Faculty of Science and Engineering of Rijksuniversiteit Groningen

Prepulse inhibition as an early schizophrenia biomarker

Bachelor's Thesis in Behaviour and Neurosciences

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Abstract

Introduction
An early schizophrenia biomarker is useful for diagnosis of the disease in an early stage. Thus, intervention can be performed before the onset of full-blown symptoms. Prepulse inhibition (PPI) is presented as a potential early schizophrenia biomarker. This is a measurement tool by which a prepulse is applied in order to inhibit the startle response to a following pulse. It is a measure of sensorimotor gating, which is impaired in schizophrenic patients. Since PPI is already decreased in schizophrenia patients before the onset of first psychosis, its use as a diagnostic tool is discussed.
Consequences of impaired sensorimotor gating
PPI is variable among schizophrenia patients. Likewise, symptoms of schizophrenia are also variable. In order to decide if PPI is a good early diagnostic tool, it is important to know if impaired gating is linked to specific symptoms. Research suggests that PPI is mainly linked to the cognitive- and positive symptoms of schizophrenia.
Neurobiology of schizophrenia and PPI
There is still unclarity about the neurobiological processes that underlie schizophrenia. If there is more insight in the neurobiology of the prodromal state of schizophrenia, it helps in detecting the disease at an early stage. Additionally, it will also help in developing more reliable animal models of schizophrenia. The mechanism of PPI impairment is proposed, but evidence on this matter is still lacking.
PPI as an early schizophrenia biomarker
PPI is a promising marker, because it is impaired in prodromal schizophrenics and it is stable across time. Though, the use of PPI as an early biomarker for schizophrenia has some challenges. It is not disease-specific and not homogenous among schizophrenic patients.
Conclusion
Additional research is needed in order to determine if these challenges can be overcome. For now, PPI is not a reliable biomarker in isolation, but is a promising tool that aids in detecting people at high risk of schizophrenia.

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Introduction

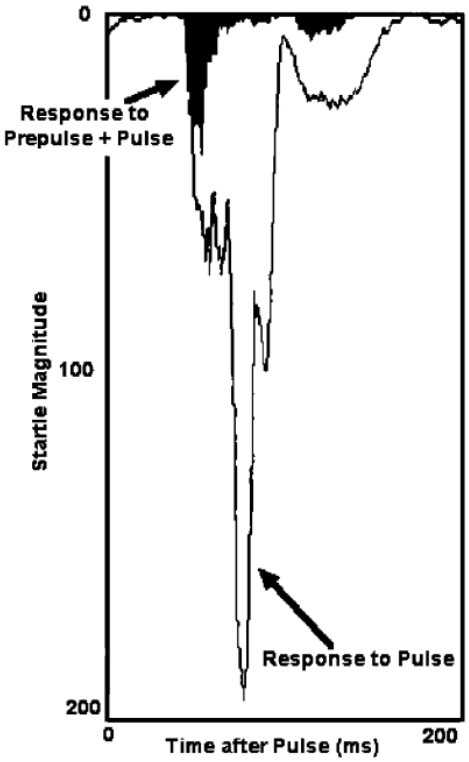

Figure 1. Schematic representation of the tracing of the startle response to the pulse and the prepulse+pulse in humans (76).

Schizophrenia is a long-term mental disorder. People with schizophrenia suffer from psychosis, which is characterized by losing touch with reality. Schizophrenic patients differ from healthy people in brain physiology. They have a thinner cortex and smaller surface area of the brain (84). Patients can suffer from different types of symptoms. The symptoms are divided into three categories: positive-, negative-, and cognitive symptoms. First, the main positive symptoms are hallucinations and delusions. Delusions are incorrect beliefs that are not in line with reality. Hallucinations are usually observations of something that does not exist (59). Second of all, negative symptoms mainly consist of anhedonia and apathy. Anhedonia means the loss of the sensation of pleasure (35). Apathy means, in the case of schizophrenia, the lack of interest in everyday things, such as working or going to school (86). Finally, there are cognitive symptoms that consist of impaired working memory, verbal fluency, attention, executive functions and information processing (57). The processing of information is mediated by sensorimotor gating. Sensorimotor gating is the process of filtering useful information from useless information (74). It modulates information that is transmitted to the motor regions of the brain. It serves as a protective mechanism that can prevent sensory overload of the brain. Due to the impaired gating in schizophrenic patients, their information management is less efficient (60). Studying gating mechanisms has provided insight in the underlying causes and effects of neurological disorders such as schizophrenia. A measure of sensorimotor gating is the process of prepulse inhibition (PPI). An acoustic stimulus, named a pulse, is applied and leads to an acoustic startle response. This response is characterized by a short muscle contraction. In PPI, this response is prevented (or reduced) by a shorter stimulus is applied prior to the pulse. This is shown in figure 1. In schizophrenic patients, this phenomenon has been shown to be deficient (8, 9, 34, 77, 78). In these studies, the healthy controls were better able to inhibit acoustic startle response to a prepulse than patients with schizophrenia.

Impaired PPI can possibly serve as an early diagnostic tool to detect schizophrenia, which is a disease that generally does not occur before someone's 20s (50). Compared to other neurological disorders associated with a lower PPI like autism and ADHD (61, 42), schizophrenia occurs relatively late in life. Schizophrenia is challenging to detect in an early state. This early state is called the prodromal state. This is a stage of a disorder that appears before the serious symptoms start. The prodromal state in schizophrenia can currently be recognized by memory- or attention issues (72). These are, however, challenging to detect, because they are small during this state and people do not immediately seek help. Ways are needed to detect this prodromal state, to start treatment in an early state. It is proven that, the earlier the disease is diagnosed and treated, the better the prognosis (77). When diagnosed, mostly antipsychotic medicine is administered. Patients that receive antipsychotics in an early stage of the disease are proven to have a higher chance of reduced symptoms (53). It is hypothesized that patients who are untreated relatively long have more pronounced symptoms and therefore it is harder to reach full recovery. If treated early, a patient has a better long-term prognosis (43). The neurobiological basis of this is not uncovered yet. To detect the prodromal state, multiple factors are taken into account like psychotic symptoms, genetic risk and social functioning (15). The prodromal state is difficult to define, because it is very variable among

individuals due to the heterogeneity of the disease (4). This heterogeneity suggests that different causes and mechanisms underlie the disease. It also means that the disease can lead to different outcomes in different individuals. In an early stage, one person can show anxiety, whereas another patient might suffer more from a depression or mood swings (16). Therefore, there is a need for defining clear, generalizable indications of the prodromal state. There are some additional challenges for defining an explicit marker for risk of schizophrenia. Schizophrenia patients have a high comorbidity (35). This means that they often have multiple disorders at a time. Thus, a symptom of a patient may be linked to schizophrenia, but it is actually a symptom of another disease. Examples of comorbidities are depression, substance abuse and obsessive-compulsive disorder. The comorbidities make it harder to determine a marker for schizophrenia, because other diseases have to be ruled out first. In the prodromal state, signs like depression and anxiety can be present. It is difficult to determine whether these signs are symptoms of the schizophrenia prodrome or something else. These symptoms may also occur by themselves without it being linked to another disorder. This is why it is important to find additional markers of the schizophrenia prodromal state.

In the search for early schizophrenia diagnostic markers, the use of sensorimotor gating models is proposed (66). The study of gating mechanisms in schizophrenia has resulted in a better understanding of the neurobiological mechanisms that underlie this phenomenon and its role in the disease (54). Like previously stated, PPI is impaired in schizophrenic patients. There is also proof that PPI is already deficient before the occurrence of the major symptoms of the disease (54). It is suggested in (15) that it can serve as a biomarker in the prodromal state. There are multiple reasons for this suggestion. The first reason that is mentioned is the fact that PPI is decreased in schizophrenia patients. The second reason is that PPI is stable across time. This is important for the validity of the obtained results. PPI is something that can be measured relatively easily and can be studied in animal models and humans. Scientists are able to modify animals so that schizophrenia symptoms are expressed (77). These animal models can be put into three categories: developmental-, drug induced- and genetic models (25). In developmental models, compounds can be administered during development which results in physiological-, behavioural- and neuroanatomical changes that occur in schizophrenia. In drug-induced models, psychosis can be induced by the administration of agonists or antagonist of certain neurotransmitter-receptors. In genetic models, candidate genes that are associated with schizophrenia are expressed in animals. There is a lot of overlap in neural circuits in regulation of PPI across species (44), which is why it has been proposed and assessed as a biomarker of schizophrenia (54). In another paper, it has been proposed as an endophenotype (30). This means that it is a trait that is genetically programmed. Thus, the reduction in PPI might be heritable and, therefore, the risk of schizophrenia as well.

The use of PPI as a biomarker has, however, some challenges too. First of all, there is a lot of individual variation in PPI. PPI is affected by factors like gender, fatigue, medication, stress, smoking and other factors (54).The paper by Light and Swerdlow in 2014 (50) mentions the following facts: It is proven that women have a lower PPI than men. Another insight is that nicotine use increases PPI. Around 70-80% of schizophrenia patients smoke (87). This prevalence is way higher than the global smoking rate which is around 23% (88). Cognitive performance has been shown to be worse in patients who never smoked tobacco (7). It is therefore hypothesized that schizophrenic patients smoke as a means of self-medication (87). The improvement in sensory gating in schizophrenic smokers has spiked interest in the role of nicotinic receptors in schizophrenia and if it can be targeted by therapeutics. Besides its implications in treatment, the effect of nicotine on PPI should be taken into account when collecting information on test subjects in PPI studies in order to correct for the increased PPI. PPI is also increased in patients that receive medication that treats psychosis, so this needs to be taken into account when studying PPI. This means that, if used as a biomarker, there are a lot of factors to correct for. Furthermore, there are conflicting results in studies that evaluate the long term stability of PPI. Some studies show that PPI remains constant over time (18, 3), other studies show that PPI normalizes over time (19, 24). If used as a

biomarker in the early detection of schizophrenia, it is important to know about the changes in PPI over time and which factors facilitate these changes. The final challenge that will be covered in this review is specificity. When using a biomarker for diagnosis, it is very important that it is disease-specific. Next to schizophrenia, PPI is impaired in conditions like obsessive compulsive disorder, schizotypal personality disorder, Huntington's disease (6), autism (61), Tourette syndrome (75) and blepharospasm (28). The latter is uncontrolled eye movements, like twitching. When doing diagnosis in patients, it is important that schizophrenia patients can be distinguished from the patients with the beforementioned disorders.

In order to tackle these challenges, it is important to be aware of the neurobiology of schizophrenia. Nowadays there is still a lot of unclarity about the neuropathology of the disease. It is a very complex disorder that involves many different genes. Additionally, the numerous symptoms have been linked to many neurotransmitters. But the key factor appears to be dopamine dysfunction (52). Dopamine is a neurotransmitter that is associated with the reward system in the brain. Additionally, it is also involved in the areas of the brain that control motor function. Schizophrenia patients appear to have an overactivity of dopamine (11). This dopaminergic hyperactivity is thought to directly affect PPI (67).

In order to decide if PPI is a valid biomarker, it is important to be aware of how schizophrenia affects information processing and how PPI deficits reflect the deficiency in sensorimotor gating. To make proper judgement, behavioural changes in schizophrenia need to be linked to impaired PPI. This comparison will be addressed in this essay. Additionally, it is very important to be aware of the neurobiology of schizophrenia and PPI to fully understand the link between them. Even though PPI is already widely used in research on schizophrenia, little is known about its link to the neurobiological basis of the disorder. In order to gain proper understanding of the underlying mechanisms of deficient PPI in schizophrenics, this essay will summarize the findings on this matter. Finally, it will focus on summarizing and comparing the results that have been published about the use of PPI as a schizophrenia biomarker. Based on this overview, the following question will be addressed: Is PPI a suitable biomarker for early diagnosis of schizophrenia? It is hypothesized that PPI is a very promising early schizophrenia marker, but more insight is needed to determine how it can be used in early diagnostics.

Consequences of impaired sensorimotor gating in schizophrenia

By knowing the effects of impaired PPI, the link can be made to schizophrenia symptoms. There is individual variety in PPI in schizophrenic patients (77). It is important to know why this is the case and what factors facilitate the difference in PPI across patients. By studying the effects of impaired PPI, it may be linked to specific symptoms that are shown by patients. If there is more information about the effect of deficient sensorimotor gating, PPI will be a more valuable marker in diagnostics, and it can be better implicated in study models. In this chapter, consequences of deficient PPI will be evaluated and linked to schizophrenia symptoms.

As mentioned before, schizophrenia symptoms include cognitive impairments. Patients often report that they suffer from a high sensitivity to auditory and visual stimuli (44). This causes them to be more easily distracted, since they are less able to filter out background information than healthy persons. This makes it more challenging to focus. This phenomenon is called sensory flooding. Research has shown that this sensory flooding causes schizophrenic patients to perform worse in attention tasks in the presence of distracting noise than healthy controls (69). To show the severity of sensory flooding, one striking quote from an interview with a patient by Kiev et al in 1961: "*Things are coming in too fast. I lose my grip of it and get lost. I am attending to everything at once and as a result I do not really attend to anything."* (44). It has been hypothesized that sensory flooding is due to deficient sensorimotor gating in schizophrenia patients (70). Since PPI is a measure of sensorimotor gating, it is studied widely in schizophrenic patients.

Next to the idea that sensory flooding underlies the cognitive deficits in schizophrenia, the question arose if sensorimotor gating also underlies negative and/or positive symptoms. Some patients suffer more from negative symptoms, whereas other patients suffer more from positive symptoms. Since PPI is not decreased in all patients, it is thought that decreased PPI is related to one of these categories of symptoms. There is a hypothesis that impaired gating might be more related to positive symptoms than negative symptoms (42). More severe gating deficits are associated with more severe positive symptoms. It is thought that sensory flooding might lead to hallucinations, which is a positive symptom. The same study shows that negative symptoms are not associated with gating deficits. This is supported by another study that shows there is no link between negative symptoms and sensory processing gating defects (2). This might explain the variety in PPI among schizophrenia patients. These conflicting results indicate the need for better understanding of what the exact effects are of deficient sensorimotor gating.

Consequences of sensory gating deficits have an impact on cognitive symptoms. Even though it is mainly thought to affect positive symptoms, there are conflicting results in literature. Additionally, since negative symptoms are already present in the prodromal state (82), future studies should focus on how and if a gating deficit might reflect this. If this is known, it can be taken into account during diagnosis. If there is more knowledge on how sensory flooding contributes to schizophrenia symptoms, differences in PPI may be linked to differences in the symptoms shown by the patients.

Neurobiology of schizophrenia and prepulse inhibition

Now focus will lie on the neurobiological basis of schizophrenia and prepulse inhibition. It is important to gain as much knowledge as we can on the underlying mechanisms of schizophrenia. It will help with defining the symptoms and treatment methods. Schizophrenia is usually diagnosed when major symptoms like delusions or hallucinations are present and if daily activities are limited by the symptoms. This means that it is usually diagnosed by the time the patient already shows full blown symptoms. Before major symptoms of the disease are observable, there are already processes going on in the brain that are not easily observed. By only studying and screening for full blown symptoms, pathology might go unnoticed longer than necessary. By knowing what neurobiological processes indicate schizophrenia, more methods might be developed that are able to detect the disease in an early state. Furthermore, it is important to understand the neurobiological process of PPI and how it relates to schizophrenia. Thus, PPI differences in schizophrenia can be compared to PPI deficits in other diseases.

In schizophrenia patients, changes in the neuroanatomy have been observed. These changes have aided in understanding which areas of the brain are affected. The gray matter of the brain is decreased in the prefrontal, medial and temporal lobes (48). These regions in the central nervous system seem to be involved in the pathology of schizophrenia. The frontal lobe is affected, which is responsible for memory and execution. Another brain area that is affected is the temporal lobe, which mediates language understanding, episodic memory and perception of auditory stimuli (12). Next to the changes in gray matter, white matter is also affected. In schizophrenia, myelination is shown to be decreased in the neuronal tracts that usually collaborate to mediate cognition (81).

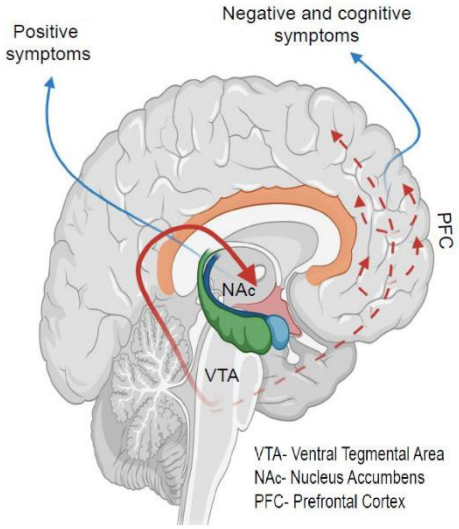

Figure 2. Roles of two dopamine pathways in schizophrenia. Overactivation of the mesocortical pathway leads to negative symptoms and under-activation of the mesolimbic system leads to positive symptoms (1).

The brain circuit that is mainly responsible for the symptoms of schizophrenia is formed between the thalamus, cerebral cortex and the striatum (52). Other brain regions that are involved are the amygdala and the hippocampus, which mediate perception and emotion. The occurrence of positive-, negative- and cognitive symptoms is linked to several neurotransmitters. Dopamine is a neurotransmitter that is mainly mentioned in literature about neurotransmitter-effects on the pathology of schizophrenia. Dopamine is a neurotransmitter that has a large variety of effects in the body. Some of these affects are movement, memory, reward and cognition. Dopamine is associated with four different pathways. One of these pathways is the mesolimbic pathway. This pathway is associated with the reward system, goal-oriented behaviour, attention and locomotion (59). In schizophrenic patients dopamine is hyperactive in the mesolimbic pathway. It is shown that mesolimbic regions are more active during psychosis (39). Another dopaminergic pathway is the mesocortical pathway. This is involved in cognition, motivation and emotion. In schizophrenia this pathway is hypoactive (96). This leads to the emergence of negative symptoms. The pathways of the emergence of both types of symptoms are shown in figure 2. Dopamine can bind to five different receptors. The two receptors that have been linked to schizophrenia the most are the D1- and D2 receptor. D1 receptors have an excitatory effect and are under-expressed in the prefrontal cortex (58). This receptor is related to basal activity and prefrontal function. D2 receptors have an inhibitory effect and are overexpressed in the striatum (68). The negative symptoms of schizophrenia are a consequence of decreased expression of the D1 receptor in the mesocortical pathway (14).There is a postsynaptic increase of D2 receptor expression in schizophrenia (67). This process contributes to the onset of psychosis. In genetic research, it was found that genes that encode the D2 receptor are more expressed in schizophrenic patients (52). In schizophrenia, there is a shift in the excitation/inhibition balance in favour of inhibition. This can disrupt the circuit between the prefrontal cortex, striatum and thalamus, which results in psychosis (31).

For a long time, dopamine has been thought as the dominant player in the onset of psychosis. However, dopamine is dependent on levels of other neurotransmitters, such as GABA, serotonin and glutamate (72). One hypothesis is that the dopamine hyperactivity is due to glutamate overactivity (71). Glutamate is the most abundant excitatory neurotransmitter. GABA interneurons are inhibitory neurons that can suppress glutamate. NMDA receptors are receptors that can activate GABAergic neurons. If these receptors are bound, glutamate can be inhibited. A theory suggests that there is a hypoactivity of these NMDA receptors in schizophrenia, leading to decreased GABA signaling, leading to increased glutamate signaling (7). The pathway can be seen in figure 3. It can be seen that NMDA binding leads to GABA activation, which then inhibits glutamate function. In schizophrenia, NMDA dysfunction can lead to glutamate overactivity. The excessive glutamate can stimulate mesolimbic dopamine release that leads to hallucinations and delusions. Another hypothesis is that serotonin activation and increased 5HT2A receptor expression leads to an increased release of glutamate (73). This is associated with mesolimbic activation. These hypotheses highlight the interconnectivity between several neurotransmitters. It can be valuable to detect the differences in neurotransmitter activity in schizophrenia patients. There are metabolites that are related to neurotransmitters. An example is homovanillic acid, which is a metabolite of dopamine. It has been proposed that its concentration can indicate dopamine activity (93). But according to Lynn et al (16), neurotransmitter levels are not a reliable biomarker for schizophrenia, due to the fluctuating levels and the interdependency. Therefore, research focuses on other potential biomarkers.

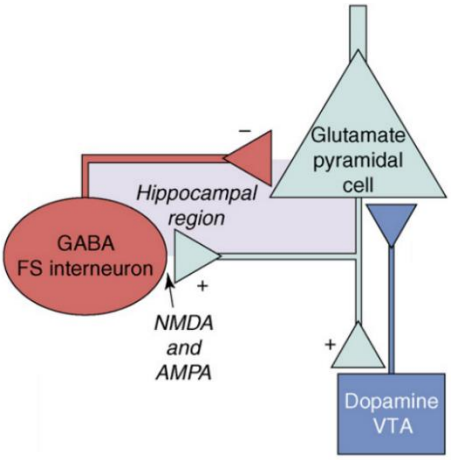

Figure 3. Schematic representation of the connections between dopaminergic-, GABAergic- and glutamatergic neurons (51).

In order to find another biomarker, research focuses on the biology of the filtering of irrelevant information, which is a crucial phenomenon that prevents sensory overflow of the cortical centers. Sensorimotor gating is measured by PPI. The amplitude of the muscle reflex after the auditory pulse is measured. In the presence of a prepulse, the inhibition of the acoustic startle response relates to better sensorimotor gating. The acoustic startle response is controlled by activating glutamatergic neurons which relay auditory information in the caudal pontine reticular nucleus (PnC) in the brain (46). This area is located in the lower pons. When the pulse is applied, motor neurons are activated in the brain stem and the spinal cord. These motor neurons mediate the startle reflex. In a medical hypothesis by Sato (66), the neurobiological relation of PPI and schizophrenia is proposed. In PPI, an auditory stimulus is transmitted to the PnC via so-called M2-like muscarinic cholinergic synapses. These originate from the pedunculopontine and the laterodorsal tegmental nuclei (PDT/LDT). These synapses mediate an inhibitory response of motor neurons (66). This pathway is shown in figure 4. In PPI, the signal transmission from PDT/LDT to PnC is crucial. In schizophrenia, this signal is impaired. Acetylcholine is released from PDT/LDT. This binds to the M2-like muscarinic acetylcholine receptors. These receptors have an interaction with the alpha subunit of the GTP-binding protein. Thus, adenylyl cyclase is inhibited. This results in inhibition of PnC (66). Like previously mentioned, D2 signaling is enhanced in schizophrenia. These receptors inhibit adenylyl cyclase (57) in the same way as the M2-like acetylcholine receptors. It is hypothesized that the two receptors both use the GTP-binding protein, competitively. This theory proposes that the overactivation of D2 receptors decreases M2-like acetylcholine receptor function and, thus, impairs PPI (67). There is no evidence that justifies this theory and it is not known if the same mechanism is related to other diseased that are related to lowered PPI.

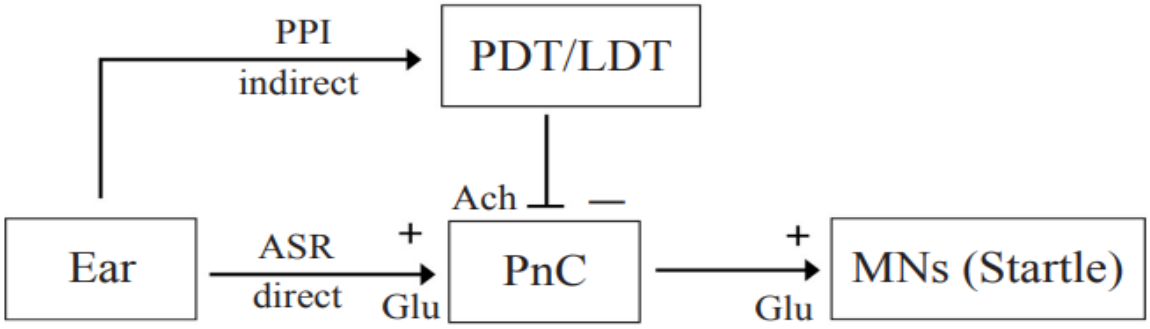

Figure 4. Schematic representation of the neural circuit of PPI (66).

In order to study schizophrenia in animals, the neurobiology of the disease needs to be well understood. Methods to mimic the neurobiology of the disease in animal models are already established. Like previously mentioned, there are three categories of animal models related to schizophrenia: developmental-, drug-induced and genetic models. One developmental method is the performance of neonatal lesions of the hippocampus of the rat. This results in hippocampal cell loss and reduced neuronal projection to the prefrontal cortex and the striatum. This leads to a large number of symptoms that occur in humans after puberty, which is the usual time of onset (74). These symptoms include a deficit in working memory, less social behaviour and decreased PPI (13). A drawback of this method is that lesions require highly precise operations that are associated with high risk of mortality. Another developmental model is postnatal social isolation. This results in behavioural alterations in adulthood, such as sensorimotor deficit, anxiety and cognitive impairment (25). In another model, methylazomethanol, which is a compound that prevents mitosis, is administered into pregnant rats. The offspring will then show changes, such as increased dopamine function, decreased social interaction, decreased PPI and anxiety (59). These symptoms are consistent with schizophrenia. A benefit of neurodevelopmental models of schizophrenia is that it aids in investigating the causes of schizophrenia in the prodromal phase. By trying to mimic the development of the disease, more can be learned about the developmental pathway. An example of a drug-induced schizophrenia model is the administration of NMDA receptor

antagonists. By preventing NMDA signaling, GABA signaling is prevented, leading to increased glutamate activity. Not all NMDA antagonists induce hallucinations. This is mainly because they affect different neural pathways. PCP, which is an NMDA-antagonist, results in social withdrawal, impaired PPI and cognitive deficits (53). It is injected in an adult rat prior to performing a PPI measurement. PCP induces prefrontal cortex dysfunction, which is also the case in schizophrenia (62). Another method is the injection of compounds in brain areas in order to mimic the pathogenesis of schizophrenia. For instance, decreasing the number of GABAergic interneurons is linked to schizophrenia (29). This leads to a disturbance of the circuit between the prefrontal cortex, striatum and thalamus. There are also animal models in which dopaminergic and serotonergic agonists are administered (11). Due to the large genetic contribution to schizophrenia, researchers have put effort in finding genes that are affiliated with schizophrenia and implementing this in animal models. One example is the insertion of the human G72 gene into mice. This results in a model in which behavioural and cognitive traits of schizophrenia are shown (22). A drawback from genetic modification to mimic schizophrenia symptoms is that it is a complicated and expensive procedure. Furthermore, the disorder is thought to be polygenic, so many genetic modifications are needed to fully mimic the complexity of schizophrenia.

Even though there is already a lot of knowledge on factors that influence the neuropathology of schizophrenia, which are implicated in animal models, there are still gaps in our understanding of the disease. It is known that dopamine abnormalities are involved in schizophrenia, but evidence is still lacking about how dopamine levels fluctuate over different stages of schizophrenia (16). Furthermore, the neurobiological mechanisms of schizophrenia that have been discussed in this essay mainly relate to negative- and cognitive symptoms of the disease. It is unclear if it is possible to replicate positive symptoms in animal models and how this could be done. This would result in more insight in how to mimic the disease in animals and will provide more ways to offer effective treatment. The mechanism of the relation between PPI and schizophrenia that has been mentioned in this essay is only a hypothesis. There is no evidence of this mechanism, so future research should focus of validating or rejecting this hypothesis. As soon as the exact mechanism of decreased PPI is shown in schizophrenia and other diseases, it can be compared, and disease-specific traits of PPI can be detected.

PPI as an early biomarker for schizophrenia

In treatment, the complete recovery is the ultimate goal. Since schizophrenia has been defined, researchers have put extensive work in finding the optimal treatment. In figure 5, the trajectory of a schizophrenic patient over time is shown. One factor that determines chance of recovery is the timing of treatment. So studies have focused on the optimal timepoint at which treatment can be offered. In determining the best time of treatment, the reaction to treatment of first-episode psychosis schizophrenic patients has been studied. This means that treatment is offered to patients who have recently had their first signs of a positive symptom (63). So, treatment is offered soon after the first positive symptom-timepoint shown in figure 5. A shorter duration of untreated first-episode psychosis is associated with a higher chance of recovery (21). Thus, in promoting recovery, early identification of the disorder is a crucial part, so

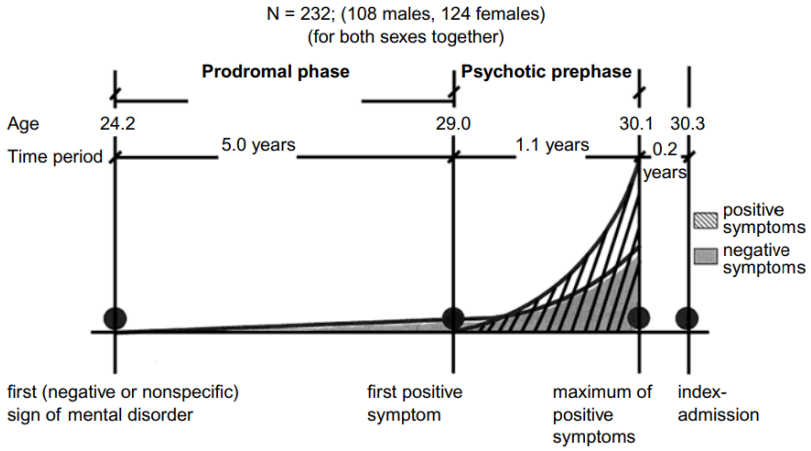

Figure 4. Schematic representation of the phases of schizophrenia over time (37).

treatment can be offered as early as possible. Nowadays, treatment is offered as soon as the patient has the first psychotic episode. It has been stated that diagnosing based on the presence of major symptoms limits the development of better treatment strategies (50). Thus, finding a way to offer treatment prior to the onset of the first psychosis may give a better prognosis. Currently there is a lot of debate on how this early treatment should be offered. There is no consensus on which therapeutics can be accepted for use on prodromal schizophrenics. However, there is some evidence that shows that psychological treatment of UHR patients delays the onset of the first psychotic episode (92). While the optimal treatment of early schizophrenics is studied, a treatment option would be redundant if we are unable to detect the schizophrenia prodrome. Therefore, a biomarker is needed to detect schizophrenia in the prodromal state. A biomarker is an unprejudiced indicator of a condition or a disease. It is used in the medical field and can give information about the prognosis, diagnosis and response-to-treatment (50). Finding a biomarker of the schizophrenia prodrome would improve early diagnosis and, therefore, treatment outcome.

Currently there is no clear biomarker that aids in identifying the prodromal state and early treatment of schizophrenia. For this, there are multiple reasons. First of all, the prodromal state of schizophrenia is very heterogenous. This means that there are many factors that contribute to the onset of the disease and that there are individual differences in what behaviours are shown. Examples of behaviours in the prodromal state are: social isolation, impairment in personal hygiene, overelaborate and circumstantial speech, odd beliefs, mood swings, anger, lack of interests and lack of energy (36). Not all of these signs are shown in every patient. The fact that there are many different symptoms of the prodromal state makes it hard to define a clear biomarker that is relevant in all patients. Secondly, the prodromal state is not a constant state. It changes over time. Docherty et al. (17) described it as a 'moment to moment march of psychological changes'. This makes it challenging to detect the prodrome, since different symptoms may be shown in between assessments. Lastly, the symptoms that are associated with the prodromal state are not schizophrenia-specific. They may not immediately be linked to schizophrenia, because there are many disorders that show similar symptoms. Examples are anxiety disorders and depression (64). It is unlikely that patients will visit the doctor immediately when the prodrome symptoms are present. The state may be painted off as "a phase that will resolve itself in the nearby future". The specificity-issue confronts clinicians with a challenge because they might be unsure what disorder to diagnose when they speak to a person showing prodromal symptoms. Therefore, they need a biomarker that is schizophrenia-specific, which is currently not clinically available.

In the search of a suitable early schizophrenia biomarker, two initiatives have been launched to define the criteria that research on the cognitive symptoms schizophrenia interventions have to meet. The first one is called Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). This panel of experts has proposed five norms that cognitive tests in research and clinical trials need to meet (33). In the MATRICS initiative, the advantages of biomarkers was also assessed. The second initiative is called the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative. The purpose of this panel was to identify cognitive constructs and tasks that can be part of future research and clinical trials and what criteria need to be met (5). These criteria consist of: clear links to neural circuits and availability of an animal model. Based on the criteria on neuropsychological measures that were set by these two panels one of the tools that is accepted for future study and development is PPI (32). Thus, PPI is a promising measure in schizophrenia research.

Since PPI has been applied as a promising measurement tool, interest has spiked in sensory gating. The study of sensorimotor gating in schizophrenia has delivered substantial knowledge on the causes and mechanisms of the disease. Gating deficits are shown to be impaired prior to the first psychotic symptoms and serve as a predictor (85). PPI has some promising traits for the use as an early schizophrenia biomarker. In order to determine if PPI is decreased in the prodromal state of schizophrenia, subjects were examined are at ultra-high risk (UHR) for psychosis (15). UHR is detected based on assessment of

psychotic symptoms, genetic risk and social functioning (91). PPI is shown to be reduced in UHR subjects at an early age (12-18 years) (94). This is a promising result, because it shows that deficient PPI is already present at a young age, so intervention can happen in an early stage. It is also shown that impaired PPI, unlike other symptoms of the schizophrenia prodrome, remains stable over time (94, 54). This makes it easier to detect and more reliable. Another advantage of PPI is that it is easy to measure in people and in animals. Evaluating PPI is a relatively simple procedure and it is easy to repeat. This makes it useful to perform by researchers and clinicians. Furthermore, PPI is proposed as an endophenotype (54). An endophenotype is a heritable, quantitative trait that reflects a process that underlies schizophrenia, which is not visible from the outside. This trait is a measurable component that can be a neuroanatomical, neurophysiological, cognitive or neuropsychological characteristic. An endophenotype of schizophrenia typically reflects irregularities of a neural system that is regulated by a relatively small number of genes (65). Endophenotypes have some benefits when determining risk of disease. It helps in understanding what process a gene encodes for and how its expression relates to the pathology. So, it helps in detecting genes that influence the risk of a disease and ranking people quantitatively based on their risk. According to Glahn et al (26), an endophenotype can help in explaining heterogeneity between diagnostic methods, because it uses a biological classification, rather than a psychiatric approach.

Even though PPI has some promising qualities, the extent to which PPI can serve as a biomarker for the schizophrenia prodrome is heavily debated. This is due to several reasons. First, there is the heterogeneity issue. It is still unclear if PPI is decreased in all patients that are in the prodromal phase of schizophrenia. Someone might be at risk of becoming schizophrenic, even though that person has a normal PPI. Studies have shown that there is overlap in PPI values between schizophrenic patients and healthy controls (77). This overlap is not desired, since schizophrenic patients need to be distinguished from healthy people. The overlap in PPI is shown to be dependent on the stimulus parameters. Thus, the relationship between PPI and parameters like prepulse volume, intensity and intervals need to be evaluated. Secondly, apart from disease, there are other reasons for variety in PPI values. PPI is sensitive to factors like medication, fatigue, gender, smoking and stress (77). While factors like gender, medication and smoking can be controlled for, stress and fatigue are more challenging to evaluate. This is because they are much more difficult to quantify. Thirdly, next to these factors, PPI might also be decreased due to the presence of another illness than schizophrenia. Likewise, scientists are unsure if PPI deficits are schizophrenia specific. In diagnosis, it is desired that other disorders can be ruled out completely. Disorders in which PPI is impaired include obsessive compulsive disorder, Huntington's disease (39), autism (61), Tourette syndrome (75) and blepharospasm (46). In order to rule out these disorders, the subject needs to be screened for symptoms for all disorders. An advantage is that the majority of these disorders have symptoms that do not overlap with schizophrenia. A disadvantage is that PPI can not be exclusively used as a marker, because additional evaluation is needed to rule out other diseases than schizophrenia.

PPI is a measurement tool that has promising qualities in early schizophrenia diagnosis, but some of the mentioned challenges need to be addressed in future research.

Discussion

In order to determine if PPI can be accepted as an early schizophrenia biomarker, some discussion points need to be addressed. A good biomarker is supposed to be stable over time. Since PPI is shown to have a high test-retest reliability, it is proposed as a schizophrenia biomarker (23, 54). High test-retest reliability means that if a test is performed twice over time on the same subject, it yields relatively the same results. Another noteworthy point is that PPI deficits are associated with multiple other neurological disorders. This makes the use of PPI as a biomarker more challenging, since other diseases have to be ruled out first. One disorder that is related to lower PPI is autism (61). While having some resembling symptoms, like impaired goal-directed behaviour and problem solving, it is generally diagnosed earlier in life than

schizophrenia (27). Another disorder that is associated with decreased PPI is ADHD (55). ADHD is often reported in young people who later develop schizophrenia (38). So, when ADHD is diagnosed, the prodromal state of schizophrenia should not be ruled out yet. This does mean, however, that the PPI deficit does not provide enough information for the diagnosis of schizophrenia. Huntington's disease is also affiliated with impaired PPI (39). In 6 to 25% of the cases, schizophrenic-like symptoms occur. So, it is important that clinicians are aware of this overlap in symptoms when performing diagnosis. Finally, blepharospasm, which is also linked to a PPI deficit, is associated with involuntary eyelid movement (46). So, it is unlikely that a patient in the prodromal state will be diagnosed with blepharospasm in the absence of eye twitching. So, most of these diseases are relatively easy to rule out in the case of a PPI deficit.

Standardized levels of a biomarker that indicate health and pathology are useful in diagnostics. An example is diagnosis of hyperglycemia. If a health professional measures a glucose level of 48 mmol/mol, hyperglycemia is diagnosed (40). In diagnosing schizophrenia, it would be very helpful if such standardized levels of PPI are determined. If PPI is going to be used as a biomarker, values of PPI need to be linked to the pathological state. Unfortunately, this is not as straightforward as diagnosing hyperglycemia. This is because lower PPI levels are not always pathogenic. Therefore, the fact that low PPI levels are often deemed as "poor" is a misconception. It is proven that men have a higher PPI than women (50). Another finding is that PPI fluctuates across the menstrual cycle (41). It can not be concluded that men have "poorer" PPI than women or that sensory gating in the luteal phase is "worse" than in the follicular phase. Next to gender and the menstrual cycle, there are other factors that make a standard pathogenic PPI value unrealistic. These factors include smoking, fatigue, stress and medication. Another difficulty is the fact that schizophrenic patients do not always have lower PPI. So, if a clinician measures a normal PPI value, schizophrenia can not yet be ruled out. Additional screening for symptoms is needed. The fact that many factors influence PPI, and that PPI differs among schizophrenic patients make it an unreliable biomarker as an isolated measure.

Before the exact causes and effects of the mentioned factors and reasons for individual PPI variability have been determined, it is not realistic to use PPI as an isolated measure in diagnostics. But, it can still be useful in the diagnosis of schizophrenia. Since PPI deficits are present in the prodromal state, they can still offer information about the risk of schizophrenia. It is presented as an addition to clinical assessment beside the full blown symptom-based approach that is used nowadays (49). The first step in diagnosis is the establishment of contact between the clinician and the patient. One way of promoting this contact is to perform routine screening of people who are member of a family in which schizophrenia is prevalent. When screening is performed nowadays, schizophrenia is diagnosed if two of the following symptoms are shown: delusions, hallucinations, disorganized speech, disorganized behaviour and negative symptoms. Due to the better prognosis in early diagnosed patients it is valuable to also consider for ultra-high risk of schizophrenia if full blown symptoms are not shown yet (103). People can be screened for factors that are related to high risk of psychosis. These include brief intermittent psychotic symptoms, a lower score in a global functioning test and a family history of schizophrenia (103). PPI measurement can be added to the methods that are used to assess ultra-high-risk. Due to the heterogenous nature of schizophrenia, methods should be able to reflect all symptoms related to schizophrenia, to minimize the number of false-negatives. Therefore, it can be valuable to combine PPI with other markers in order to account for the individual differences in symptoms. Two measures of forebrain inhibitory function that are proposed to be combined with PPI in determining the risk of schizophrenia are P50 event-related potential (ERP) and antisaccade deficits (76). ERP is similar to PPI, but in this case both pulses that are applied are identical. In PPI, the prepulse is much weaker than the pulse. In the antisaccade test, a subject focuses on an immobile target. A visual stimulus is shown on a side of the target. The subject is asked to make an eye movement away from the stimulus. If the subject fails, it is an error. Both ERP- and antisaccade deficits are observed in schizophrenia patients (24, 88). Both measures have been shown to have no significant

correlation with PPI (24, 83). Therefore, they are expected to be measures of different processes. Another measurement tool that is proposed as a combination with PPI is pharmaco-SPECT procedure. This models dopaminergic neurotransmission in the striatum (15). This study shows that PPI and striatal dopamine concentration show no correlation, which indicates that they measure different aspects of pathology. More research is needed in order to see if a combination of PPI with ERP, antisaccade task and dopamine concentration assessment could be valuable for early schizophrenia diagnosis. Next to the addition to diagnosis, screening for PPI deficits can also help in deciding on the therapeutic intervention. Research focuses on improving clinical assessment by screening for different domains of pathology. Since schizophrenia is very heterogenous, treatment should match this heterogeneity. This means that treatment should be personalized based on the symptoms that the patient shows. If PPI is shown to be deficient, a judgement of affected areas and circuits can be made and treatment can be applied that acts on this.

To conclude, PPI has some promising qualities in serving as an early diagnostic tool for schizophrenia. At this point it is unrealistic to use PPI as an isolated diagnostic biomarker. However, it can be combined with other factors in risk-assessment of schizophrenia in order to offer treatment to prodromal schizophrenia patients. Despite the number of unanswered questions, PPI is presented here as a tool to diagnose and treat schizophrenia more efficiently in the future.

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