan penyakit neurodegeneratif yang mengubah persepsi, pemikiran dan tingkah laku individu. Retina dianggap sebahagian daripada sistem saraf pusat pada manusia. Oleh kerana skizofrenia merupakan sejenis penyakit neurodegenerasi, maka perubahan pada lapisan retina boleh wujud di kalangan pesakit skizofrenia.

Objektif

Objektif kajian ini adalah untuk mengkaji ketebalan lapisan gentian saraf retina (LGSR), ketebalan macula pusat (CMT) dan ujian visual evoked potential (VEP) di kalangan pesakit skizofrenia. Kajian ini juga bertujuan untuk mencari korelasi antara ketebalan LGSR dan ketebalan CMT dengan keputusan ujian VEP di kalangan pesakit skizofrenia.

Kaedah

Sebuah kajian perbandingan keratan rentas telah dijalankan di Hospital Universiti Sains Malaysia yang melibatkan 60 subjek skizofrenia dan 60 subjek kawalan. Calon yang memenuhi syarat kajian menjalani pemeriksaan mata dan seterusnya pemeriksaan *Optical Coherent Tomography* pada mata kanan untuk mengukur ketebalan LGSR dan ketebalan CMT. Mereka juga akan menjalani ujian VEP pada mata kanan.

Keputusan

Terdapat penipisan yang signifikan pada lapisan LGSR di kalangan pesakit skizofrenia. Di kalangan pesakit skizofrenia, min ubah ketebalan LGSR secara purata adalah (min yang diselaraskan 89.24μm berbanding 103.50μm, P <0.001) berbanding subjek kawalan. Penipisan

yang signifikan turut diperhatikan pada ketebalan LGSR kuadran superior (min diselaraskan 110.86µm berbanding 132.34µm, P <0.001), kuadran inferior (min diselaraskan 116.41µm berbanding 125.71µm, P = 0.003), kuadran 'nasal' (min diselaraskan 63.21µm berbanding 75.74µm, P <0.001), dan kuadran 'temporal' (min diselaraskan 66.28µm berbanding 80.13µm, P<0.001) dalam kumpulan skizofrenia berbanding kumpulan kawalan. Kajian ini juga menunjukkan kelewatan latensi puncak gelombang P100 yang signifikan di kalangan pesakit skizofrenia berbanding subjek kawalan dengan 60-minit arc, (min diselaraskan 111.16ms berbanding 102.44ms, P <0.001) dan dengan 15-minit arc (min diselaraskan 119.16ms berbanding 114.72ms, P <0.001) dalam kumpulan skizofrenia berbanding kumpulan kawalan. Tiada perbezaan ketara dalam ketebalan makula pusat dalam pesakit skizofrenia berbanding kumpulan kawalan (min diselaraskan 238.56µm vs 244.44µm, P = 0.262). Walau bagaimanapun, tidak terdapat korelasi yang signifikan antara ketebalan purata LGSR dan ketebalan CMT dengan semua parameter bacaan VEP di kalangan pesakit skizofrenia.

Kesimpulan

Pesakit skizofrenia mempunyai lapisan LGSR yang lebih tipis dan latensi puncak gelombang P100 yang lebih lewat berbanding subjek kawalan. Perubahan ketebalan CMT adalah tidak signifikan. Ini menjurus kepada perubahan neurodegenerasi yang melibatkan saraf mata.

.

Kata kunci: Ketebalan Lapisan Gentian Saraf Retina (LGSR), Ketebalan Macula Pusat (CMT) dan Visual Evoked Potential (VEP), Skizofrenia

ABSTRACT

Background

Schizophrenia is a neurodegenerative condition, that alters an individual's perception, thoughts, affects, and behaviour. The retina is considered part of the central nervous system in a human. Thus, there would be anatomical changes in the retina if a patient has been diagnosed with neurodegenerative conditions like schizophrenia. Retinal Nerve Fibre Layer (RNFL), Central Macula Thickness (CMT), and Visual Evoked Potential (VEP) are useful parameters to screen and evaluate the progression of schizophrenia.

Objective

To evaluate the RNFL, CMT, and VEP measurements in patients with schizophrenia. The correlation between RNFL and CMT with VEP was also conducted in this study.

Methods:

A comparative cross-sectional study was conducted at Hospital Universiti Sains Malaysia. 60 schizophrenia subjects in remission and 60 controls were recruited. Candidates that fulfilled the criteria with normal ocular examinations underwent Optical Coherent Tomography for evaluation of RNFL, CMT, and VEP test of the right eye.

Results

There was a statistically significant reduction in average RNFL thickness (adjusted mean 89.24µm vs 103.50µm, $P < 0.001$), superior RNFL thickness (adjusted mean 110.86µm vs 132.34µm, $P < 0.001$), inferior RNFL thickness (adjusted mean 116.41µm vs 125.71µm, $P = 0.003$), nasal RNFL thickness (adjusted mean 63.21µm vs 75.74µm, $P <0.001$), and temporal

RNFL thickness (adjusted mean 66.28µm vs 80.13µm, P <0.001) in schizophrenia group compared to the control group. As for VEP results, there was a statistically significant delay in latency of P100 with 60-min of arc (adjusted mean 111.16ms vs 102.44ms, P < 0.001) and in P100 with 15-min of arc (adjusted mean 119.16ms vs 114.72ms, P < 0.001) in schizophrenia group compared to control group. There was no significant difference in the CMT in schizophrenia patients compared to the control group (adjusted mean 238.56µm vs 244.44µm, P = 0.262). However, there was no significant correlation between average RNFL thickness and CMT with all parameters of VEP readings among schizophrenia patients.

Conclusion

Schizophrenia patients have thinner RNFL, and delayed peak latency compared to the controls suggesting neurodegeneration of the optic nerve. However, the macula is preserved.

Keywords: Retinal Nerve Fibre Layer (RNFL), Visual Evoked Potential (VEP), Central Macula Thickness (CMT), Schizophrenia

TABLE OF CONTENT

CHAPTER 1

INTRODUCTION

1.1 Schizophrenia

Schizophrenia is a major psychiatric disorder that alters an individual's perception, thought, affect and behaviour (Malaysian Psychiatric Association, 2021) . It is a mental illness characterized by hearing voices, delusions (false beliefs), disordered thinking, social withdrawal, decreased emotional expression, and lack of motivation (McCutcheon et al., 2020). It is a chronic and relapsing illness which is usually associated with incomplete remissions. It is characterized by a combination of positive, negative, cognitive, and mood symptoms (McCutcheon et al., 2020). Although the prevalence is low with a worldwide prevalence estimates range between 0.5% and 1.1%, it is a highly debilitating disease and ranked as the 10th leading cause of disability globally (Maiocco et al., 2017). The total estimated number of treated schizophrenia cases in Malaysia in 2015 was 15,104 with the total economic burden of USD 100 million which was equivalent to 0.04% of the national gross domestic product (Teoh et al., 2017). Age at first episode is typically 21 years among men and 27 years among women (Maiocco et al., 2017).

1.1.1 Phases of Schizophrenia

Schizophrenia may be divided into the following phases which are prodromal, acute, and residual phase (American Psychiatric Association, 2013). Prodromal symptoms often precede the acute phase, and residual symptoms may follow it. Prodromal phase is characterised by impairments in psychosocial functioning, odd and eccentric behaviour, poor communication, and motivation, and neglect of personal hygiene (Malaysian Psychiatric Association, 2009). Acute phase is when positive symptoms (hallucinations, delusions and

behavioural disturbances) of schizophrenia manifest (Malaysian Psychiatric Association, 2009).

With adequate treatment, the symptoms will disappear in most patients. Nevertheless, in the residual phase negative symptoms (affective flattening, alogia and avolition) may persist and it is akin to that of the prodromal phase (Malaysian Psychiatric Association, 2009). The course of illness varies greatly between individuals varying from almost complete recovery to total disability with many relapses. Roughly half of them will have excellent adjustment over the long term with few further relapses, and a small proportion of these will recover completely (American Psychiatric Association, 2013; Vita and Barlati, 2018) . However, for most patients, schizophrenia is a chronic disease that causes some degree of disability (Malaysian Psychiatric Association, 2009).

1.1.2 Pathogenesis of Schizophrenia

Schizophrenia is a complex disease with interaction of multiple factors including neurodegenerative, genetics and environmental influence. (Lakhan and Vieira, 2009). Although studies on specific genes such as ZDHHC8 and DTNBPI suggested susceptibility on the onset of this disorder, no single gene has been linked to schizophrenia (Lakhan and Vieira, 2009). Environmental insults that is commonly associated with schizophrenia include *in utero* exposure to infection, lack of nutrients, maternal stress, perinatal complications, social disadvantage, urban upbringing, ethnic minority status, childhood maltreatment, bullying and traumatic events (Uher, 2014).

One of the most proposed models associated with the positive and negative symptoms of schizophrenia are the dopamine and glutamate models (Correll & Schooler, 2020). Schizophrenia is hypothesized to be related to dopamine dysregulation observed by hyperactive dopamine transmission in the mesolimbic areas and hypoactive dopamine transmission in the prefrontal cortex (Brisch et al., 2014). Dopamine systems in the mesolimbic pathway may be related to the 'positive symptoms' of schizophrenia, whilst ‘negative symptoms’ may be contributed by dopamine function within the mesocortical pathway (Heinz, 2002).

The glutamate hypothesis of schizophrenia links alterations between glutamatergic neurotransmission and the neural oscillations that affect connections between the thalamus and the cortex (Pratt et al., 2017). The underlying pathogenesis of schizophrenia is related to neural excitotoxicity due to excess of glutamate which is attributed to inhibition of N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission and a subsequent failure to stimulate inhibitory gamma-aminobutyric acid (GABA)–ergic interneurons which could lead to anatomic degeneration of inhibitory GABAergic interneurons (Deutsch et al., 2001; Lee et al., 2013) . "Disinhibition" of glutamatergic projection to hippocampal and cortical areas leads to progressive excitotoxic neuronal cell death (Deutsch et al., 2001).

Previous studies have shown that there was significant reduction of total brain volume in schizophrenia patients as compared to age-matched controls through neuroimaging techniques (Cahn et al., 2002; Lieberman et al., 2001; Woods et al., 2005). Magnetic resonance imaging (MRI) brain of patients with schizophrenia in relation to control groups shows regional structural differences in patients with schizophrenia which include bilaterally reduced volume

of medial temporal lobe structures (Wright et al., 2000) . Progressive volume reduction of the left posterior superior temporal gyrus gray matter in patients with first-episode schizophrenia at initial hospitalization and 1.5 years later was seen in high spatial MRI study (Kasai et al., 2003). However, the precise neuropathologic, perhaps neurodegenerative changes that may explain this grey matter volume deficit remains to be proven (Kasai et al., 2003; Stone et al., 2022).

1.1.3 Diagnosis of Schizophrenia

Diagnosis of schizophrenia is based on Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which is published by the American Psychiatric Association (American Psychiatric Association, 2013). According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (*DSM-5*), to meet the criteria for diagnosis of schizophrenia, the patient must have experienced at least 2 of the following symptoms each present for a significant portion of time during a 1-month period (or less if successfully treated), with at least 1 of them being (1), (2), or (3): (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behaviour, and (5) negative symptoms.

Continuous signs of the disturbance must persist for at least 6 months, during which the patient must experience at least 1 month of active symptoms (or less if successfully treated), with social or occupational deterioration problems occurring over a significant amount of time. These problems however must not be attributable to another condition. The diagnosis of schizophrenia is established by ruling out other mental health disorders and determining that

symptoms are not due to substance abuse, medication, or a medical condition (Tandon et al., 2013) .

Evaluation of the severity ranges of schizophrenia can be done using the Brief Psychiatric Rating Scale- 6 (BPRS-6). The BPRS-6 items include expressed delusions, conceptual disorganization, hallucinations, blunted affect, emotional withdrawal, and poverty of speech. The severity range scale of schizophrenia is mild, moderate, and severe corresponding to a BPRS-6 total score of 5–9, 10–19, and >20, respectively. Remission in schizophrenia is defined as having a BPRS-6 total score <5 (Park et al., 2019).

BPRS -6		
1	Expressed delusions (at interview)	(0-6)
2	Conceptual disorganization (at interview)	(0-6)
3.	Hallucinations (at interview)	(0-6)
4	Blunted incongruous effect (at interview)	(0-6)
5	Emotional withdrawal (at interview)	(0-6)
6	Poverty of speech (at interview)	(0-6)
Theoretical score range (0-36)		

1.1.4 Treatment of Schizophrenia

The modalities of treatment in schizophrenia includes pharmacological treatment, physical intervention, psychosocial therapy, and service level intervention. Mainstay of pharmacological treatment is with antipsychotics. Antipsychotics are dopamine antagonists that block D2 receptors, and affect the neurotransmission of dopamine which subsequently effects the positive symptoms of schizophrenia. Example of first-generation antipsychotics are Chlorpromazine and Sulpride, whereas second generation antipsychotics are Aripriprazole and Clozapine (Kane and Correll, 2010). Choice of antipsychotics depends on their differences in side-effect profiles. Parenteral [intramuscular (IM) or intravenous (IV)] medications are used during acute exacerbation of schizophrenia to calm them down (Malaysian Psychiatric Association, 2021). Depot or long-acting injectable antipsychotics like Risperidone are used to achieve remission especially when they are unable to adhere to oral medications and frequent follow ups (Leucht et al., 2012; Malaysian Psychiatric Association, 2021)

Physical intervention is referred to Electroconvulsive therapy (ECT) which serves as an adjunct to antipsychotics when rapid improvement is needed or if patient has resistant response to antipsychotics (Malaysian Psychiatric Association, 2021). Apart from that, psychosocial therapy mainly psychoeducation is of crucial importance. This includes educating a schizophrenia patient regarding the symptoms, treatments, and prognosis of that illness. According to a study brief psychoeducation reduces relapse in the medium term and promote medication compliance in the short term (Zhao et al., 2015). On the other hand, other psychosocial approach includes supported employment, cognitive remediation therapy, social

skills training, peer support services, family therapy and counselling (Malaysian Psychiatric Association, 2021).

1.2 Schizophrenia and the Eye

Schizophrenia has been linked to visual processing impairment as evident by many previous studies (Adams and Nasrallah, 2018; Jurišić et al., 2020; Silverstein and Rosen, 2015). Multiple retinal functional and structural abnormalities are observed in schizophrenia patients which could be attributed to the visual symptoms (Adams and Nasrallah, 2018). The strongest association involves the markers of widened retinal venules, thinning of the RNFL, reduced macular volume and abnormal ERG (a and b) waveforms (Jurišić et al., 2020; Silverstein and Rosen, 2015). However, some of these can be associated to the illness itself, whereas others may be due to medication use or comorbid conditions. Apart from that, disrupted visual processing of the magnocellular pathway has been notable in schizophrenia patients which results in a decrease of contrast sensitivity, sensory processing, orientation discrimination, visual integration, trajectory and spatial localization, backward masking, and motion tracking (Jurišić et al., 2020).

There are postulations that this could be due to dopamine dysregulation, as there is evidence that dopamine is a major neurotransmitter and modulator in the retina (Ivanova et al., 2016). Biehlmaier et al have shown that rat model of Parkinsonism with dopaminergic deficiency loses a subset of retinal amacrine cells (Biehlmaier et al., 2007). Glutamate excess is identified act as a neurotoxin causing destruction of retinal ganglion cells (Ishikawa, 2013). Histological changes in the inner retinal of albino rats following intravitreal injection of

glutamate showed severe retinal degeneration particularly involving inner retina, amacrine cell, ganglion cell (Fernandez et al., 2009).

Chronic blockade of dopamine receptors in the retina could lead to reductions of dendrites, axonal and cell death. Thus, the usage of antipsychotics which is predominantly dopamine antagonists that block D2 receptors could reflect toxic effects of antipsychotic medications on neural and/or vascular structures within the retina (Silverstein et al., 2020) The permeability of most antipsychotic medications across the blood-retinal barrier is not known. Preliminary evidence suggests that at least some antipsychotic medications can have negative effects on retinal structures. Clozapine or fluphenazine use can lead to maculopathy (M. S. Lee and Fern, 2004; Tong et al., 2017). Atypical antipsychotics, aripiprazole, and thioridazine use have been linked to chorioretinopathy (Faure et al., 2015). Chlorpromazine, and haloperidol, lowers ERG amplitudes and prolongs latencies in healthy people (Silverstein et al., 2020).

1.3 Retinal Nerve Fibre Layer (RNFL) and Central Macula Thickness (CMT) in Schizophrenia

The retina is a unique structure of the central nervous system (CNS) as it contains axons and glia in the absence of myelin (Frohman et al., 2008). During embryonic development, the retina and optic nerve extend from the diencephalon, and are thus considered part of the CNS (London et al., 2013). Retinal ganglion cells (RGCs), the first neurons to arise from multipotent progenitors during retinal development which migrate across the retina, forming the ganglion cell layer (Hertz et al., 2014). RGCs extend axons toward the optic nerve head, eventually

forming the optic nerve connecting the eye to the brain (London et al., 2013). RGCs also proceed to form synaptic connections with presynaptic amacrine and bipolar interneurons (Hertz et al., 2014). The RNFL is made up of axons of RGC. RNFL leaves the globe as the optic nerve and synapse with the lateral geniculate body, mesencephalon, and hypothalamus in the CNS (London et al., 2013).

Similar to the CNS neurons, injury to RNFL or axon of ganglion cells will produce permanent degenerative changes manifested as thinning of RNFL (London et al., 2013). In neurodegenerative illness, reduction in peripapillary RNFL thickness can predict cortical atrophy as RNFL reflects axonal atrophy whereas a ganglion cell layer and inner plexiform layer (IPL) reflects neuronal atrophy occurring simultaneously (Celik et al., 2016; Frohman et al., 2008; Kalenderoglu et al., 2016)

.

The evaluation of RNFL thickness using optical coherence tomography (OCT) is a sensitive and non-invasive imaging modality that provides a cross sectional with a high-resolution image of the retina (Kalenderoglu et al., 2016) . It also studies the thickness profile of the RNFL, which is the axons of the RGC, and other retinal layer parameters thickness such as the ganglion cell layer (body of ganglion cells) and inner plexiform layer (dendrites of ganglion cells) (Frohman et al., 2008).

.

RNFL thickness is a morphological measurement which can be affected in the early stages of many optic nerve conditions such as glaucoma and optic neuropathy (Na et al., 2011). RNFL and CMT in patients with schizophrenia studied by Lee et al. 2013 shows that there is

thinning of RNFL and CMT (W. W. Lee et al., 2013). On the contrary, another research only documented reduced macular thickness measurements but did not indicate any significant change in RNFL or choroid in patients with schizophrenia (Topcu-Yilmaz et al. 2019).

A study done by Lubman et al. 2002, shows that nearly 30% of all MRI brain scans of schizophrenic patients especially chronic ones were reported as abnormal by radiologists (Lubman et al., 2002) Progressive neurodegeneration in schizophrenia could be measurable in the retina through the study of RNFL and CMT since it lacks myelin. Any changes in the RNFL will reflect axonal damage, providing us a window to the brain.

1.4 Visual Evoked Potential (VEP) in Schizophrenia

Functional integrity of the visual system can be monitored with VEP. VEP is an objective, non-invasive, simple technique used to evaluate the functional integrity of the visual system and graphically illustrates cerebral electrical potentials produced by the occipital cortical areas evoked visually. It evaluates the bioelectrical activity of the retinal ganglion cells and optic nerve (Donnell J. Creel, 2016). Visual evoked electrophysiological signals obtained from the electroencephalographic activity in the visual cortex are recorded from the overlying scalp (Mendes et al., 2009).

PVEP checkerboard is elicited by checkerboard stimuli with large 1° (60 min of arc) and small 0.25° (15 min of arc) checks (Donnell J. Creel, 2016; Mendes et al., 2009). The PVEP consists of a prominent positive peak latency component at approximately 100ms (P100), preceded by negative peak latency (N75) and followed by another negative peak latency (N135). The amplitudes are N75-P100 and P100- N135. (Donnell J. Creel, 2016)

Dysfunction of visual pathway in schizophrenia could be evaluated with the VEP (Babhulkar et al., 2017) . The functional assessment of early visual dysfunctions in schizophrenia could be demonstrated by alterations of the VEP component P1 at the occipital region. Disturbances of magnocellular pathway which is linked to higher order visual processing has been demonstrated in schizophrenia patients using different visual stimuli of VEP testing (Butler et al., 2001). Magnocellular related ganglion cell death was postulated (Butler et al., 2001).

Multiple studies have shown impairment of VEPs in patients of schizophrenia as compared to healthy controls in the past (Babhulkar et al., 2017; González-Hernández et al., 2014; Rady et al., 2012). The early marker of this impairment has been hypothesized in the variations of topographical form of P100 component of VEP (González-Hernández et al. 2014).

1.5 Rationale of Study

Despite intensive study and research done to investigate the pathogenesis of schizophrenia, no pinpointed specific theory exists (Gupta and Kulhara, 2010). A critical analysis done by Gupta et al. concluded that, schizophrenia is a complex and unique disorder that cannot be explained by a single process of development or degeneration (Gupta and Kulhara, 2010).

In a study done by Roiz et al. 2014 whereby a three-year longitudinal volumetric MRI study in first episode schizophrenia patient revealed that clinical and cognitive outcomes were not associated with progressive brain volume changes during the early years (Roiz-Santiáñez

et al., 2014). Hence the calculation of gray matter volume is difficult to determine using imaging techniques such as MRI as it does not accurately correlate with schizophrenia clinically. Furthermore, MRI is not readily available and costly to be used as a potential biomarker for schizophrenia.

Neurodegenerative diseases could be studied through evaluation of retinal status since it lacks myelin. Thus, any neurodegenerative changes that occurs in the brain can be observed directly by degenerative changes of the RGC. Parallel decrease can be seen in the RGC and the RNFL as it reflects neuronal and axonal atrophy respectively (Celik et al., 2016; Kalenderoglu et al., 2016).

Spectral domain OCT enables to demonstrate significant decrease in GCL, IPL and RNFL volume in schizophrenia patients (Bodis-Wollner and and Antal, 2006; Ngoo et al., 2019; Qarni Fadil et al., 2020). Disturbances of visual pathway in schizophrenia can be observed with visual evoked potential (VEP). The disturbance of visual pathway in schizophrenia could also be evaluated by the alterations of the visual evoked potential (VEP) component P1 at the occipital region (Babhulkar et al., 2017; González-Hernández et al., 2014; Rady et al., 2012).

The disturbances of visual pathway detected by the VEP could be possibly directly related to the associated retinal ganglion cell death if they are correlated. This study aims to prove that schizophrenia causes generalized neurodegeneration which include optic nerve

using non-invasive imaging. RNFL, CMT and VEP evaluation has the potential to be a neurodegenerative biomarker in schizophrenia to assist clinicians.

REFERENCES

Adams, S. A., & Nasrallah, H. A. (2018, May 1). Multiple retinal anomalies in schizophrenia. *Schizophrenia Research*. Elsevier B.V. doi:10.1016/j.schres.2017.07.018

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of DSM 5*. Washington DC.

Babhulkar, S., Kothari, R., & Khairkar, P. (2017). Atypical waveform morphology in schizophrenia-visual evoked potential as a promising endophenotype. *Industrial Psychiatry Journal*, **26**(**2**), 155. doi:10.4103/ipj.ipj_37_17

Biehlmaier, O., Alam, M., & Schmidt, W. J. (2007). A rat model of Parkinsonism shows depletion of dopamine in the retina. *Neurochemistry International*, **50**(**1**), 189–195. doi:10.1016/j.neuint.2006.08.001

Bodis-Wollner, I., & and Antal, A. (2006). . *Optic nerve and central nervous dysfunctions: Parkinson's disease and multiple sclerosis.* (Vol. 2). Principles and practice of clinical electrophysiology of vision,.

Brisch, R., Saniotis, A., Wolf, R., Bielau, H., Bernstein, H. G., Steiner, J., … Gos, T. (2014, January 1). The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: Old fashioned, but still in vogue. *Frontiers in Psychiatry*. Frontiers Media S.A. doi:10.3389/fpsyt.2014.00047

Butler, P. D., & Javitt, D. C. (2005). *Early-stage visual processing deficits in schizophrenia*.

Cahn, W., Hilleke, ;, Hulshoff Pol, E., Elleke, ;, Lems, B. T. E., Neeltje, ;, … Kahn, R. S. (2002). *Brain Volume Changes in First-Episode Schizophrenia A 1-Year Follow-up Study*.

Celik, M., Kalenderoglu, A., Sevgi Karadag, A., Bekir Egilmez, O., Han-Almis, B., & Şimşek, A. (2016). Decreases in ganglion cell layer and inner plexiform layer volumes correlate better with disease severity in schizophrenia patients than retinal nerve fiber layer thickness: Findings from spectral optic coherence tomography. *European Psychiatry*, **32**, 9–15. doi:10.1016/j.eurpsy.2015.10.006

Correll, C. U., & Schooler, N. R. (2020). Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatric Disease and Treatment*. Dove Medical Press Ltd. doi:10.2147/NDT.S225643

Deutsch, S. I., Rosse, R. B., Schwartz, B. L., & Mastropaolo, J. (2001). *A Revised Excitotoxic Hypothesis of Schizophrenia: Therapeutic Implications*.

Donnell J. Creel. (2016). Visually evoked potentials. Webvision: The Organization of the Retina and Visual System

Faure, C., Audo, I., Zeitz, C., Letessier, J. B., & Robert, M. P. (2015). Aripiprazole-induced chorioretinopathy: multimodal imaging and electrophysiological features. *Documenta Ophthalmologica*, **131**(**1**), 35–41. doi:10.1007/s10633-015-9494-x

Fernandez, D. C., Chianelli, M. S., & Rosenstein, R. E. (2009). Involvement of glutamate in retinal protection against ischemia/reperfusion damage induced by post-conditioning. *Journal of Neurochemistry*, **111**(**2**), 488–498. doi:10.1111/j.1471-4159.2009.06334.x

Frohman, E. M., Fujimoto, J. G., Frohman, T. C., Calabresi, P. A., Cutter, G., & Balcer, L. J. (2008). Optical coherence tomography: A window into the mechanisms of multiple sclerosis. *Nature Clinical Practice Neurology*. doi:10.1038/ncpneuro0950

González-Hernández, J. A., Pita-Alcorta, C., Wolters, C. H., Padrón, A., Finalé, A., Galán-García, L., Lencer, R. (2014). Specificity and sensitivity of visual evoked potentials in the diagnosis of schizophrenia: Rethinking VEPs. *Schizophrenia Research*, **166**(**1–3**), 231–234. doi:10.1016/j.schres.2015.05.007

Gupta, S., & Kulhara, P. (2010, January 1). What is schizophrenia: A neurodevelopmental or neurodegenerative disorder or a combination of both A critical analysis. *Indian Journal of Psychiatry*. doi:10.4103/0019-5545.58891

Heinz, A. (2002). Dopaminergic dysfunction in alcoholism and schizophrenia-psychopathological and behavioral correlates.

Hertz, J., Qu, B., Hu, Y., Patel, R. D., Valenzuela, D. A., & Goldberg, J. L. (2014). Survival and integration of developing and progenitor-derived retinal ganglion cells following transplantation. *Cell Transplantation*, **23**(**7**), 855–872. doi:10.3727/096368913X667024

Ishikawa, M. (2013). Abnormalities in Glutamate Metabolism and Excitotoxicity in the Retinal Diseases. *Scientifica*, **2013**, 1–13. doi:10.1155/2013/528940

Ivanova, E., Yee, C. W., & Sagdullaev, B. T. (2016). Disruption in dopaminergic innervation during photoreceptor degeneration. *Journal of Comparative Neurology*, **524**(**6**), 1208–1221. doi:10.1002/cne.23899

Jurišić, D., Ćavar, I., Sesar, A., Sesar, I., Vukojević, J., & Ćurković, M. (2020). New insights into schizophrenia: A look at the eye and related structures. *Psychiatria Danubina*, **32**(**1**), 60–69. doi:10.24869/psyd.2020.60

Kalenderoglu, A., Sevgi-Karadag, A., Celik, M., Egilmez, O. B., Han-Almis, B., & Ozen, M. E. (2016). Can the retinal ganglion cell layer (GCL) volume be a new marker to detect

neurodegeneration in bipolar disorder? *Comprehensive Psychiatry*, **67**, 66–72. doi:10.1016/j.comppsych.2016.02.005

Kane, J. M., & Correll, C. U. (2010). Pharmacologic treatment of schizophrenia. *Dialogues in Clinical Neuroscience*, **12**(**3**), 345–357. doi:10.31887/DCNS.2010.12.3/jkane

Kasai, K., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Lee, C.-U., Ciszewski, A. A., McCarley, R. W. (2003). *Article Progressive Decrease of Left Superior Temporal Gyrus Gray Matter Volume in Patients With First-Episode Schizophrenia*. *Am J Psychiatry* (Vol. 160). Retrieved from http://ajp.psychiatryonline.org

Lakhan, S. E., & Vieira, K. F. (2009, May 15). Schizophrenia pathophysiology: Are we any closer to a complete model? *Annals of General Psychiatry*. doi:10.1186/1744-859X-8-12

Lee, M. S., & Fern, A. I. (2004). Fluphenazine and its toxic maculopathy. *Ophthalmic Research*, **36**(**4**), 237–239. doi:10.1159/000078784

Lee, W. W., Tajunisah, I., Sharmilla, K., Peyman, M., & Subrayan, V. (2013a). Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: Evidence from optical coherence tomography. *Investigative Ophthalmology and Visual Science*, **54**(**12**), 7785–7792. doi:10.1167/iovs.13-12534

Lee, W. W., Tajunisah, I., Sharmilla, K., Peyman, M., & Subrayan, V. (2013b). Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: Evidence from optical coherence tomography. *Investigative Ophthalmology and Visual Science*, **54**(**12**), 7785–7792. doi:10.1167/iovs.13-12534

Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., & Davis, J. M. (2012). Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *The Lancet*, **379**, 2063–2071. doi:10.1016/S0140

Lieberman, J., Chakos, M., Wu, H., Alvir, J., Hoffman, E., Robinson, D., & Bilder, R. (2001). *ZISKIND SOMERFELD RESEARCH AWARD Longitudinal Study of Brain Morphology in First Episode Schizophrenia*. *Biol Psychiatry* (Vol. 49).

London, A., Benhar, I., & Schwartz, M. (2013, January). The retina as a window to the brain - From eye research to CNS disorders. *Nature Reviews Neurology*. doi:10.1038/nrneurol.2012.227

Lubman, D. I., Velakoulis, D., McGorry, P. D., Smith, D. J., Brewer, W., Stuart, G., Pantelis, C. (2002). Incidental radiological findings on brain magnetic resonance imaging in first-episode psychosis and chronic schizophrenia. *Acta Psychiatrica Scandinavica*, **106**(**5**), 331–336. doi:10.1034/j.1600-0447.2002.02217.x

Maiocco, S., Shelley, E., Salmond, S., Jewell, S. T., Caldwell, B., & Lieggi, M. (2017, June 1). Experiences of stigma among family members of persons living with schizophrenia: A systematic review protocol. *JBI Database of Systematic Reviews and Implementation Reports*. Joanna Briggs Institute. doi:10.11124/JBISRIR-2016-003150

Malaysian Psychiatric Association. (2009). *Clinical Practice and Guidelines Management of Schizophrenia in Adults*.

Malaysian Psychiatric Association. (2021). *Clinical Practice Guidelines Management of Schizophrenia (Second Edition)*. Retrieved from https://www.psychiatry-malaysia.org

McCutcheon, R. A., Reis Marques, T., & Howes, O. D. (2020, February 1). Schizophrenia - An Overview. *JAMA Psychiatry*. American Medical Association. doi:10.1001/jamapsychiatry.2019.3360

Mendes, T. S., de Almeida Sobrinho, E. F., Rosa, A. A. M., Anjos, L. M., Costa, G. M., de Silva Souza, G. de Lima Silveira, L. C. (2009). Dengue maculopathy: Visual electrophysiology and optical coherence tomography. *Documenta Ophthalmologica*, **119**(**2**), 145–155. doi:10.1007/s10633-009-9178-5

Na, J. H., Sung, K. R., Baek, S., Sun, J. H., & Lee, Y. (2011). Macular and retinal nerve fiber layer thickness: Which is more helpful in the diagnosis of glaucoma? *Investigative Ophthalmology and Visual Science*, **52**(**11**), 8094–8101. doi:10.1167/iovs.11-7833

Ngoo, Q. Z., Wan Hitam, W. H., & Ab Razak, A. (2019). Evaluation of Retinal Nerve Fiber Layer Thickness, Electroretinogram and Visual Evoked Potential in Patients with Alzheimer's Disease. *Journal of Ophthalmology*, **2019**. doi:10.1155/2019/6248185

Park, S. C., Jang, E. Y., Kim, K., Lee, H., Choi, J., Dan, A., Park, Y. C. (2019). Establishing the cut-off scores for the severity ranges of schizophrenia on the BPRS-6 scale: findings from the REAP-AP. *Psychiatry and Clinical Psychopharmacology*, **29**(**4**), 895–898. doi:10.1080/24750573.2019.1695994

Pratt, J., Dawson, N., Morris, B. J., Grent T'jong, T., Roux, F., & Uhlhaas, P. J. (2017). *Schizophrenia Research Special Thematic Issue title "Pathologies of the Thalamus in Schizophrenia" 'Thalamo-Cortical Communication, Glutamatergic Neurotransmission and Neural Oscillations: A Unique Window into the Origins of ScZ?' 1*.

Qarni Fadil, A., Hazabbah Wan Hitam, W., Ab Razak, A., & Faruque Reza, M. (2020). *Evaluation of Retinal Nerve Fiber Layer Thickness and Visual Evoked Potential in Patients with Bipolar Disorder*.

Rady, A., Elsheshai, A., Elkholy, O., Abou El Wafa, H., & Ramadan, I. (2012). P-1293 - Visual processing in schizophrenia assessed by visual evoked potential. *European Psychiatry*, **27**, 1. doi:10.1016/s0924-9338(12)75460-3

Roiz-Santiáñez, R., Ayesa-Arriola, R., Tordesillas-Gutiérrez, D., Ortiz-García De La Foz, V., Pérez-Iglesias, R., Pazos, A., Crespo-Facorro, B. (2014). Three-year longitudinal population-based volumetric MRI study in first-episode schizophrenia spectrum patients. *Psychological Medicine*, **44**(**8**), 1591–1604. doi:10.1017/S0033291713002365

Silverstein, S. M., Fradkin, S. I., & Demmin, D. L. (2020). Schizophrenia and the retina: Towards a 2020 perspective. *Schizophrenia Research*, **219**, 84–94. doi:10.1016/j.schres.2019.09.016

Silverstein, S. M., & Rosen, R. (2015, June 1). Schizophrenia and the eye. *Schizophrenia Research: Cognition*. Elsevier Inc. doi:10.1016/j.scog.2015.03.004

Stone, W. S., Phillips, M. R., Yang, L. H., Kegeles, L. S., Susser, E. S., & Lieberman, J. A. (2022, May 1). Neurodegenerative model of schizophrenia: Growing evidence to support a revisit. *Schizophrenia Research*. Elsevier B.V. doi:10.1016/j.schres.2022.03.004

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., Carpenter, W. (2013, October). Definition and description of schizophrenia in the DSM-5. *Schizophrenia Research*. doi:10.1016/j.schres.2013.05.028

Teoh, S. L., Chong, H. Y., Aziz, S. A., Chemi, N., Othman, A. R., Zaki, N. M., Chaiyakunapruk, N. (2017). The economic burden of schizophrenia in Malaysia. *Neuropsychiatric Disease and Treatment*, **13**, 1979–1987. doi:10.2147/NDT.S137140

Tong, J. Y., Pai, A., Heydon, P., & Young, S. H. (2017). Clozapine-induced maculopathy. *Medical Journal of Australia*, **206**(**6**), 246-246.e1. doi:10.5694/MJA16.00563

Topcu-Yilmaz, P., Aydin, M., & Cetin Ilhan, B. (2019). Evaluation of retinal nerve fiber layer, macular, and choroidal thickness in schizophrenia: spectral optic coherence tomography findings. *Psychiatry and Clinical Psychopharmacology*, **29**(**1**), 28–33. doi:10.1080/24750573.2018.1426693

Uher, R. (2014). Gene-environment interactions in severe mental illness. *Frontiers in Psychiatry*. Frontiers Research Foundation. doi:10.3389/fpsyt.2014.00048

Vita, A., & Barlati, S. (2018, May 1). Recovery from schizophrenia: Is it possible? *Current Opinion in Psychiatry*. Lippincott Williams and Wilkins. doi:10.1097/YCO.0000000000000407

Woods, B. T., Ward, K. E., & Johnson, E. H. (2005). Meta-analysis of the time-course of brain volume reduction in schizophrenia: Implications for pathogenesis and early treatment. *Schizophrenia Research*, **73**(**2–3**), 221–228. doi:10.1016/j.schres.2004.05.014

Wright, I. C., Psych, M. R. C., Rabe-Hesketh, S., Woodruff, P. W. R., David, A. S., Psych, F. R. C., Bullmore, E. T. (2000). *Meta-Analysis of Regional Brain Volumes in Schizophrenia*. *Am J Psychiatry* (Vol. 157).

Zhao, S., Sampson, S., Xia, J., & Jayaram, M. B. (2015, April 9). Psychoeducation (brief) for people with serious mental illness. *Cochrane Database of Systematic Reviews*. John Wiley and Sons Ltd. doi:10.1002/14651858.CD010823.pub2

CHAPTER 2

OBJECTIVES