TARGETING INFORMATION-PROCESSING DEFICIT IN SCHIZOPHRENIA

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Summary

Neurocognitive deficits are one of the most serious problems related with Schizophrenia. A novel phenotype strategy in schizophrenia, targeting different neurocognitive domains, neurobehavioral features, and selected personality traits, has allowed us to identify a homogeneous familial subtype of the disease, characterized by pervasive neurocognitive deficit.

Keywords: schizophrenia, Neurocognitive deficits, brain

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SCHIZOPHRENIA – GENERAL OVERVIEW

Two million people suffer from schizophrenia at some point in their life, making it one of the most common health problems in the United States. Schizophrenia has also been found to be hereditary [1]. This biological disorder of the brain is a result of abnormalities which arise early in life and disrupt the normal development of the brain. These abnormalities involve structural differences between a schizophrenic brain and a healthy brain. Schizophrenic brains tend to have larger lateral ventricles and a smaller volume of tissue in the left temporal lobe in comparison to healthy brains. The chemical nature of a schizophrenic brain is also different in the manner the brain handles dopamine, a neurotransmitter [2].

The disease schizophrenia can be characterized by disturbances in the areas of the brain that are associated with thought, perception, attention, motor behavior, emotion, and life functioning. The symptoms are divided into negative and positive categories. Negative symptoms consist of behavioral deficits such as blunting of emotions, language deficits, and lack of energy. Positron emission tomography (PET) has been used to show that schizophrenics with negative symptoms have reduced brain activity in the prefrontal cortex of the brain. PET measures the blood flow in the brain by measuring particles (positrons) that are emitted from a radioactive chemical injected into the patient. The rate of positron emission is used to evaluate the metabolic rate of nerve cells in particular regions of the brain. PET allows scientists to determine which areas of the brain are being used as people perform certain tasks [3].

Anti-schizophrenic drugs are called neuroleptics. A dopamine antagonist is chlorpromazine (Thorazine), and reserpine operates by depleting transmitter stores. Ligand-binding techniques, which use neuroleptic drugs labeled with radioisotopes, demonstrate that such drugs bind to dopamine receptors [4]. A correlation exists between this ability to bind dopamine and the dosage required to improve schizophrenic symptoms in patients. This effect could also be directly observed by PET in living subjects. Controlling dopamine and dopamine receptors is essential for the treatment of schizophrenia. Because schizophrenia is hereditary, it is important to see progress in the next generation. In the future there will be more sophisticated drugs that do not merely suppress symptoms, but also allow for normal cognitive functioning. Although schizophrenics may never be normal, their lives can still be made more tolerable [2, 5].

Electroencephalography recordings represent the collective activity of cortical neurons, which reflects potential-difference fluctuations that are generated largely by excitatory postsynaptic potentials and inhibitory postsynaptic potentials on apical dendrites of pyramidal neurons. EEG activity correlates with the sleep–wake cycle, alertness and various cortical functions. Several neurological disorders are associated with characteristic abnormalities in EEG recordings, and EEG activity might provide a diagnostic tool to determine the severity of cerebral dysfunctions and predict their prognosis. Alzheimer's disease, the most common neurodegenerative disorder, is characterized by EEG abnormalities such as a shift of the EEG power spectrum to lower frequencies and a decrease in coherence of fast rhythms. By contrast, schizophrenia is not associated with an easily recognizable abnormality in spontaneous EEG activity. Before 1954 (preceding the introduction of antipsychotic drugs), EEG studies identified significantly more abnormal EEG patterns in schizophrenic patients then in controls, but no single pattern of abnormality emerged from these studies [1].

EEG reading involves the interpretation of wave forms largely by their frequency and to a lesser extent by the wave or of the wave complex of several waves. The difficulty lies, in part, in recognizing artifacts and also in being able to differentiate normal variants from abnormalities. Frequency means the number of waves per unit time - per second. The frequencies of the EEG waves run from 0.5 per second to hundreds/second. The machines however usually show frequencies of up to 26/second. [1] Waves are usually defined by their frequency and are divided, on this basis, into alpha, beta, theta and delta.

Recently, additional insight into processing in schizophrenic brains has been provided by analyzing EEG microstate duration and syntax in acute, medication-free schizophrenic patients. Unlike the traditional method of analyzing how signals from a single electrode change over time relative to a specific reference point, EEG microstates represent instantaneous ‘scalp maps’ (potential-difference maps) of the differences in relative potential between arrays of electrodes positioned over the scalp [1].

NEURONAL-NETWORK OSCILLATION AND GABA RECEPTORS

Recent postmortem studies provide consistent evidence to support abnormalities of GABA(Gamma-Amino-Butyric-Acid) neuronal networks in schizophrenic brains, including altered synaptic markers of GABA neurotransmission and deficits in parvalbumin-containing GABA interneuron's in the cortex .Because network oscillation is maintained by GABA interneuron's, selective manipulation of GABA neurotransmission at sub-unit-specific receptor levels might impact and rectify abnormal oscillatory activity in schizophrenia. [1]

NEURONAL-NETWORK OSCILLATION AND A7 NICOTINIC ACETYLCHOLINE RECEPTORS

Genetic-linkage studies demonstrate an association between polymorphism in the gene that encodes the α7 nicotinic acetylcholine (nACh) receptor and a predisposition to schizophrenia α7 nACh receptors are present predominantly on GABA inter neurons in the hippocampus, and their activation increases GABA-mediated neurotransmission in the hippocampus, thereby influencing oscillatory activity. Using slices of rat hippocampus in vitro, it has been demonstrated that the gamma oscillation induced by tetanic stimulation is enhanced by α7 nACh receptors. A recent study that describes the pharmacology of a selective α7 nACh receptor agonist PNU282987: (N-[(3R)-1-azabicyclo [2.2.2] oct-3-yl]-4-chlorobenzamide hydrochloride) reports that although the agonist does not elicit hippocampal oscillatory activity in anaesthetized rats, it significantly enhances amphetamine-induced theta and gamma oscillations. Similarly, recording brainstem-stimulation-induced theta oscillation in the hippocampus shows that PNU282987 significantly enhances the total power of oscillation at theta frequency. Based on these observations, activation of α7 nACh receptors enhances on-going oscillations that might, in turn, contribute to the known mnemonic effects of α7 nACh receptor agonists. The table below gives an insight on advantages and disadvantages of electrophysiological signals as biomarkers. [6, 7, 8]

Advantages	Disadvantages
Signal directly linked to neuronal activity	Uncertainty of encoding behavior by neuronal activity
Real-time resolution (ms) with high spatial specificity	Limitations in spatial resolution by non-invasive methods
Measuring the well-defined physical parameters of either potential difference or current	Data analysis and interpretation
Signal generators (neurons and neuronal circuits) are conservative, translating between species	Correlating electrophysiological signals between species (i.e. cortical EEG bands and identifying corresponding evoked potentials)

Table 1: Advantages and Disadvantages of Electrophysiological Signals as Biomarkers

DIMINISHED INFORMATION PROCESSING IN SCHIZOPHRENIA

Auditory-evoked potentials (AEPs) are forms of event-related potentials that follow acoustic stimulation (sound) and are recorded routinely from the scalp. Evoked potentials can be characterized by their latency and the direction of their deflection (either positive or negative).

Acoustic stimulation elicits several auditory-evoked potentials (AEPs) with various latencies that are detected by scalp EEG electrodes at the vertex. However, repeating the same acoustic stimulation within sufficiently short intervals (typically between 0.5–2.0 s) significantly attenuates the AEPs associated with the second stimuli. This phenomenon, which is known as auditory gating was demonstrated first by using AEPs that occur at 50 ms latency and a positive deflection. Auditory gating has attracted considerable interest over the past two decades, partly to evaluate whether the P50-gating deficit represents an endophenotype of schizophrenia that might, therefore, be utilized in genetic studies of the disease.

If only sensory processing that leads to AEPs is compromised, AEPs might still show auditory gating. However, gating deficit in schizophrenia is probably associated with impaired sensory processing, as indicated by aberrant event-related oscillations and diminished AEPs to conditioning stimuli. In addition, the gating process is insufficient to attenuate AEPs to the 'test' stimuli. Pharmacologically induced gating deficit, following, for example amphetamine-administration, is associated with a reduction of AEPs to conditioning stimuli and impairment in sensory-gating process [1].

DIRECT COMPARISON OF SCHIZOPHRENIC AND BIPOLAR COGNITIVE IMPAIRMENT

Cognitive impairments in schizophrenia are not epiphenomena. That is, they are not secondary to psychological issues that involve delusions, distracting effects of hallucinations, or gross motivational defects. This has been shown by several approaches. First, correlations between symptoms and cognition are weak in schizophrenia (they are, however, very strong in bipolar disorder). Second, critical impairments in working memory and executive functions in schizophrenia do not respond to teaching or cognitive rehabilitation to a marked degree. Third, symptoms and cognition can be dissociated using pharmacological tools: A study of Clozapine has found that while symptoms showed significant improvement over a one-year interval, cognitive impairment remained stable and marked [3].

Direct comparisons of patients with schizophrenia and those with bipolar disorder indicate that patients with schizophrenia have more severe and widespread deficits. Nevertheless, a subgroup of institutionalized patients with bipolar disorder appears to have chronic and severe cognitive impairments

One important measure that discriminates between patients with schizophrenia and those with bipolar disorder is intelligence. In general, patients with schizophrenia exhibit a 10-point decline of intelligence once their illness begins. That is, patients with schizophrenia have normal or near normal IQ's pre morbidly but, even during the early phases of their illness, exhibit a marked attenuation in intellectual function. In contrast, patients with bipolar disorder generally are able to maintain their IQ level. This is clinically significant and suggests that patients with schizophrenia will be less attentive and slower, have less mental precision in day-to-day cognitive operations, and may have difficulties in bringing their knowledge base to bear on social problems. In contrast, patients with bipolar disorder do not exhibit such global decline in intellectual efficiency [3, 4].

ANIMAL MODELS OF AUDITORY-GATING DEFICIT

Modeling sensory-gating deficits in experimental animals involves compromising their normal physiological gating processes. Several pharmacological agents disrupt sensory processing, including direct and indirect dopamine receptor agonists (amphetamine, apomorphine and cocaine) and NMDA receptor antagonists (PCP, ketamine). Many of these compounds disrupt sensory gating in humans and/or elicit psychosis. However, given the developmental and neuroanatomical abnormalities that characterize schizophrenia, it is naïve to expect that pharmacologically induced gating deficits will mimic perfectly gating deficits in this disease.

Nevertheless, pharmacologically induced gating deficits provide valuable animal models that resemble some characteristics of gating abnormalities and can be utilized in exploratory pharmacological studies. The receptors that are involved in pharmacologically induced gating deficits are known, so interacting with these should be expected to restore auditory gating. The true value of these pharmacologically induced gating-deficit models is their ability to reveal the efficacy of compounds that do not act at receptors that are involved directly in the disruption of gating. For example, amphetamine-induced gating deficit is reversed not only by the dopamine receptor antagonist haloperidol but also by nicotine, selective agonists and modulators of α7 nACh receptors, and rolipram, a phosphodiesterase-4 inhibitor [1].

FUTURE DIRECTIONS

Although individual drugs differ in the range and severity of their side-effects, no currently marketed agents are effective at addressing all the symptoms of this multi-faceted disorder. Cognitive impairment, which is one of the core symptoms of schizophrenia, is largely unaffected by present treatments. As understanding of the brain processes that are associated with perception and cognitive function (such as neuronal-network oscillation) advances, so should the ability to develop better treatments that address cognitive dysfunction in schizophrenia. The exact treatment for schizophrenia and cognitive disorder associated with it is yet to be found out, but this article suggest newer methods of analysis of the disease and gives a perspective on newer sites of research.

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