Examensarbete

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Schizophrenia-like psychosis of epilepsy: Functional abnormalities and structural changes

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Abstract

Psychosis has intrigued and confused neuroscientists for many years, yet there seems to be no clear explanation for why and how it occurs. There is also not just one disorder of psychosis, such as schizophrenia, some epileptic patients experience the same symptoms. That is called schizophrenia-like psychosis of epilepsy (SLPE), which is similar to primary schizophrenia but also very different. This systematic review will explain SLPE as a disorder in itself, compare it to other psychotic disorders, provide research findings and conclude what we can learn from better understanding psychosis in general.

[Keywords: schizophrenia-like psychosis of epilepsy, temporal lobe epilepsy, psychotic symptoms.]

Schizophrenia-like psychosis of epilepsy: Neural abnormalities and structural changes

Epilepsy

Epilepsy is a multidimensional disorder of the nervous system, which can manifest in a number of ways that lead to different symptoms. Epileptic patients suffer from recurrent seizures in the brain, these seizures can be either focal or generalized. Focal seizures start in one area of the brain and then spread across the brain structures and affect other areas in the same hemisphere. Focal seizures are confined to only one hemisphere, which is different from generalized seizures since the latter affects both hemispheres. Temporal lobe epilepsy (TLE) is the most common form of epilepsy in which the patient suffers from chronic and unprovoked focal seizures that originate in the temporal lobe. During a seizure it is common for the patient to exhibit alterations in posture and responsiveness, also changes in behavior and memory do occur (Stafstrom & Carmant, 2015).

Schizophrenia-like psychosis of epilepsy

Some epileptic patients also suffer from schizophrenia-like psychosis of epilepsy (SLPE). In this psychiatric disorder, epileptic patients experience similar symptoms to those that are present in primary schizophrenia. In primary schizophrenia there is a recurrence of psychotic episodes that can be described in two groups of symptoms, namely positive and negative symptoms. The positive symptoms that occur in schizophrenia are hallucinations (such as hearing voices or seeing something that is not really there), delusions (often bizarre convictions and paranoia) and disorganized speech and thoughts. These positive symptoms are commonly known as psychotic symptoms, due to the presence of the same symptoms in other psychotic disorders, such as SLPE. The negative symptoms are affective flattening (less emotional expression, eye contact and minimum use of body language), avolition (inability to participate in goal-directed activities, such as work or school) and alogia (poverty of speech) (Maguire et al., 2018).

SLPE patients share some of the clinical symptoms that are present in primary schizophrenia, which is the reason behind the name of the disorder. The clinical symptoms that are the same in both disorders are those that are classified as “positive symptoms" in primary schizophrenia. Often visual or auditory hallucinations. SLPE patients rarely experience the “negative symptoms" of primary schizophrenia (Maguire et al., 2018). Other

differences between the disorders are the later onset of psychotic symptoms in SLPE patients compared to schizophrenic patients and the fact that SLPE patients suffer from psychotic symptoms due to their epileptic seizures, which is not the case for primary schizophrenic patients (Kanner & Rivas-Grajales, 2016). Depending on the relationship between the onset of psychotic symptoms and seizure occurrence, SLPE could be further divided into the subcategories: Ictal (during the seizure), interictal (between seizures) and postictal (after seizure) psychosis. Interictal psychosis (IIP) is the one that most resembles that of primary schizophrenia due to its independence of seizure occurrence (Kandratavicius et al., 2014). Therefore, SLPE and IIP refer to the same syndrome and this study will mainly use the term SLPE to avoid confusion.

Due to the fact that primary schizophrenia shares some of the symptoms that are present in SLPE, schizophrenia will also be mentioned in this study. Even though it will not be the focus or one of the main topics. Some of the studies that will be included have for example patient groups with primary schizophrenia so that they can compare them to patients with SLPE.

How does neuroscience view schizophrenia-like psychosis of epilepsy?

Sachdev (1998) states that the relationship between epilepsy and schizophrenia-like psychosis of epilepsy (SLPE) is something that has been up for discussion in the scientific community since the 19th century. SLPE occurs in 4-10% of epilepsy patients with either focal or generalized seizures, but it seems to be even more common in patients with temporal lobe epilepsy (TLE). SLPE closely resembles primary schizophrenic disorder on a clinical level, but the underlying pathophysiological mechanisms have not been established.

Flügel, Cercignani, et al. (2006) wrote in their article that the cognitive abnormalities in primary schizophrenia and SLPE have been investigated and established, while neural correlates of SLPE in TLE patients are still unknown. They used magnetization transfer imaging (MTI) in their study to categorize the pattern of cognitive deficits in TLE patients with SLPE and compared it to non-psychotic TLE patients. They also used the Positive and Negative Syndrome Scale (PANSS) to assess the patients' psychiatric symptoms, which is a scale that is normally used to assess the severity of primary schizophrenia. It consists of a "positive scale" (positive symptoms), a "negative scale" (negative symptoms) and a "general psychopathology scale", making it possible to assess both the psychotic symptoms and the general mental health of the patient. The results showed that patients with SLPE were more

cognitively impaired than non-psychotic patients. This was clearly apparent in the executive (spatial span task) and semantic memory (verbal fluency task) tasks that the participants performed. These findings had a strong correlation with the MTI findings since these showed a reduction of brain activity in the left fusiform gyrus. This brain area is known for its role in object and face recognition, but also semantic memories. They also found magnetization transfer ratio (MTR) reduction in the left middle and superior temporal gyri, which correlates to the SLPE patients performing badly in a verbal fluency task.

Another study by Canuet et al. (2011) used electroencephalography (EEG) to investigate cognitive abnormalities in epileptic patients with SLPE. This study wanted to examine abnormal patterns of resting-state EEG oscillatory activity and functional activity in SLPE patients. Before recording the EEG the patients were psychologically assessed using the Brief Psychiatric Rating Scale (BPRS). In this scale, there are four groups of symptoms consisting of “positive symptoms”, “negative symptoms”, “disorganization” and “affect”. In this study they found increased connectivity between the temporal and the prefrontal regions in the right hemisphere in SLPE patients compared to the non-psychotic patients. There was also increased interhemispheric phase synchronization between the auditory cortex in the affected temporal lobe and Broca’s area. The increased connectivity between temporal and prefrontal regions was correlated to the patients’ scores of “positive symptoms", while the increased interhemispheric synchronization between the auditory cortex and Broca’s area correlated with the patients’ “hallucination scores”. They also found dysfunction in parts of the default mode network (DMN) that are located in the parietal lobe, indicating that the DMN might play a role in SLPE.

Maguire et al. (2018) suggest that the dopamine circuits in the brain play a role in SLPE since the dopamine circuitry’s relation to schizophrenia is already well established. The dopamine circuitry, or dopaminergic pathways, in the brain consists of sets of individual dopamine neurons. These pathways are involved in many different processes that are important for the brain to function properly, including motivation, executive functions, movement and cognition. One of these pathways is the mesolimbic pathway, which connects the ventral tegmental area (VTA) which is located in the midbrain, to the ventral striatum and the basal ganglia in the forebrain. This means that there are a lot of mesolimbic structures that are affected when there is a disturbance in this particular pathway, such as the amygdala and hippocampus. These structures are also affected by seizures located in the temporal lobe. When the positive symptoms of schizophrenia are present in the absence of

seizures, it has been coupled with a reduction in dopamine activity in the dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC). This pattern of activity might explain the dysexecutive cognitive deficits that may appear in psychotic disorders since many of the executive functions are located in the prefrontal cortex. While there is a reduction of dopamine activity in DLPFC and VLPFC, there is an overactivity in the mesolimbic dopaminergic pathway. This overactivity might explain the positive symptoms of delusions and hallucinations (Maguire et al., 2018).

The main question that will be investigated in this study is whether epileptic patients with SLPE differ from epileptic patients without any psychotic symptoms. This will be specifically investigated in terms of cognitive functions and neural abnormalities. If we could understand what exactly creates the shared symptoms of SLPE, schizophrenia and other psychotic disorders, we would have a better understanding of psychosis in general.

The importance of further investigation to establish clear distinctions between SLPE and primary schizophrenia is stated in Maguire et al. (2018). In Maguire et al. (2018) it is stated that there is an increased risk for misdiagnosis in SLPE patients due to the resemblance to schizophrenia, this is coupled with the problems in the medications used. More specifically that some antiepileptic drugs may increase psychotic symptoms, while some antipsychotics may increase seizures. To investigate the phenomenon that is SLPE could thereby help us better understand other psychotic disorders and it could also help in the treatment of patients suffering from SLPE.

This study aims to further investigate the relationship between TLE and SLPE, to distinguish TLE patients with SLPE from TLE patients without it. This will be done by comparing results from brain imaging techniques between the patient groups, coupled with their performances in tasks and scores on psychopathological assessment scales.

This present systematic review will also investigate the neural correlates of SLPE patients and how they differ from other patient groups. This is in terms of structural abnormalities such as volumetric decreases or increases, enlargement of ventricles and how intact neural structures are. As well as structural abnormalities will be discussed in this review, so will functional abnormalities. Both important regions, such as the auditory cortex, Broca's area, hippocampus, amygdala, left fusiform gyrus and superior temporal gyri, also the mesolimbic dopaminergic pathway. As well as functional processes will be investigated, e.g.

dysfunction in limbic structures, frontal control mechanisms, parts of the DMN and impairment in cognitive functioning.

Methods

Search strategy

The electronic databases Web of Science and Medline EBSCO were used to find information on the topic. The following numbers of results were retrieved from Web of Science and Medline EBSCO on March 10th 2022.

When using the search string ("Schizophrenia-like psychosis of epilepsy" OR "interictal psychosis" OR SLPE AND epilepsy OR seizures OR epileptic) there were 134 results on Web of Science. Using the same search string on Medline EBSCO resulted in 105 articles, making the total number of articles 239.

This was the number of articles after applying the limitations in years and language. The literature will not be limited to only newer publications since several important findings in this area were published in 1996 or 1998. Because of that this study will at least include articles from 1990. In terms of language, this study will only include articles available in English since the majority of scientific publications are written in or translated into that language.

These results were then exported to EndNote Web to be further managed. When choosing to delete all duplicates from the results in EndNote, the program found 19 duplicates. Removing those changed the number of articles to 220. After that, another 69 duplicates were removed manually, making the total number of duplicates 88.

After removing the duplicates there were 151 articles left. Out of those 151 articles, 114 were excluded according to my inclusion and exclusion criteria stated below. The title and abstract were searched to see if the study fulfilled this study's PICO criteria, in terms of patient group, types of interventions and measures and also outcomes. All articles that did not fit the PICO model were excluded, leaving 37 articles to be further assessed.

Out of those 37 articles, 28 were excluded in total for the following reasons. Three were excluded due to the studies focusing mostly on comparing the duration of psychotic episodes between patients, rather than comparing psychotic patients to non-psychotic ones. Eleven articles were excluded since their focus was on the treatment and medications used in SLPE patients, which is not what will be researched in this paper.

12 articles were excluded because there was a focus on other neurological or psychological disorders than epilepsy and SLPE (e.g. Alzheimer's disease, Parkinson's disease, primary schizophrenia).

Finally, two articles were excluded since they could not be accessed in full text, only abstract. Making the number of articles that will be included in this paper 9. The steps in this process are accounted for in Figure 1.

Inclusion and exclusion criteria

Only peer-reviewed original articles that fit the PICO model will be included in this paper.

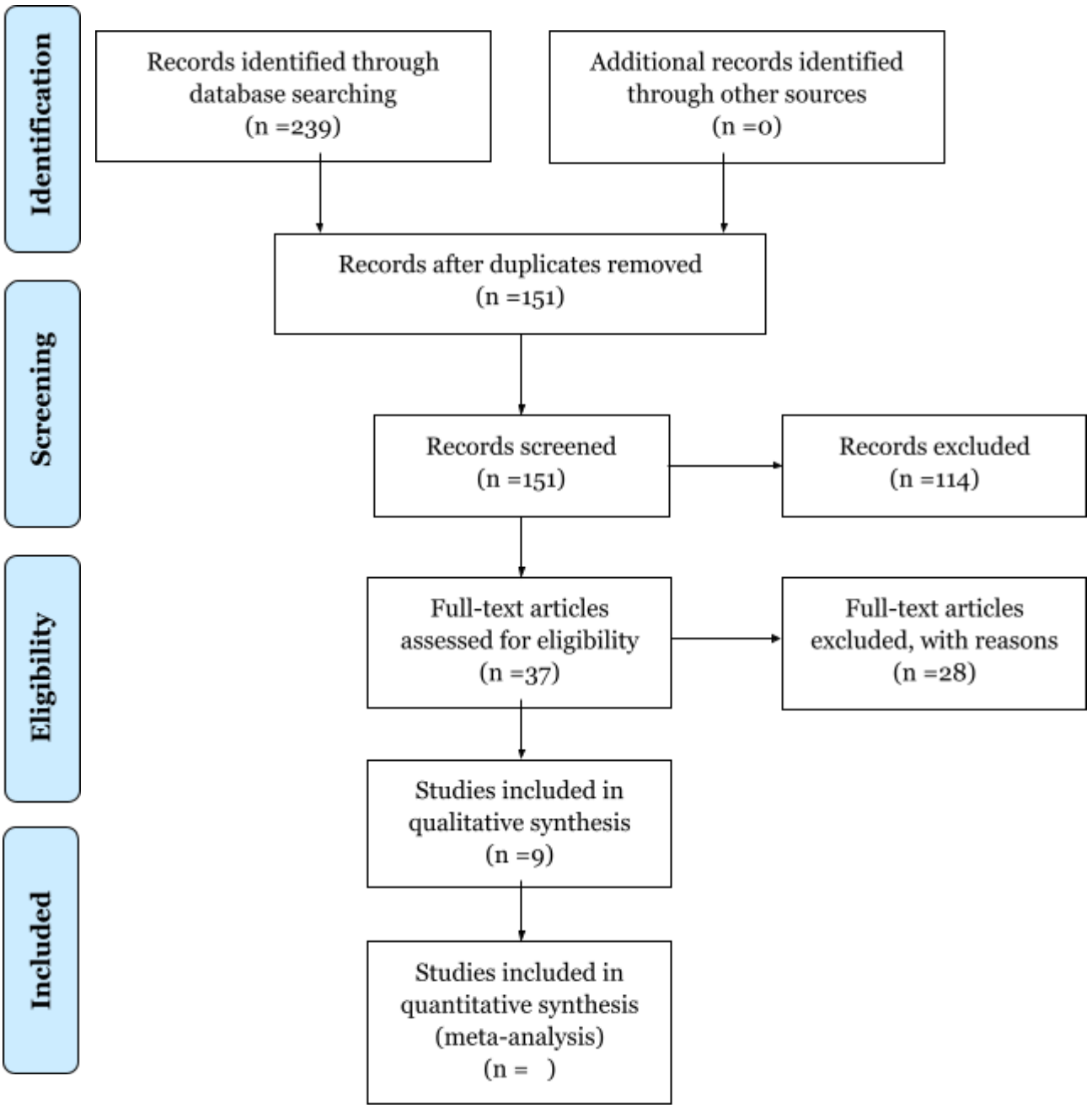
P: Patients with temporal lobe epilepsy.
I: Brain imaging methods (MTI, EEG) coupled with scales for psychopathological assessment (e.g. Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale).
C: Patients with or without SLPE.
O: Neural differences in temporal regions (e.g. hippocampal area, fusiform gyrus) and functional abnormalities in areas typically associated with SLPE symptoms (e.g. primary auditory cortex and Broca's area)

Data extraction

The data that will be extracted from the articles are the types of measure being used in the study (brain imaging methods, EEG, MTI) and the types of interventions used in the study (psychopathological assessment scales, Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale). The functional neural differences and cognitive abnormalities between the two patient groups (epileptic patients with or without SLPE) will be extracted as the outcome of the types of measures and interventions.

Figure 1

PRISMA 2009 Flow Diagram: standard flow diagram used to document the literature search process. Use the following citation: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097



Results

Table 1

Summary of the studies and central findings

Study	Aim of the study	Types of measure	Patient group	Outcome
Adachi, N., Akanuma, N., Ito, M., Okazaki, M., Kato, M., & Onuma, T. (2012)	To examine clinical factors and duration of SLPE.	EEG.	SLPE patients and epileptic patients without psychotic symptoms.	Individual vulnerability could increase the duration of psychotic episodes.
Allebone, J., Kanaan, R. A., Maller, J. J., O'Brien, T., Mullen, S., Cook, M., Adams, S., Vogrin, S., Vaughan, D., Connelly, A., Kwan, P., Berkovic, S. F., D'Souza, W., Jackson, G., Velakoulis, D., & Wilson, S. J. (2020)	Previous studies have shown conflicting results about volume reduction in hippocampus in SLPE patients, this study wanted to determine the effects of SLPE to the hippocampal structures.	MRI and EEG.	SLPE patients and epileptic patients without psychotic symptoms.	SLPE patients had larger hippocampal fissure than the other group.
Butler, T., Weisholtz, D., Isenberg, N., Harding, E., Epstein, J., Stern, E., & Silbersweig, D. (2012)	To assess findings from previous studies, provide classifications for epilepsy-related psychosis. Report findings from research in their own laboratory and give further	PET, fMRI and intracranial EEG.	Patients with SLPE or schizophrenia.	Volumetric changes bilaterally or left-sided in temporal lobes. Increased volume in amygdalae. Abnormal activity in limbic structures. (Dopamine) Impaired frontal lobe control mechanisms.

	directions.			
Canuet, L., Ishii, R., Pascual-Marqui, R. D., Iwase, M., Kurimoto, R., Aoki, Y., . . . Takeda, M. (2011)	To examine abnormal patterns of resting-state EEG oscillatory activity and functional activity in SLPE patients.	EEG and Brief Psychiatric Rating Scale (BPRS).	Patients with SLPE and a healthy control group.	Increased synchronization from the right auditory cortex to Broca's area. Increased synchronization in the right hemisphere, medial temporal cortex → ACC, and mPFC. Dysfunction in lateral parietal structures associated with the DMN.
Flügel, D., O'Toole, A., Thompson, P. J., Koepp, M. J., Cercignani, M., Symms, M. R., & Foong, J. (2006)	To investigate patterns of cognitive deficits in TLE patients with SLPE using MTI.	MTI.	SLPE patients and epileptic patients without psychotic symptoms.	MTR reduction in left fusiform gyrus, impaired episodic memory.
Flügel, D., Cercignani, M., Symms, M. R., Koepp, M. J., & Foong, J. (2006)	To further investigate structural abnormalities in SLPE using MTR. Also, to establish whether the findings were different between the two groups.	MRI, MTI, and MTR. Also Positive and Negative Syndrome Scale (PANSS).	Patients with SLPE and a healthy control group.	Reduced MTR in left temporal lobe, left middle and superior temporal gyri.
Gutierrez-Galve, L., Flugel, D., Thompson,	To determine whether cortical abnormalities are more severe	SBM, CANTAB and PANSS.	TLE patients with SLPE, TLE patients without psychosis and a	Frontal cortical thinning, specifically in inferior frontal

P. J., Koepp, M. J., Symms, M. R., Ron, M. A., & Foong, J. (2012)	and widespread in TLE patients with SLPE.		healthy control group.	gyrus (IFG).
Marsh, L., Sullivan, E. V., Morrell, M., Lim, K. O., & Pfefferbaum, A. (2001)	To examine if there are specific temporal abnormalities that are common in SLPE. Also if there is shared neuropathology between SLPE patients and schizophrenic patients.	MRI.	SLPE patients, TLE patients without psychosis, patients with schizophrenia and a healthy control group.	Cortical gray matter abnormalities were greater in SLPE patients, also enlargement in ventricles. Suggesting deficits in SLPE is cortical rather than in limbic structures.
Nathaniel-James, D. A., Brown, R. G., Maier, M., Mellers, J., Toone, B., & Ron, M. A. (2004)	To determine the contribution of psychosis to cognitive functions.	Verbal, memory and executive function tasks.	SLPE patients, TLE patients without psychosis, patients with schizophrenia and a healthy control group.	The neuropsychological impairments in SLPE patients resemble those in other psychotic patients. These are verbal, memory and executive function impairments.

Structural findings in schizophrenia-like psychosis of epilepsy

In Butler et al. (2012) it is stated that psychosis, in general, is important to have a better understanding of. Both structural and functional neuroimaging studies are leaning toward dysfunction in frontal and medial temporal limbic brain regions as an explanation for psychotic symptoms emerging. When it comes to psychosis that is associated with TLE it might be better understood in the scientific community than primary psychosis, such as schizophrenia. Structural changes in SLPE suggest volumetric changes bilaterally or left-sided in the temporal lobe in these patients, compared to TLE patients without psychosis.

Continuing on the same route of exploring SLPE Gutierrez-Galve et al. (2012) aimed to establish whether cortical abnormalities occur in SLPE patients, but not in epileptic patients without psychosis and a healthy control group. This study mainly used the technique

of surface-based morphometry (SBM) to explore cortical parameters (volume, thickness and area) in all patient groups.

Not only have TLE patients been found to have a higher risk of developing SLPE, but patients with hippocampal sclerosis seem even more prone to experience these types of psychotic symptoms. Previous imaging studies have found both a loss in volume in the hippocampus and amygdala, but similar studies have also found an increase in volume for the amygdala bilaterally. Even though previous imaging research has had such varying results, Guiterrez-Galve et al. (2012) state that there is an interesting finding that was made thanks to that research.

What was shown in this study was that SLPE patients had more frontal cortical thinning than the healthy controls. Although previous studies have found decreases in cortical thickness in both temporal and frontal lobes, Guiterrez-Gavle et al. (2012) only found this decrease in the frontal lobe. Specifically, they found that there was a reduction of cortical thickness in the inferior frontal gyrus (IFG), this area contains Broca's area, which is an important hub for language processing. The IFG is located in the prefrontal cortex, which is believed to be responsible for a number of executive functions, such as working memory and mediating cognitive, emotional and sensory processing. All of which are relevant functions for the symptoms that SLPE patients exhibit.

They explain that the differences in their findings compared to others may be due to the smaller sample size that this study used. These differences could also be due to the method used in this study compared to the others, even if they also used brain imaging techniques. In this study, they used SBM instead of voxel-based morphometry (VBM), which was used in the other studies mentioned. Guiterrez-Galve et al. (2012) state that since SBM and VBM can detect different aspects of cortical abnormalities, this is probably a contributing factor for their findings being different from similar studies (Gutierrez-Galve et al., 2012).

Adachi et al. (2012) also examined what makes some epileptic patients more susceptible to psychosis while others are not. In their study, they aimed to investigate different clinical factors that may or may not cause psychosis to develop later in life. They did so using EEG and comparing SLPE patients with non-psychotic epileptic patients. What Adachi et al. (2012) found was that there are individual vulnerabilities that may not only

kindle psychosis but also impact the duration of the psychotic episodes. One important clinical factor is the age of onset for both epileptic seizures and psychotic episodes.

Another study that also focused on structural abnormalities in SLPE is Marsh et al. (2001), who wanted to examine what abnormalities could be found in the temporal regions in SLPE patients. Researchers used MRI to determine regional specificity for abnormalities, which were found to not only be constricted to the temporal lobe. Like several other studies published on the topic, Marsh et al. (2001) found that SLPE patients had gray matter volume deficits in the temporal lobe and frontoparietal lobe bilaterally, smaller superior temporal gyri and more enlarged lateral ventricles bilaterally. Volumetric changes like these are common findings in SLPE patients.

Continuing on structural findings, Flügel, Cercignani, et al. (2006) conducted an MTI study performed on patients with TLE and SLPE. In this study it is stated, like in many other studies, that SLPE seems to be more common in epileptic patients with a seizure focus in the temporal lobe. The researchers point out the advantages of advanced in vivo MRI to further understand the underlying mechanisms of SLPE. However, they also put a lot of focus on the technique of MTI. Since the latter allows more detailed visualization of structural changes in the brain. The aim of this study was to explore structural abnormalities in epileptic patients with and without psychosis, to see if there are differences between the two patient groups.

Not only did Flügel, Cercignani, et al. (2006) use MTI to investigate SLPE, they coupled this technique with a psychiatric evaluation scale. Namely the Positive and Negative Syndrome Scale (PANSS), which includes the symptoms that are generally associated with psychotic disorders. Since SLPE patients usually do not exhibit the negative symptoms that are common in schizophrenia, researchers in this study mainly focused on what the patients scored on the positive symptoms (hallucinations and delusions) on the scale. The findings in this study showed not a lot of differences in structural changes between the two patient groups. What was discovered was reduced MTR in the left temporal lobe, more specifically in the left middle and superior temporal gyri. This is similar to other findings that were found in schizophrenic patients (Flügel, Cercignani, et al., 2006).

Since structural findings have been so conflicting in SLPE research, Allebone et. al. (2020) aimed to examine further the volumetric differences that can be seen in SLPE patients but not in other patient groups. In this particular study, researchers wanted to especially

focus on the hippocampal structures since these have been shown in previous studies to have a loss in volume in these patients. The hippocampus is a key limbic structure and it has been observed to be affected in other psychotic disorders, such as schizophrenia and bipolar disorder, making it a relevant region to examine in psychosis of epilepsy.

For instance, it has been suggested that changes in the glutamate transmission in the dentate gyrus (where the hippocampus is also located), could cause faulty encoding of memories and possibly lead to delusional states of the mind. The hippocampal fissure, which is located in the dentate gyrus and supposed to fuse together over time, has been found to be larger in some schizophrenic and SLPE patients. Volume reduction in this region of the brain has been associated with hyperexcitability, suggesting that volume loss could make them more vulnerable to abnormal functioning, such as psychosis (Allebone et al., 2020).

Functional abnormalities found in schizophrenia-like psychosis of epilepsy

MTI was also used in Flügel, O'Toole, et al. (2006), where researchers wanted to further establish the cognitive impairments that affect SLPE patients. To do this they compared two patient groups with each other, SLPE patients and non-psychotic epileptic patients. In this study, researchers coupled the brain imaging technique with a battery of tests to assess the intellectual level, memory and executive function. They also used PANSS to score the participants' psychotic symptoms. The battery of tests included National Adult Reading Test (NART) which is used to test intellectual functioning, episodic memory functioning was tested in The Story Recall subtest and executive functions were tested in Spatial Span tasks and Verbal fluency tasks.

In this study, researchers found that the patient group consisting of SLPE patients obtained significantly lower scores in both episodic and semantic memory tasks. This was also true for the tasks that tested executive functioning. When coupling these scores with MTI, Flügel, O'Toole, et al. (2006) were able to give possible explanations for these cognitive deficits in SLPE patients. For instance, there was an MTR reduction in the left fusiform gyrus in SLPE patients, which is consistent with these patients performing worse than other groups on vocabulary tasks.

In another study, conducted by Canuet et al. (2011), researchers instead combined EEG with psychiatric scales to score hallucinatory symptoms. Making their results very interesting, since they were able to show with EEG that functional abnormalities in these

patients were consistent with the patients' scores. The scale that was used was the Brief Psychiatric Rating Scale (BPRS), which is used to assess four groups of symptoms, namely positive symptoms, negative symptoms, affective symptoms and disorganization. Since the core symptoms of SLPE are the positive symptoms (hallucinations and delusions) the researchers also took raw data from those scores for their analysis. In their functional connectivity analysis they included all 42 Brodmann areas in both hemispheres as regions of interest (ROI). The majority of the patients in this study had epilepsy with a focus on the temporal lobe. All patients in this study that exhibited hallucinatory symptoms had a verbal auditory type of hallucinations.

Their results showed that there was increased connectivity in several brain regions. For instance, there was increased synchronization in the right hemisphere from medial temporal cortex to anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC). This finding was correlated to the positive symptoms that the SLPE patients showed in BPRS. Canuet et al. (2011) also found increased synchronization from the right auditory cortex to Broca's area, this finding was also clearly correlated to the positive symptoms that are present in SLPE, namely auditory hallucinations.

Another interesting finding in this study was in association with the default mode network (DMN). Researchers suggest a cortical dysfunction in resting-state connectivity in SLPE patients, specifically for the areas in the lateral parietal cortex that are connected to DMN, this dysfunction disrupts the areas that are supposed to be active during rest. The lateral parietal cortex has earlier been established to be involved in functions such as working memory, spatial attention (cognition) and social cognition. Abnormal parietal activation has also been linked to the delusional state that psychotic patients (both schizophrenic and SLPE) may experience (Canuet et al., 2011).

Gutierrez-Galve et al. (2012) state that it has been shown in structural MRI studies that structural abnormalities in TLE patients with SLPE are not confined to the temporal lobe, which is the focus of epileptic seizures. These changes can also be seen in the frontal cortex. These findings line up with the cognitive deficits that these patients can display, which are not only functions that the temporal lobe is mainly responsible for. Memory impairment is usually attributed to the hippocampus, while deficits in language, executive functions, motor speed and a decline in IQ are extratemporal functions. These functions are more affected in TLE patients with SLPE than in non-psychotic epileptic patients.

Except for psychiatric evaluation that was made with PANSS, researchers also used a battery of tests to examine the executive functions of the patients. All tests were derived from the Cambridge Neuropsychological Test Battery (CANTAB). Working memory span was evaluated using a spatial span task while working memory manipulation was evaluated by a spatial working memory task. Verbal episodic memory was tested using the story recall test. However, the scores obtained by the cognitive tasks did not show a significant association with the cortical thickness in corresponding brain regions (Gutierrez-Galve et al., 2012).

Nathaniel-James et al. (2004) also relied on a number of tasks to examine functional abnormalities in SLPE patients. These tasks covered memory and executive functions and the participants in the study were either diagnosed with schizophrenia or SLPE prior to participating. The tasks that were used were NART, California Verbal Learning Test, Verbal Fluency Test and Modified Card Sorting Test. The results in Nathaniel-James et al. (2004) were significant enough to show that SLPE patients exhibit similar deficits in memory and executive functioning as schizophrenic patients, suggesting shared neuropathology between psychotic disorders.

Butler et al. (2012) wrote about the importance of frontal lobe structures, even if it is outside of the temporal regions. The frontal lobes are of importance due to them modulating the limbic structures, however, they are also important in terms of psychosis. The frontal lobes are responsible for a lot of functions, among others, reality testing and cognitive controls. When the frontal lobes fail to mediate these functions, it may lead to an incorrect perception of reality, eventually developing into delusions and hallucinations being believable to the person. Thereby, abnormal activity in limbic structures and impaired frontal control mechanisms could explain why some epileptic patients experience psychosis while others do not.

Discussion

The findings that have been presented in this systematic review are both relevant and interesting to the current state of research, especially when it comes to the understanding of psychosis in general and psychotic symptoms. To better understand the underlying mechanisms for psychotic disorders such as SLPE could provide answers for why some people experience these symptoms while others do not, why they emerge to begin with and also what they tell us about overall brain mechanisms. Some of the studies that were included

in this review are older (e.g. published in 1998) and some are rather recently published (e.g. published in 2018). This makes the combined presented findings relevant and current.

My own conclusions are that SLPE is a very complex disorder, there are structural abnormalities, and dysfunction in cognitive functions and the studies that have conducted research in this patient group do not agree on everything that has been suggested about this disorder. What seems clear to me, however, is that SLPE is not only one set of symptoms, it is multifaceted.

Volumetric changes and cortical thinning are common findings in SLPE patients, which can be correlated to areas of seizure focus and regions which are responsible for functions that are typically impaired in SLPE. The temporal regions such as hippocampus and amygdala are usually affected structurally and cortical thinning can be seen in the frontal regions, such as inferior frontal gyrus. Other common findings are dysfunction or disruption in different functional processes in the brain, such as dopaminergic pathways, the limbic system and DMN. The latter hints at SLPE and the emerging symptoms do not occur due to one function being affected, but rather that it affects the networks in the brain.

The limitations that I faced during the work on this thesis were mostly the lack of research in this specific area. There are not a lot of studies that specifically investigated mainly SLPE patients, the focus is often on patients with primary psychosis and then they add SLPE patients to the study. Which made it harder to find relevant research to put into this review. Another aspect that made this review harder to write was the terminology in neuroscientific research in psychotic epileptic patients. There are a lot of different terms for SLPE, there interictal psychosis (IIP) and psychosis of epilepsy (POE) just to mention two of them. Due to this, I encountered studies with many different names for the same condition, making it more difficult to search, find and understand all studies for this review. Researchers do not only disagree in terms of what to call this disorder, but they also disagree on which technique is more appropriate to use in these studies. That is why I included a lot of different brain imaging techniques in this review.

Because the terminology varies so much in the scientific community, I have to consider the possibility of a selection bias when I searched and selected studies for this review. Also, the need for studies that are available in English might have caused me to miss interesting publications, due to them not being translated yet for example. I also had to discard a few publications simply because I could not access them in full text, which is also something that might have affected the outcome of this review.

Final conclusions

As stated previously in this discussion, I do not think that SLPE is a disorder with simple explanations, clear causation or just one type of neural abnormalities in the brain. It is clear that there are widespread changes in SLPE patients, structural changes in many different regions in the brain, disruptions in several different functional networks and a number of symptoms and cognitive impairments. In general, the findings in neuropathology are similar to those found in patients with primary schizophrenia, the most significant difference seems to be the lack of negative and affective symptoms in SLPE patients compared to those with schizophrenia. However, these similarities indicate that there are structures and functions in our brain that mediate psychosis since the same abnormalities can be seen in different psychotic disorders. Indicating that we might be able to understand exactly what makes our brain behave in this way, by establishing general neuropathology for psychosis, not only for schizophrenia.

[Final word count: 5803]

References:

Adachi, N., Akanuma, N., Ito, M., Okazaki, M., Kato, M., & Onuma, T. (2012). Interictal psychotic episodes in epilepsy: Duration and associated clinical factors. *Epilepsia*, *53*(6), 1088–1094. https://doi.org/10.1111/j.1528-1167.2012.03438.x

Allebone, J., Kanaan, R. A., Maller, J. J., O'Brien, T., Mullen, S., Cook, M., Adams, S., Vogrin, S., Vaughan, D., Connelly, A., Kwan, P., Berkovic, S. F., D'Souza, W., Jackson, G., Velakoulis, D., & Wilson, S. J. (2020). Enlarged hippocampal fissure

in psychosis of epilepsy. *Epilepsy & Behavior*, *111*, 107290. https://doi.org/10.1016/j.yebeh.2020.107290

Butler, T., Weisholtz, D., Isenberg, N., Harding, E., Epstein, J., Stern, E., & Silbersweig, D. (2012). Neuroimaging of frontal-limbic dysfunction in schizophrenia and epilepsy-related psychosis: Toward a convergent neurobiology. *Epilepsy & Behavior*, *23*(2), 113-122. https://doi.org/10.1016/j.yebeh.2011.11.004

Canuet, L., Ishii, R., Pascual-Marqui, R. D., Iwase, M., Kurimoto, R., Aoki, Y., . . . Takeda, M. (2011). Resting-state EEG source localization and functional connectivity in schizophrenia-like psychosis of epilepsy. *PloS one*, *6*(11), e27863. https://doi.org/10.1371/journal.pone.0027863

Flügel, D., Cercignani, M., Symms, M. R., Koepp, M. J., & Foong, J. (2006). A magnetization transfer imaging study in patients with temporal lobe epilepsy and interictal psychosis. *Biological psychiatry*, *59*(6), 560-567. https://doi.org/10.1016/j.biopsych.2005.07.023

Flügel, D., O'Toole, A., Thompson, P. J., Koepp, M. J., Cercignani, M., Symms, M. R., & Foong, J. (2006). A neuropsychological study of patients with temporal lobe epilepsy and chronic interictal psychosis. *Epilepsy Research*, *71*(2–3), 117–128. https://doi.org/10.1016/j.eplepsyres.2006.05.018

Gutierrez-Galve, L., Flugel, D., Thompson, P. J., Koepp, M. J., Symms, M. R., Ron, M. A., & Foong, J. (2012). Cortical abnormalities and their cognitive correlates in patients with temporal lobe epilepsy and interictal psychosis. *Epilepsia*, *53*(6), 1077-1087. https://doi.org/10.1111/j.1528-1167.2012.03504.x

Kandratavicius, L., Hallak, J. E., & Leite, J. P. (2014). What are the similarities and differences between schizophrenia and schizophrenia-like psychosis of epilepsy? A neuropathological approach to the understanding of schizophrenia spectrum and epilepsy. *Epilepsy & Behavior*, *38*, 143–147. https://doi.org/10.1016/j.yebeh.2014.01.005

Kanner, A. M., & Rivas-Grajales, A. M. (2016). Psychosis of epilepsy: a multifaceted neuropsychiatric disorder. *CNS spectrums*, *21*(3), 247-257. https://doi.org/10.1017/S1092852916000250

Maguire, M., Singh, J., & Marson, A. (2018). Epilepsy and psychosis: a practical approach. *Practical neurology*, *18*(2), 106-114. https://doi.org/10.1136/practneurol-2017-001775

Marsh, L., Sullivan, E. V., Morrell, M., Lim, K. O., & Pfefferbaum, A. (2001). Structural brain abnormalities in patients with schizophrenia, epilepsy, and epilepsy with chronic interictal psychosis. *Psychiatry Research: Neuroimaging*, *108*(1), 1–15. https://doi.org/10.1016/s0925-4927(01)00115-9

Nathaniel-James, D. A., Brown, R. G., Maier, M., Mellers, J., Toone, B., & Ron, M. A. (2004). Cognitive Abnormalities in Schizophrenia and Schizophrenia-Like Psychosis of Epilepsy. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *16*(4), 472–479. https://doi.org/10.1176/jnp.16.4.472

Sachdev, P. (1998). Schizophrenia-like psychosis and epilepsy: the status of the association. *The American journal of psychiatry*, *155*(3), 325-336. https://doi.org/10.1176/ajp.155.3.325

Stafstrom, C. E., & Carmant, L. (2015). Seizures and Epilepsy: An Overview for Neuroscientists. *Cold Spring Harbor Perspectives in Medicine*, *5*(6), a022426. https://doi.org/10.1101/cshperspect.a022426