

EPV1312

Electrophysiological characterization of schizophrenia-associated variants in NaV1.2 sodium channel

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Introduction: A major pathophysiological hypothesis of schizophrenia states an increased activity of glutamatergic neurons leading to an imbalance of neural excitation and inhibition (E/I-imbalance). One potential molecular mechanism of E/I-imbalance is a dysfunction of voltage-gated sodium channels, which are crucial for the generation of action potentials, the fundamental event of neuronal excitation. Indeed, patients with schizophrenia exhibit an increased burden of rare exonic variants of sodium channel genes, but the literature describing their electrophysiological effect is scarce.

Objectives: The aim of this project is to assess the functional impact of three mutations of the Sodium Voltage-Gated Channel Alpha Subunit 2 (SCN2A) gene / Na_v1.2 channel which were identified in four patients with schizophrenia, using a heterologous expression system.

Methods: Three variants of the human SCN2A gene (R850P, V1282F and S1656P) were created using site-directed mutagenesis. HEK293T cells transfected with either the mutant or wild type constructs are being investigated by voltage-clamp technique, applying activation, steady-state fast inactivation, use dependency and ramp protocols.

Results: All three mutated constructs were successfully created. Preliminary recordings from the V1282F mutant indicate a shift of both the activation and steady-state fast inactivation to the hyperpolarized direction.

Conclusions: In a subgroup of patients, E/I imbalance may be a consequence of Nav1.2 mutations leading to increased excitability of glutamatergic neurons. By integrating insights from different mutations we aim to identify traits of a potentially shared disease pathway which may provide a basis for the development of novel therapeutics.

Disclosure: No significant relationships.

Keywords: schizophrenia; Electrophysiology; site-directed mutagenesis; Voltage-gated sodium channels

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The psychopathological trajectories to delusion in Schizophrenia: the affective and schizotypal pathways

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Introduction: Delusions are a key feature of schizophrenia psychopathology. From a phenomenological approach, Jaspers (1913) differentiates between “primary” or true schizophrenic delusions,

defined as an unmediated phenomenon that cannot be understood in terms of prior psychological origin or motivation, and “secondary” delusions, understandable from the patient’s mood state or personality. Primary delusions have been considered the hallmark of reality distortion dimension in schizophrenia, disregarding a possible affective pathway to delusional belief.

Objectives: The present study was aimed at elucidating the psychopathological trajectories to delusion in schizophrenia through the investigation of both affective and schizotypal trait dispositions.

Methods: Seventy-eight participants affected by schizophrenia were administered the Peters Delusional Inventory (PDI), the Positive and Negative Affective Scale (PANAS), the Experience of Shame Scale (ESS), the Referential Thinking Scale (REF), the Magical Ideation Scale (MIS) and the Perceptual Aberration Scale (PAS).

Results: The severity of delusional ideation (PDI) was positively related to both affective (PANAS positive dimension, ESS) and schizotypal traits (MIS, PAS and REF). Moreover, referential thinking (REF) mediated the relationship between “magical ideation” (MIS) and delusions severity (Fig. 1), whereas experience of shame (ESS) was a moderating factor in the between referential thinking and delusion severity (Fig. 2).

Fig. 1. Mediation model between schizotypal traits and delusion severity.

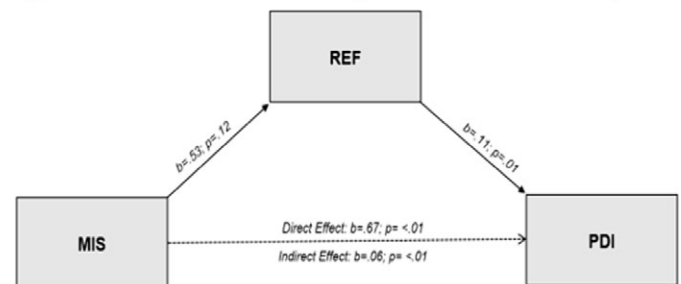
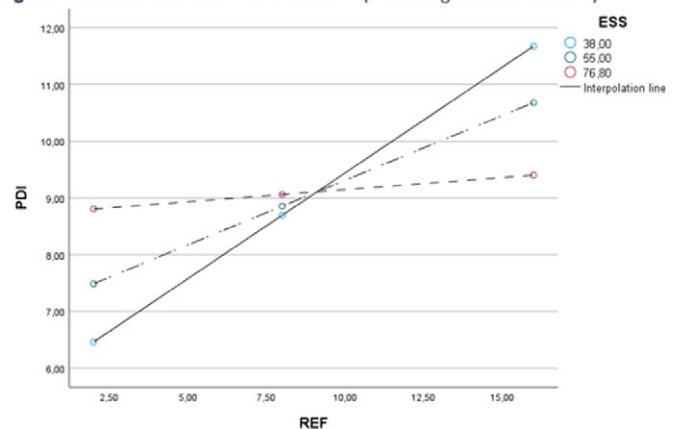


Fig. 2. Interaction between REF and ESS in predicting delusion severity.



Conclusions: The study findings suggest that in schizophrenia patients, severity of delusions is underpinned by an intertwining of both affective and schizotypal pathways.

Disclosure: No significant relationships.

Keywords: delusion; Psychosis; Psychopathology; schizophrenia