# The Endophenotypic Involvement of Neuroticism, REM Sleep Abnormalities, and Cognitive Deficits in Depression and Schizophrenia.

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## Abstract:

While genes refer to the bases that encode our phenotypes, a phenotype often refers to observable characteristics, such as hair color, eye color, or height. However, a common mistake is overgeneralizing phenotypes to solely equate to an outward appearance rather than having any merit at a genetic level. In neuroscience, phenotypes bridge the genetic information underlying neurocognitive disorders. Neuronal phenotypes, or endophenotypes, link measurable traits and genetic mutations. As intermediate traits between a psychiatric disorder's genetic level and physical presentation, researchers can now efficiently identify the associated genes and defined characteristics. Notably, two common neuropsychiatric disorders, depression and schizophrenia, share overlapping endophenotypes: neuroticism, REM sleep abnormalities, and neurocognitive deficits. Firstly, neuroticism has earned itself a spot amongst psychology's "Big 5" personality traits, in which it presents itself as an individual's tendency to spiral into anxious and depressive habits. These neurotic tendencies additionally act as genetic predictors for the future onset of schizophrenia. Secondly, REM sleep abnormalities act as biological markers for schizophrenia due to shorter sleep latency and increased REM density correlating with severe schizophrenic symptoms. These abnormalities are not limited to schizophrenia, though, as REM sleep alterations also relate to depression due to disruptions in the neurotransmitters responsible for REM sleep. Finally, cognitive control deficits impact an individual's ability to achieve goals by impeding focus and fluidity between tasks, traits associated with both depressive and schizophrenic behavior. The purpose of this study was to provide an in-depth analysis of the leading genetic markers within both depression and schizophrenia. This study hypothesizes that neuroticism, REM sleep abnormalities, and cognitive deficits are foundational to both depression and schizophrenia despite each endophenotype having their respective impacts on each disorder.

## Introduction:

Neurotic personality types describe an individual's tendency to experience negative emotions, such as anxiety, loneliness, and irritability. Accordingly, a neurotic background increases the risk of developing depression, with neuroticism a common factor in diagnosing individuals as depressed and non-depressed. Several family and twin studies revealed neuroticism to have a significant genetic overlap with depression, making it a likely phenotype passed down through generations within families where depression is present (Navrady, Ritchie, Chan, et. al 2001). However, neuroticism is not limited to depression since additional studies showed adolescents who exhibited neuroticism also have a genetic predisposition for

developing adult schizophrenia. Furthermore, neuroticism's counterpart, extraversion, evidently reduced the risk of developing schizophrenia, as seen with a 44% correlation between extraversion and lack of mental illness (Van Os & Jones, 2001).

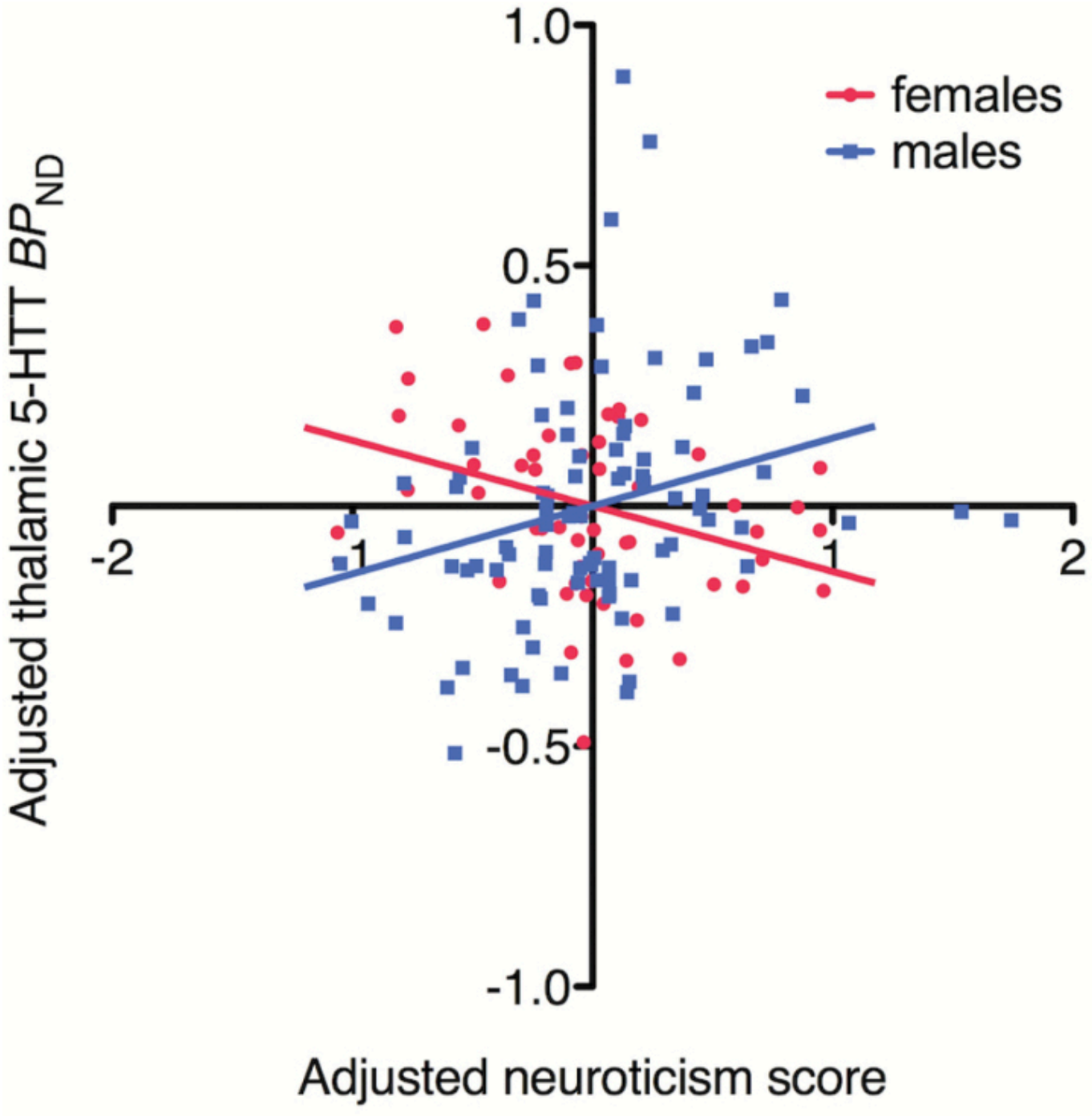
REM sleep, also known as Rapid Eye Movement sleep, is characterized by rapid eye movement, vivid dreams, and increased brain activity. REM sleep abnormalities are a type of sleep disorder that results in parasomnia due to an individual's tendencies to act out dreams physically during REM sleep. REM sleep abnormalities are considered accurate depression-based endophenotypes due to symptoms of depression usually correlating with decreased sleep latency and neurotransmitters affected during sleep dysregulation. The biological significance of such sleep patterns and abnormalities heightens cognitive distortions and the consolidation of emotionally damaging memories (Palagini, Baglioni, Ciapparelli, et al., 2013). With sleep alterations severely impacting memories, REM sleep disorders decrease brain plasticity, also known as brain adaptation. Notably, stunted memory is a common schizophrenic symptom, explaining the significance of REM sleep as an endophenotype for not only depression but also schizophrenia. Meta-analysis results reveal individuals with schizophrenia suffer from a range of sleep disorders, whether it be insomnia or reduced sleep efficiency, which severely influences the psychosis episodes schizophrenics are known to have (Sprecher, Ferrarelli, and Benca, 2016).

Finally, cognitive deficits impair an individual's mental processes, such as memory retention or attention. Regarding major depressive disorder, cognitive deficits contrast both neuroticism and REM sleep, as they result in an acute rather than gradual onset of depression. While individuals who suffer from depression-based cognitive deficits tend to have a previous psychiatric history, the rapid progression of cognitive deficits related to depression correlates with the sudden onset of memory disorders and impaired behavior (Perini, Cotta Ramusino, Sinforiani, et. al, 2019). Impeded memory can increase hopelessness, further strengthening the endophenotypic relationship between the two. On the other hand, individuals who have schizophrenia face issues with both working and verbal memory. The former arises from schizophrenia patients lacking the attention required to effectively and simultaneously process multiple streams of information, whereas the latter occurs due to absent semantic networks (Bowie & Harvey, 2006).

**Neuroticism:**

The driving force behind the relationship between neurotic individuals who have a predicted onset for depression is the neurotransmitters impacted via neuroticism. Individuals who display high levels of neuroticism also typically have decreased levels of serotonin, dopamine, and norepinephrine, all of which are key monoamines. Monoamines are a subset of neurotransmitters critical in mood, sleep, and arousal regulation. While the decrease of these

neurotransmitters does not primarily cause depression, their combined dysregulation correlates with contributing to a depressive mood that can develop into major depressive disorder. The way elevated neuroticism levels impact neurotransmitter levels is by increasing 5-HT1A, an inhibitory autoreceptor that negatively regulates serotonin release, and decreasing 5-HT2A receptor binding, which increases serotonin release in the prefrontal cortex and limbic system (Tuominen, Miettunen, Cannon, et al., 2017). As for norepinephrine, neuroticism heightens noradrenergic system activity, leading to increased arousal and stress responses and, therefore, decreased norepinephrine secretion, leading to mood instability, anxiety, and depression. Finally, for dopamine, correlations portray neuroticism as reducing dopamine transporter availability within the brain. Responsible for motivation and reactivity to rewards, symptoms such as blunted reward sensitivity, another considerable endophenotype for depression, occur.




**Caption:** The diagram illustrated above is a partial regression plot which depicts the statistical correlation between neuroticism levels and the potential of serotonin to bind to the receptor 5-HTT BPND in the limbic system, specifically the thalamus, in both females and males. While neuroticism scores are the residuals when regressing neuroticism levels against age and center, 5-HTT BPND values are not included within the diagram. Then, when the 5-HTT BPND became the residuals, neuroticism levels were omitted. These circumstances allow for

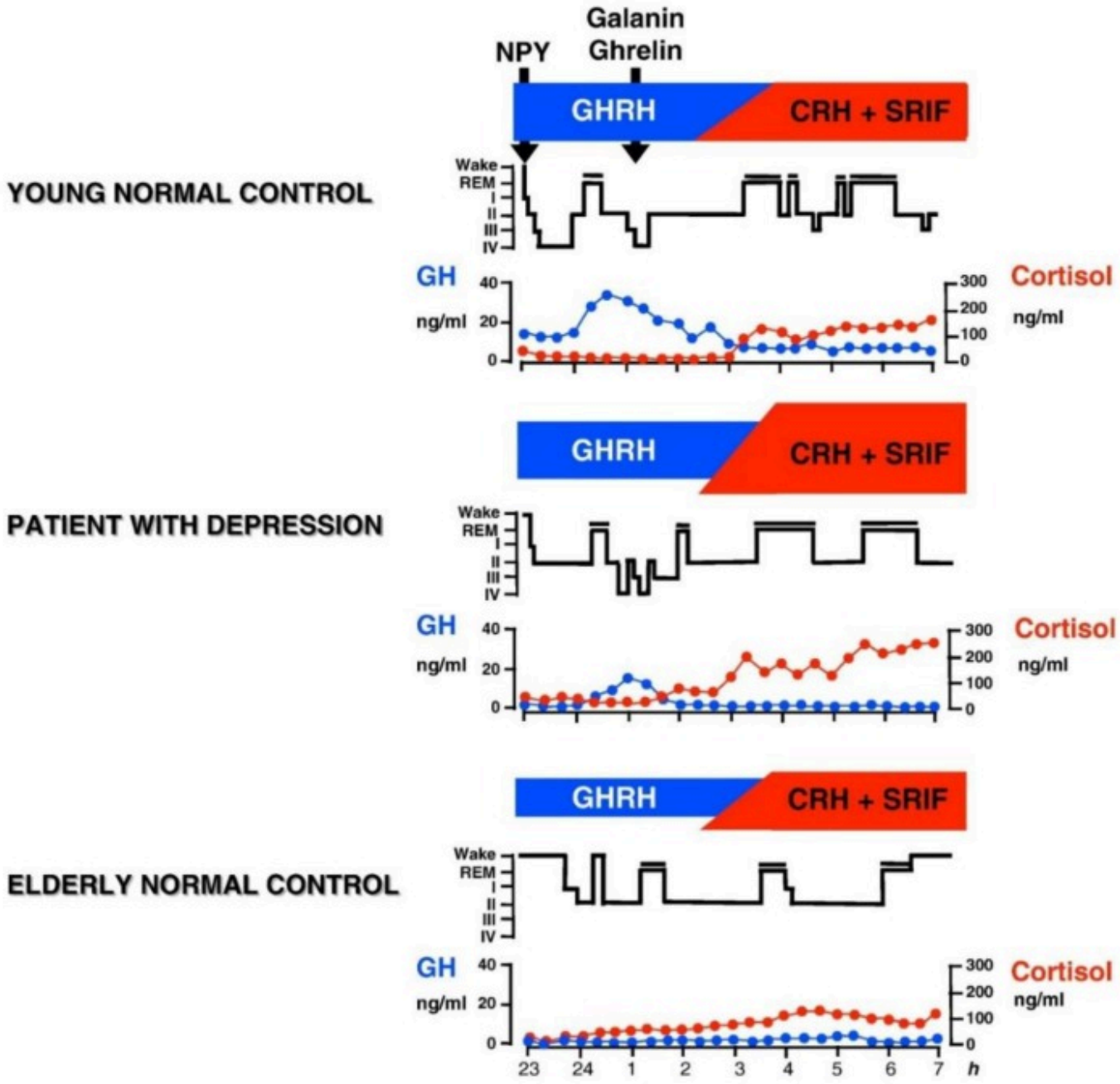
mean centered neuroticism scores and corrected BPND values for the age of the study's participants.

Now, while neuroticism is not a definite endophenotype for schizophrenia due to its instability and tendency to overlap with other disorders, it still acts as an essential genetic marker due to its correlation with predicting later schizophrenia. Neuroticism's primary association with schizophrenia is neuroticism levels associated with a schizophrenic patient's likelihood to suffer from a psychotic episode. Individuals who exhibit neurotic signs also tend to have less extraversion and compliance traits, with low neuroticism levels correlating to a higher quality of life (Franquillo, Guccione, Angelini, et al., 2021). As a result, neuroticism-induced psychotic episodes result in positive or manic symptoms, as well as social impairment and dysfunctional coping mechanisms. These life factors then function systematically, with lack of treatment leading to other disorders such as somatic or psychic anxiety, increased irritability and aggression, and physiological tensions or hyper-sensations. However, these notable symptoms and characteristics allow for the majority of schizophrenia treatments to concentrate on such personalities, as seen with psychotic disorders often integrating elements of neurology, psychiatry, and psychotherapeutic techniques. While neuroticism may go against endophenotype classification for schizophrenic individuals, it is undeniable how neuroticism intertwines with personality characteristics, life quality, vulnerability to develop other disorders, such as chronic hallucinatory psychosis, and treatment specifications.

**REM Sleep Abnormalities:**

REM sleep abnormalities typically consist of a decrease in REM latency (or the amount of time it takes a person to fall asleep once they lie down in bed), combined with increases in REM density and sleep duration. All of these characteristics are notable risks for future major depressive disorder onset since the endophenotypic mechanisms that underlie these symptoms are neurobiological and neurochemical imbalances combined with harmful memory consolidation. A prominent gene is P2RX7, a susceptibility gene for affective disorders located on chromosome 12, which is known for its associations with major depression disorder and bipolar disorder (Steiger & Pawlowski, 2019). A notable study concentrated on the importance of the P2RX7 gene conducted in a sleep laboratory involved individuals who were at risk for developing mood disorders as well as individuals who lacked any psychiatric disorder prevalence within their own medical history and family history. The results proved that the currently healthy volunteers with a potential risk for developing a psychiatric disorder differed not only in electroencephalographic (EEG) sleep more than their low-risk counterparts but also had such sleep alterations attributed to the presence of the P2RX7 genotype. Genotypes, as seen with P2RX7 and REM sleep endophenotypes, work to increase negative symptoms since REM sleep plays a role in mood regulation and emotional memory processing, with alterations

affecting which information a depressive patient may choose to retain, systematically leading to other notable phenotypes such as blunted reward learning.




**Caption:** The diagram above illustrates characteristic hypnograms measuring three patients: a young patient who does not have depression, an elderly patient who does not have depression, and finally, a patient with depression. The hypnograms measure each patient's

cortisol (CRH) and growth hormone (GH) secretion patterns. The two controls show that the balance between CRH and GH changes during normal aging; however, CRH secretion increases once GH decreases during depressive episodes. These patterns mirror how an individual responds to stress and when an individual is sleeping. Given that both scenarios occur more often for a depressed individual, the resulting hormone patterns depicted above support the idea of how sleep is one of the contributing factors to the neurobiological and neurochemical imbalances that increase an individual's risk for later depression. (Springer, Nervenarzt, Schlafendokrinologie, et al., 1995).

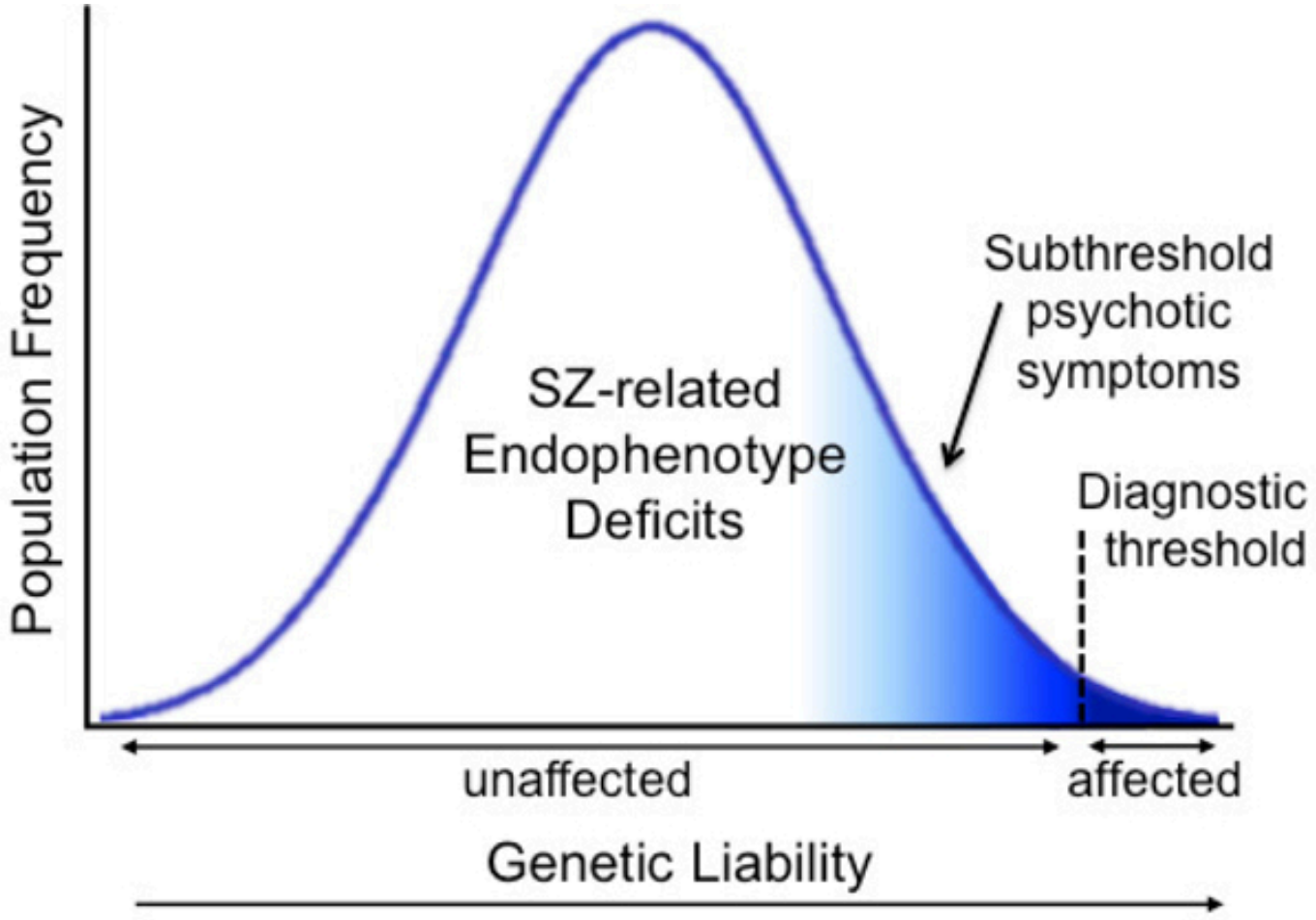
While the aforementioned REM sleep abnormalities that increase an individual's risk for depressive disorders are, for the most part, the same sleep characteristics that individuals predisposed to schizophrenia, there is one significant difference. One of the primary REM sleep endophenotypes for individuals with depression consists of an increase in sleep duration. However, individuals with schizophrenia experience a severe reduction in REM sleep duration, yet it is also important to note that such findings are compact with inconsistencies. Instead, schizophrenia has a more stable relationship with reduced slow-wave sleep, or NREM (Non-Rapid Eye Movement sleep). These reductions correlate to an increase in positive symptoms, leading to an increase in psychosis episodes. Slow waves accomplish this due to their consistent findings, which lead to aberrant neural development and spindle-mediated plasticity abnormalities (Sprecher, Ferrarelli, & Benca, 2016). Both developments contribute to the cognitive disorders and negative memory consolidation associated with schizophrenia, with sleep-mediated plasticity overarching the behavioral and molecular levels of schizophrenia, pointing findings toward sleep's involvement in schizophrenia's pathophysiological mechanisms. Furthermore, slow-wave abnormalities harm the brain's cortical regions, with cortical maturation acting as a marker of schizophrenia due to schizophrenic individuals having less coordination and neural development than healthy. REM sleep is an endophenotype for depression, the way NREM sleep is for schizophrenia, with both disorders experiencing similar neurobiological symptoms.

**Cognitive Deficiencies:**

Given that neuroticism and REM sleep abnormalities have both been proven to be critical biological markers for detecting individuals at risk for depressive disorder and explaining the molecular levels as to why depressed individuals experience specific symptoms, cognitive deficiencies are a likewise endophenotype. Cognitive impairment is a notable symptom of both neuroticism and REM sleep abnormalities due to how both endophenotypes alter the brain's biological structures and neurochemical patterns. With neurotic levels indicating an individual's sensitivity to negative symptoms such as irritability, aggression, and anxiety, common cognitive deficiencies contributing to or resulting from depression deal with an individual's social impairments due to a tendency to think in black and white. For instance, heightened negative

symptoms result in individuals viewing situations as all good or all bad, with these distortions in judgment leading to an increased sense of hopelessness since depressed individuals will lean towards expecting the worst possible outcome (catastrophizing). Furthermore, REM sleep abnormalities provide the basis as to why depressed individuals are vulnerable to such moods since reduced sleep can lead to an increase in gray matter or unmyelinated nerve tissue. Myelin sheath coats the main body of neurons to accelerate cognitive processing. Accordingly, the presence of gray matter leads to slowed cognitive speeds, resulting in increased feelings of anxiety, lack of focus and attention, and memory problems, all of which contribute to the burdens a depressed patient might feel. Neuroticism and REM sleep abnormalities are not just significant depression-based endophenotypes but the foundation of another one of depression's endophenotypes, cognitive deficiencies, explaining depressive disorder mechanics, biology, and symptoms.

While the past two endophenotypes, neuroticism and REM sleep abnormalities, have been both disqualified as potential candidates for a schizophrenia-based endophenotype, cognitive deficiencies are instead considered a strong and evidential endophenotype. The foundation for cognitive deficiencies as a schizophrenia endophenotype lies within the cognition's substantial heritability and genetic background when it comes to predisposing individuals for later schizophrenia. Even when families lack the presence of schizophrenia, numerous family and twin studies have discerned that cognitive traits or impairments are strongly heritable, with identical twins often sharing an entire genome nearly half of the time. Another reason why cognitive deficiencies are significant for schizophrenia genetic research is due to the neurobiological markers that occur within the brain's prefrontal cortex, where processing primarily takes place. As a result, brain and circuit dysfunctions allow for neurocognitive and neurophysiological endophenotypes to be objective and measurable due to the role of genes and endophenotypes (Greenwood, Shutes-David, & Tsuang, 2019) in constructing the neural pathways of an individual at risk for developing schizophrenia or an already schizophrenic individual. Common cognitive deficiencies associated with schizophrenia, known as the "Group of Schizophrenias," consist of social, occupational, and hygienic neglect. A highly heritable disorder, schizophrenic gene expression via cognitive deficiencies allows researchers to identify the genotypes and clinical phenotypes that account for an individual's risk for developing later schizophrenia.




**Caption:** The diagram above portrays the genetic liability threshold since schizophrenia-related endophenotypes capture the entire spectrum for liability distribution. In the model, diagnoses are defined as either unaffected or affected based on cognitive impairment via psychotic symptoms. Likewise, all the data was given via subjective symptom profiles. (Greenwood, Shutes-David, & Tsuang, 2019)

**Conclusion:**

The hypothesis of this study was, for the most part, correct. First, the mood disorder endophenotype of cognitive impairments proved to be the most stable endophenotype for both depression and schizophrenia. However, neuroticism levels and REM sleep abnormalities are definitive endophenotypes for depression only and not schizophrenia. Still, neuroticism is an undeniable risk factor for developing later schizophrenia. Furthermore, NREM sleep, while not as widely considered to be an endophenotype as REM sleep is, proved to be a consistent association and risk factor for schizophrenia as well as a foundation for numerous cognitive impairments. As a result, the symptoms of depression and schizophrenia were predominantly

similar than not, which makes sense considering both are neuropsychiatric disorders with substantial heritability and genetic levels. Despite the field of genetics concerned with neuropsychiatric disorders still facing numerous limitations, such as complex multifactorial disorders blurring the line between genetic and environmental contributions to affective disorders, along with overlapping symptoms and inconsistent findings, there have been significant technological advancements. For instance, genome editing gives way to multiple treatment options for both schizophrenia and depressive disorder. Neuroimaging provides scientists and patients with a neurobiological and neurochemical understanding of their disorders. Neurobiologically, both depression and schizophrenia experience cognitive impairments within the prefrontal cortex and limbic system. Neurochemically, neuroticism impacts the serotonin, dopamine, and epinephrine levels for depression, and sleep alterations affect neuron myelination, with both situations resulting in significant cognitive deficiencies. Overall, neuroticism, sleep abnormalities, and cognitive deficiencies are all either biological markers or definitive endophenotypes for both schizophrenia and depression. When discussed, each characteristic strengthens the genetic understanding at each disorder's behavioral and cellular levels, respectively and integratingly.

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