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Latest updates from the PRISM project

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PRISM Major Findings

PRISM (Psychiatric Ratings using Intermediate Stratified Markers) is an academic-industry collaboration funded by the EU's Horizon 2020 initiative and the private sector in equal measure within the framework the EU Innovative Medicines Initiative. Started in 2016, it built on the Research Domain Criteria concept (RDoC) to measure quantitative biomarkers associated with clinical and behavioural outcomes across four different domains (social functioning, sensory processing, working memory, and attention) in neurological and psychiatric disorders. The concepts, considerations, methodologies, and preclinical and clinical outlines of the project can be found in a series of manuscripts published as a PRISM special issue in *Neuroscience and Biobehavioral Reviews*.

Deep phenotyping of schizophrenia (SZ) and Alzheimer's disease (AD) patients and their corresponding age-matched control groups was followed by structural and functional neuroimaging (MRI), analyses of the brain's electrical activity (EEG) and objective and subjective measurement of social functioning through questionnaires and digital phenotyping through smartphones (www.behapp.com). In addition, because it is well understood that there is a biological basis to such indications, which may present at the DNA, RNA, and/or epigenome level, a blood draw was run.

DNA analyses within a genome-wide association framework identified 19 loci for sociability (Bralten et at, 2021) where associated transcripts are expressed in circuits related to the default mode network (DMN), a brain network mainly composed of the medial prefrontal cortex, posterior cingulate cortex and angular gyrus. The DMN is known to be active when a person is awake, at rest, and not focused on outside stimuli.

The project found a relationship between the DMN and social functioning irrespective of diagnosis (Saris et al, 2021). The consortium partners feel this might be a proof of concept in need of replication, ideally to be extended to a new patient group, which in PRISM2 will be major depressive disorder (MDD). The project established that variation in the DMN is associated with variation in social functioning, irrespective of diagnosis, using resting state connectivity, structural and EEG measures together with questionnaires and digital measures of social functioning (e.g., Jongs et al., 2020).

PRISM aims to go beyond the RDoC concept to define biotypes within and across the cohorts, in addition to measuring associations between symptom-based diagnoses and traits. To this end, more than 4,000 quantitative biological endpoints were used for multi-modal and unimodal supervised and unsupervised approaches.

PRISM1 developed a preclinical test-battery to assess phenotypes, which will be used in PRISM2 to relate human findings to animal models. For example, to provide causality between the identified neural network and social functioning (e.g., Peleh et al., 2020).

PRISM2 started June 1st 2021 and its goal is to build on the achievements of the original PRISM project. Specifically, it aims to validate PRISM's findings on social dysfunction in schizophrenia and Alzheimer's disease, and investigate whether they also apply to major depressive disorder.

Ultimately, the work of PRISM2 should ensure that these findings will result in more accurate diagnoses and treatments for people with Alzheimer's disease, schizophrenia and major depressive disorder.

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