D6.7 Summary report on major publications/findings

PRISM 2 – GA 101034377
Psychiatric Ratings using
Intermediate Stratified Markers 2

WP6 Dissemination, communication, exploitation and training

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Publishable summary

All PRISM 2 publications that are listed below are published and listed at the PRISM 2 website https://prism2-project.eu/en/prism-project/publications/
More data analyses are planned and some of them are already completed and will be published soon, please see details under *Conclusion* at page 9. Therefore, the PRISM 2 website will be updated also after the official project end, and IHI will be informed

Overview of all major PRISM 2 publications

1) Braak et al. (2024). **Social dysfunction relates to shifts within socioaffective brain systems among Schizophrenia and Alzheimer's disease patients.** *European Neuropsychopharmacology.*

   Social dysfunction represents one of the most common signs of neuropsychiatric disorders, such as Schizophrenia (SZ) and Alzheimer's disease (AD). Perturbed socioaffective neural processing is crucially implicated in SZ/AD and generally linked to social dysfunction. Yet, transdiagnostic properties of social dysfunction and its neurobiological underpinnings remain unknown. As part of the European PRISM project, we examined whether social dysfunction maps onto shifts within socioaffective brain systems across SZ and AD patients. We probed coupling of social dysfunction with socioaffective neural processing, as indexed by an implicit facial emotional processing fMRI task, across SZ (N = 46), AD (N = 40) and two age-matched healthy control (HC) groups (N = 26 HC-younger and N = 27 HC-older). Behavioural (i.e., social withdrawal, interpersonal dysfunction, diminished prosocial or recreational activity) and subjective (i.e., feelings of loneliness) aspects of social dysfunction were assessed using the Social Functioning Scale and De Jong-Gierveld loneliness questionnaire, respectively. Across SZ/AD/HC participants, more severe behavioural social dysfunction related to hyperactivity within fronto-parieto-limbic brain systems in response to sad emotions (P = 0.0078), along with hypoactivity of these brain systems in response to happy emotions (P = 0.0418). Such relationships were not found for subjective experiences of social dysfunction. These effects were independent of diagnosis, and not confounded by clinical and sociodemographic factors. In conclusion, behavioural aspects of social dysfunction across SZ/AD/HC participants are associated with shifts within fronto-parieto-limbic brain systems. These findings pinpoint altered socioaffective neural processing as a putative marker for social dysfunction, and could aid personalized care initiatives grounded in social behaviour.

2) Braak et al. (2024). **Social Dysfunction and Neural Processing of Emotional Valence Across Depressive and Anxiety Disorders.** *Wiley.*

   Social dysfunction is common across psychiatric disorders, including depressive and anxiety disorders. Both disorders have been associated with negative biases in socioaffective neural processing, which may impact responses to social stimuli. This study aims to determine whether social dysfunction across these psychiatric disorders is indeed coupled to altered neural processing of negative and positive valenced emotional stimuli and whether a common neurobiological correlate can be identified. An implicit emotional faces functional magnetic resonance imaging task was used to measure brain activation in response to emotional stimuli in participants with depression (N=46), anxiety (N=45), comorbid depressive and anxiety disorders (N=57), and healthy controls (N=52). Social dysfunction was indexed using five items of the World Health Organisation Disability Assessment Schedule-2.0 (i.e., perceived social disability) and with the De Jong-Gierveld Loneliness scale (LON; i.e., perceived loneliness). Higher perceived social disability scores were associated with greater brain activation in the left angular gyrus in response to sad emotional faces across all participants but did not correlate with responses to overall negative (sad, angry, and fearful) or positive (happy) emotional faces. No interaction effect of diagnosis was observed for the finding. Perceived loneliness scores did not correlate with brain activation to emotional faces. Taken together, perceived social disability across persons with and without depressive and/or anxiety disorders converges specifically on sad emotional processing of the left angular gyrus, suggesting a potential common neurobiological correlate for social dysfunction.

3) Correll et al. (2024). **Finding the Right Setting for the Right Treatment During the Acute Treatment of Individuals with Schizophrenia: A Narrative Review and Clinical Practice Guideline.** *Neuropsychiatric disease and treatment.*

Background: Schizophrenia is most times a chronic and often debilitating illness associated with poor mental health outcomes. Early and effective treatment of schizophrenia in the most appropriate setting can make a significant difference in the long-term recovery. The aim of this narrative review was to provide suggestions and recommendations for effectively managing patients with schizophrenia during acute exacerbations and to enhance awareness and skills related to personalized medicine.
Methods: A panel of academics and clinicians with experience in the field of psychosis met virtually on July 13th 2023 to narratively review and discuss the research evidence and their clinical experience about the most appropriate acute treatments for patients with schizophrenia. This manuscript represents a synthesis of the panel analysis and discussion.
Results: First contact is very important for service users, as is finding the most adequate treatment setting. If patients present to the emergency department, which may be a traumatic setting for service users, a dedicated environment with adequate space and specialized mental health support, including personnel trained in de-escalation techniques, is recommended. A well-connected continuum of care is strongly recommended, possibly with seamless links between inpatient units, day hospital services, outpatient facilities and rehabilitation services. Ideally, this should be structured as part of a coordinated step-down service line. Treatment challenges include suboptimal response, side effects, and nonadherence, which is reduced by the use of long-acting injectable antipsychotics.
Conclusion: Individual circumstances, including age, gender, and presence of hostility/aggression or self-harm, cognitive impairment and negative symptoms, comorbidities (depression, substance use disorders) or associated symptoms (anxiety, insomnia), should be considered when selecting the most appropriate treatment for the acute phase of schizophrenia. Efficacy and feasibility, as well as acceptability and tolerability of treatments, require joint consideration from the early stages of schizophrenia, thereby enhancing the possibility of improved short- and long-term outcomes.

4) Fanelli et al. (2024). **Shared genetics linking sociability with the brain's default mode network.** *medRxiv.*

The brain's default mode network (DMN) plays a role in social cognition, with altered DMN function being associated with social impairments across various neuropsychiatric disorders. In the present study, we examined the genetic relationship between sociability and DMN-related resting-state functional magnetic resonance imaging (rs-fMRI) traits.
To this end, we used genome-wide association summary statistics for sociability and 31 activity and 64 connectivity DMN-related rs-fMRI traits (N=34,691-342,461). First, we examined global and local genetic correlations between sociability and the rs-fMRI traits. Second, to assess putatively causal relationships between the traits, we conducted bi-directional Mendelian randomisation (MR) analyses. Finally, we prioritised genes influencing both sociability and rs-fMRI traits by combining three methods: gene-expression eQTL MR analyses, the CELLECT framework using single-nucleus RNA-seq data, and network propagation in the context of a protein-protein interaction network.
Significant local genetic correlations were found between sociability and two rs-fMRI traits, one representing spontaneous activity within the temporal cortex, the other representing connectivity between the frontal/cingulate and angular/temporal cortices. Sociability affected 12 rs-fMRI traits when allowing for weakly correlated genetic instruments. Combing all three methods for gene prioritisation, we defined 17 highly prioritised genes, with DRD2 and LINGO1 showing the most robust evidence across all analyses.
By integrating genetic and transcriptomics data, our gene prioritisation strategy may serve as a blueprint for future studies. The prioritised genes could be explored as potential biomarkers for social dysfunction in the context of neuropsychiatric disorders and as drug target genes.

5) Kas et al. (2024). **Towards a consensus roadmap for a new diagnostic framework for mental disorders.** *European Neuropsychopharmacology.*

Current nosology claims to separate mental disorders into distinct categories that do not overlap with each other. This nosological separation is not based on underlying pathophysiology but on convention-based clustering of qualitative symptoms of disorders which are typically measured subjectively. Yet, clinical heterogeneity and diagnostic overlap in disease symptoms and dimensions

within and across different diagnostic categories of mental disorders is huge. While diagnostic categories provide the basis for general clinical management, they do not describe the underlying neurobiology that gives rise to individual symptomatic presentations. The ability to incorporate neurobiology into the diagnostic framework and to stratify patients accordingly will be a critical step forward for the development of new treatments for mental disorders. Furthermore, it will also allow physicians to provide patients with a better understanding of their illness's complexities and management. To realize this ambition, a paradigm shift is needed to build an understanding of how neuropsychiatric conditions can be defined more precisely using quantitative (multimodal) biological processes and markers and thus to significantly improve treatment success. The ECNP New Frontiers Meeting 2024 set out to develop a consensus roadmap for building a new diagnostic framework for mental disorders by discussing its rationale, outlook, and consequences with all stakeholders involved. This framework would instantiate a set of principles and procedures by which research could continuously improve precision diagnostics while moving away from traditional nosology. In this meeting report, the speakers' summaries from their presentations are combined to address three key elements for generating such a roadmap, namely, the application of innovative technologies, understanding the biology of mental illness, and translating biological understanding into new approaches. In general, the meeting indicated a crucial need for a biology-informed framework to establish more precise diagnosis and treatment for mental disorders to facilitate bringing the right treatment to the right patient at the right time.

6) Østergaard et al. (2024). **The aperiodic exponent of neural activity varies with vigilance state in mice and men.** *PLoS One.*

Recently the 1/f signal of human electroencephalography has attracted attention, as it could potentially reveal a quantitative measure of neural excitation and inhibition in the brain, that may be relevant in a clinical setting. The purpose of this short article is to show that the 1/f signal depends on the vigilance state of the brain in both humans and mice. Therefore, proper labelling of the EEG signal is important as improper labelling may obscure disease-related changes in the 1/f signal. We demonstrate this by comparing EEG results from a longitudinal study in a genetic mouse model for synaptic dysfunction in schizophrenia and autism spectrum disorders to results from a large European cohort study with schizophrenia and mild Alzheimer's disease patients. The comparison shows when the 1/f is corrected for vigilance state there is a difference between groups, and this effect disappears when vigilance state is not corrected for. In conclusion, more attention should be paid to the vigilance state during analysis of EEG signals regardless of the species.

7) Si et al. (2024). **Mapping gray and white matter volume abnormalities in early-onset psychosis: an ENIGMA multicenter voxel-based morphometry study.** *Molecular Psychiatry.*

Introduction: Regional gray matter (GM) alterations have been reported in early-onset psychosis (EOP, onset before age 18), but previous studies have yielded conflicting results, likely due to small sample sizes and the different brain regions examined. In this study, we conducted a whole brain voxel-based morphometry (VBM) analysis in a large sample of individuals with EOP, using the newly developed ENIGMA-VBM tool.
Methods: 15 independent cohorts from the ENIGMA-EOP working group participated in the study. The overall sample comprised T1-weighted MRI data from 482 individuals with EOP and 469 healthy controls. Each site performed the VBM analysis locally using the standardized ENIGMA-VBM tool. Statistical parametric T-maps were generated from each cohort and meta-analyzed to reveal voxel-wise differences between EOP and healthy controls as well as the individual-based association between GM volume and age of onset, chlorpromazine (CPZ) equivalent dose, and other clinical variables.
Results: Compared with healthy controls, individuals with EOP showed widespread lower GM volume encompassing most of the cortex, with the most marked effect in the left median cingulate (Hedges' $g = 0.55$, $p = 0.001$ corrected), as well as small clusters of lower white matter (WM), whereas no regional GM or WM volumes were higher in EOP. Lower GM volume in the cerebellum, thalamus and left inferior parietal gyrus was associated with older age of onset. Deficits in GM in the left inferior frontal gyrus, right insula, right precentral gyrus and right superior frontal gyrus were also associated with higher CPZ equivalent doses.
Conclusion: EOP is associated with widespread reductions in cortical GM volume, while WM is affected to a smaller extent. GM volume alterations are associated with age of onset and CPZ equivalent dose but these effects are small compared to case-control differences. Mapping

anatomical abnormalities in EOP may lead to a better understanding of the role of psychosis in brain development during childhood and adolescence.

8) Sprooten et al. (2024). **Resting-state brain connectivity and sociability: a whole-brain affair.** *PsyArXiv Preprints.*

Sociability is relevant for most mental health conditions and their prognosis. The classic "social brain" maps mainly to the default mode (DMN) and salience networks (SN). Recent studies also suggest involvement of other brain regions, but results are not yet fully consistent and interpretable. We conducted a fully data-driven resting-state connectivity study of sociability in the UK Biobank (N=31,266). BOLD amplitude within, and timeseries correlations between 21 intrinsic brain networks were associated with a general sociability metric. Sociability showed modest but significant associations with many resting-state functional connectivity measures throughout the brain. Sociability was positively associated with sensorimotor network connectivity and showed intricate association patterns with SN and DMN connectivity. Based on our results, we hypothesise that there are important, probably reciprocal links between social behaviours and sensorimotor networks, and that social isolation may be accompanied by thought processes within the DMN being isolated from the rest of the brain.

9) Ronde et al. (2024). **Default mode network dynamics: an integrated neurocircuitry perspective on social dysfunction in human brain disorders.** *Neuroscience and biobehavioral reviews.*

Our intricate social brain is implicated in a range of brain disorders, where social dysfunction emerges as a common neuropsychiatric feature cutting across diagnostic boundaries. Understanding the neurocircuitry underlying social dysfunction and exploring avenues for its restoration could present a transformative and transdiagnostic approach to overcoming therapeutic challenges in these disorders. The brain's default mode network (DMN) plays a crucial role in social functioning and is implicated in various neuropsychiatric conditions. By thoroughly examining the current understanding of DMN functionality, we propose that the DMN integrates diverse social processes, and disruptions in brain communication at regional and network levels due to disease hinder the seamless integration of these social functionalities. Consequently, this leads to an altered balance between self-referential and attentional processes, alongside a compromised ability to adapt to social contexts and anticipate future social interactions. Looking ahead, we explore how adopting an integrated neurocircuitry perspective on social dysfunction could pave the way for innovative therapeutic approaches to address brain disorders.

10) Arango (2023). **Child maltreatment should be a priority for public mental health interventions.** *European Archives of Psychiatry and Clinical Neuroscience.*

Mental health disorders are not different from other medical disorders in that they too are preventable. Unfortunately, the mounting evidence that cost-effective primary preventive mental health strategies might reduce the incidence of mental health disorders or shift expected trajectories to less debilitating outcomes has not yet translated into the investment seen in other areas of medicine. Continual identification of powerful risk factors offers the prospect of a future for preventive and public heath psychiatry. Many of those factors are potentially amenable to change through preventive interventions. An evidence-based atlas of risk and protective factors for mental disorders potentially manageable through primary preventive intervention has recently been published. One of the most replicable risk factors is child maltreatment in its many forms: sexual and physical abuse, bullying (discrimination), neglect, and even war crimes. In fact, in a recent meta-umbrella systematic review, the largest global population attributable fraction for all risk factors and all mental disorders was childhood adversity, which accounted for some 38% of global cases of schizophrenia spectrum disorders. This means that reducing such childhood adversity and maltreatment should be a priority in national public health roadmaps. In this issue, many important papers deal with risk factors for mental disorders and are therefore relevant for potential implementation of preventive strategies. Prevention would benefit from a better understanding of the etiopathophysiology of mental disorders. In fact, in most instances, the link between certain psychological risk factors and the neurobiology of various mental disorders is still unknown. In this issue, Derome et al. report that subjects with high child trauma scores showed abnormal hippocampal activation and hippocampal–temporal–prefrontal connectivity during novelty detection as a salient event paradigm. This study adds evidence to the link between early stressful life experiences and environments and dysfunction of key areas for

psychopathology in disorders such as psychosis. Another piece of evidence—in this case memory impairment rather than hippocampal abnormality—is reported by Guo et al. in a large sample of untreated patients with major depression. In this study, child maltreatment contributed to memory impairment independently of a major depression diagnosis. Demonstrated risk factors that have been increasing in recent years are loneliness and social exclusion. In an elegant study, Brinker et al. conducted an online survey with an imaginary scenario in which a large group of individuals demonstrated more aggressive behaviour against excluders (one or two work colleagues excluding the participant from a social activity) than includers. Interestingly, the experience of loneliness was associated with a further increase in or lack of inhibition of aggressive behavioural tendencies. Another related potentially preventable risk factor is racism associated with minority status and migration. In addition, in this issue, Lazaridou et al. report that an umbrella review of meta-analyses shows greater psychosis risk after migration from developing countries, especially among Caribbean and African migrants. Another recent area for research has been the effect of environmental factors, such as access to clean water and hygienic sanitation services, housing conditions, air quality, work environment, and exposure to extreme weather conditions, all of which, taken together, are considered responsible for the burden of mental disorders worldwide. Among those environmental factors, climate-change-associated environmental stressors are increasingly the focus of research interest. Understanding environment- and nature-related treatments is fundamental because they could constitute a cost-effective approach to reduce and manage mental health risks. In this issue, Arabi et al. show how both increased mental health burden and exposure to climate-related environmental stressors were associated with local poverty. In their study, lack of surrounding greenspace, and high nitrogen dioxide levels, noise pollution, and particle pollution were all associated with local poverty, which accounted for a significant variance in mental health. We are at a point where good evidence shows that interventions such as parenting programmes and promotion of child/parent attachment, anti-bullying programmes in schools, and promoting physical exercise are not only effective but also reduce costs while preventing mental health problems. We are already late to the game, but with a tsunami of mental disorders pummelling the world, there can be no further excuse for delaying all of these preventive strategies.

11) Arango et al. (2023). **Delphi panel to obtain clinical consensus about using long-acting injectable antipsychotics to treat first-episode and early-phase schizophrenia: treatment goals and approaches to functional recovery.** *BMC Psychiatry.*

Background: Schizophrenia is mostly a chronic disorder whose symptoms include psychosis, negative symptoms and cognitive dysfunction. Poor adherence is common and related relapse can impair outcomes. Long-acting injectable antipsychotics (LAIs) may promote treatment adherence and decrease the likelihood of relapse and rehospitalization. Using LAIs in first-episode psychosis (FEP) and early-phase (EP) schizophrenia patients could benefit them, yet LAIs have traditionally been reserved for chronic patients.
Methods: A three-step modified Delphi panel process was used to obtain expert consensus on using LAIs with FEP and EP schizophrenia patients. A literature review and input from a steering committee of five experts in psychiatry were used to develop statements about patient population, adverse event management, and functional recovery. Recruited Delphi process psychiatrists rated the extent of their agreement with the statements over three rounds (Round 1: paper survey, 1:1 interview; Rounds 2-3: email survey). Analysis rules determined whether a statement progressed to the next round and the level of agreement deemed consensus. Measures of central tendency (mode, mean) and variability (interquartile range) were reported back to help panelists assess their previous responses in the context of those of the overall group.
Results: The Delphi panelists were 17 psychiatrists experienced in treating schizophrenia with LAIs, practicing in seven countries (France, Italy, US, Germany, Spain, Denmark, UK). Panelists were presented with 73 statements spanning three categories: patient population; medication dosage, management, and adverse events; and functional recovery domains and assessment. Fifty-five statements achieved ≥ 80% agreement (considered consensus). Statements with low agreement (40-79%) or very low agreement (< 39%) concerned initiating dosage in FEP and EP patients, and managing loss of efficacy and breakthrough episodes, reflecting current evidence gaps. The panel emphasized benefits of LAIs in FEP and EP patients, with consensus that LAIs can decrease the risk of relapse, rehospitalization, and functional dysfunction. The panel supported links between these benefits and multidimensional longer-term functional recovery beyond symptomatic remission.
Conclusions: Findings from this Delphi panel support the use of LAIs in FEP and EP schizophrenia

patients regardless of disease severity, number of relapses, or social support status. Gaps in clinician knowledge make generating evidence on using LAIs in FEP and EP patients critical.

12) Cortese et al. (2023). **The future of child and adolescent clinical psychopharmacology: A systematic review of phase 2, 3, or 4 randomized controlled trials of pharmacologic agents without regulatory approval or for unapproved indications.** *Neuroscience & Biobehavioral Reviews.*

We aimed to identify promising novel medications for child and adolescent mental health problems. We systematically searched https://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ (from 01/01/2010–08/23/2022) for phase 2 or 3 randomized controlled trials (RCTs) of medications without regulatory approval in the US, Europe or Asia, including also RCTs of dietary interventions/probiotics. Additionally, we searched phase 4 RCTs of agents targeting unlicensed indications for children/adolescents with mental health disorders. We retrieved 234 ongoing or completed RCTs, including 26 (11%) with positive findings on ≥ 1 primary outcome, 43 (18%) with negative/unavailable results on every primary outcome, and 165 (70%) without publicly available statistical results. The only two compounds with evidence of significant effects that were replicated in ≥ 1 additional RCT without any negative RCTs were dasotraline for attention-deficit/hyperactivity disorder, and carbetocin for hyperphagia in Prader-Willi syndrome. Among other strategies, targeting specific symptom dimensions in samples stratified based on clinical characteristics or established biomarkers may increase chances of success in future development programmes.

13) Fusar-Poli et al. (2023). **Examining the association between exposome score for schizophrenia and cognition in schizophrenia, siblings, and healthy controls: Results from the EUGEI study.** *Psychiatry Research.*

Background: People with schizophrenia spectrum disorders (SSD) frequently present cognitive impairments. Here, we investigated whether the exposome score for schizophrenia (ES-SCZ) - a cumulative environmental exposure score - was associated with impairments of neurocognition, social cognition, and perception in patients with SSD, their unaffected siblings, and healthy controls. Methods: This cross-sectional sample consisted of 1200 patients, 1371 siblings, and 1564 healthy controls. Neurocognition, social cognition, and perception were assesed using a short version of the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III), the Degraded Facial Affect Recognition Task (DFAR), and the Benton Facial Recognition Test (BFR), respectively. Regression models were used to analyze the association between ES-SCZ and cognitive domains in each group. Results: There were no statistically significant associations between ES-SCZ and cognitive domains in SSD. ES-SCZ was negatively associated with T-score of cognition in siblings (B=-0.40, 95% CI -0.76 to -0.03) and healthy controls (B=-0.63, 95% CI -1.06 to -0.21). Additionally, ES-SCZ was positively associated with DFAR-total in siblings (B=0.83, 95% CI 0.26 to 1.40). Sensitivity analyses excluding cannabis use history from ES-SCZ largely confirmed the main findings. Conclusions: Longitudinal cohorts may elucidate how environmental exposures influence the onset and course of cognitive impairments in trans-syndromic psychosis spectrum.

14) Sideli et al. (2023). **The relationship between genetic liability, childhood maltreatment, and IQ: findings from the EU-GEI multicentric case-control study.** *Social psychiatry and psychiatric epidemiology.*

This study investigated if the association between childhood maltreatment and cognition among psychosis patients and community controls was partially accounted for by genetic liability for psychosis. Patients with first-episode psychosis (N = 755) and unaffected controls (N = 1219) from the EU-GEI study were assessed for childhood maltreatment, intelligence quotient (IQ), family history of psychosis (FH), and polygenic risk score for schizophrenia (SZ-PRS). Controlling for FH and SZ-PRS did not attenuate the association between childhood maltreatment and IQ in cases or controls. Findings suggest that these expressions of genetic liability cannot account for the lower levels of cognition found among adults maltreated in childhood.

15) Stella et al. (2023). **Analysis of common genetic variation across targets of microRNAs dysregulated both in ASD and epilepsy reveals negative correlation.** *Frontiers in Genetics.*

Genetic overlap involving rare disrupting mutations may contribute to high comorbidity rates between autism spectrum disorders and epilepsy. Despite their polygenic nature, genome-wide association

studies have not reported a significant contribution of common genetic variation to comorbidity between both conditions. Analysis of common genetic variation affecting specific shared pathways such as miRNA dysregulation could help to elucidate the polygenic mechanisms underlying comorbidity between autism spectrum disorders and epilepsy. We evaluated here the role of common predisposing variation to autism spectrum disorders and epilepsy across target genes of 14 miRNAs selected through bibliographic research as being dysregulated in both disorders. We considered 4,581 target genes from various in silico sources. We described negative genetic correlation between autism spectrum disorders and epilepsy across variants located within target genes of the 14 miRNAs selected ($p = 0.0228$). Moreover, polygenic transmission disequilibrium test on an independent cohort of autism spectrum disorders trios ($N = 233$) revealed an under-transmission of autism spectrum disorders predisposing alleles within miRNAs' target genes across autism spectrum disorders trios without comorbid epilepsy, thus reinforcing the negative relationship at the common genetic variation between both traits. Our study provides evidence of a negative relationship between autism spectrum disorders and epilepsy at the common genetic variation level that becomes more evident when focusing on the miRNA regulatory networks, which contrasts with observed clinical comorbidity and results from rare variation studies. Our findings may help to conceptualize the genetic heterogeneity and the comorbidity with epilepsy in autism spectrum disorders.

16) Bas-Hoogendam et al. (2022). **Structural Brain Correlates of Childhood Inhibited Temperament: An ENIGMA-Anxiety Mega-analysis.** *Journal of the American Academy of Child and Adolescent Psychiatry.*

Temperament involves stable behavioral and emotional tendencies that differ between individuals, which can be first observed in infancy or early childhood and relate to behavior in many contexts and over many years. One of the most rigorously characterized temperament classifications relates to the tendency of individuals to avoid the unfamiliar and to withdraw from unfamiliar people, objects, and unexpected events. This temperament is referred to as behavioral inhibition or inhibited temperament (IT). IT is a moderately heritable trait1 that can be measured in multiple species. In humans, levels of IT can be quantified from the first year of life through direct behavioral observations or reports by caregivers or teachers. Similar approaches as well as self-report questionnaires on current and/or retrospective levels of IT can be used later in life.
Variations in IT are present on a continuous scale within the population, and research suggests that about 20% of young children are characterized by high IT, which is in general stable over time. Considerable data suggest that this high childhood IT (cIT) has adverse long-term consequences: infants with cIT often become more reserved adults, and, on average, such infants exhibit poorer outcomes than noninhibited infants with respect to social relationships and internalizing psychopathology. More specifically, almost half of all children with elevated and stable cIT will develop social anxiety disorder later in life compared with only 12% of noninhibited children. Thus, cIT predicts risk for later psychopathology, especially social anxiety disorder.
Several neuroimaging studies have examined neurobiological correlates of cIT. Such research is important, as brain characteristics – including brain structure, function, and connectivity—may mediate the cIT-related risk for poor outcomes. Previous studies have linked cIT to the structure and function of brain networks involved in emotion perception, experience, and regulation. These brain networks involve the dorsal (caudal) and ventral (rostral) anterior cingulate cortex, insula, amygdala, dorsolateral and medial prefrontal cortex, orbitofrontal cortex, and striatum, all of which have also been implicated in the familial risk for social anxiety disorder. In addition, translational work on anxious temperament has indicated involvement of the hippocampus. Despite this progress, the few available studies on the neural structural correlates of cIT are often restricted to specific regions of interest, while, to the best of our knowledge, cortical surface area and cortical thickness have been examined in only one study with an exploratory approach. Furthermore, most findings with respect to brain structure are unique to a specific sample, and crossstudy comparisons are limited by relatively small sample sizes and failure to consider potential modifying variables such as age and biological sex.
In this ENIGMA-Anxiety project, we aim to extend previous work by examining brain structure associated with cIT in a large dataset, assembling data acquired at 12 research centers worldwide (17 samples, $N = 4,681$). Compared with the individual studies, this new study is better powered owing to the larger number of research participants available for analysis. Moreover, by combining data through a mega-analytic approach, the present study facilitates the differentiation of consistent, generalizable findings from false-positive findings that could emerge from studies with smaller

samples. Such work has the potential to establish reproducible anatomical correlates and could inform the development of mechanistic studies and intervention research with clinical relevance.

17) Braak et al. (2022). **Theory of Mind and social functioning among neuropsychiatric disorders: A transdiagnostic study.** *European Neuropsychopharmacology.*

Social dysfunction is commonly present in neuropsychiatric disorders of schizophrenia (SZ) and Alzheimer's disease (AD). Theory of Mind (ToM) deficits have been linked to social dysfunction in disease-specific studies. Nevertheless, it remains unclear how ToM is related to social functioning across these disorders, and which factors contribute to this relationship. We investigated transdiagnostic associations between ToM and social functioning among SZ/AD patients and healthy controls, and explored to what extent these associations relate to information processing speed or facial emotion recognition capacity. A total of 163 participants were included (SZ: n=56, AD: n=50 and age-matched controls: n=57). Social functioning was assessed with the Social Functioning Scale (SFS) and the De Jong-Gierveld Loneliness Scale (LON). ToM was measured with the Hinting Task. Information processing speed was measured by the Digit Symbol Substitution Test (DSST) and facial emotion recognition capacity by the facial emotion recognition task (FERT). Case-control deficits in Hinting Task performance were larger in AD (rrb = -0.57) compared to SZ (rrb = -0.35). Poorer Hinting Task performance was transdiagnostically associated with the SFS (βHinting-Task = 1.20, p<0.01) and LON (βHinting-Task = -0.27, p<0.05). DSST, but not FERT, reduced the association between the SFS and Hinting Task performance, however the association remained significant (βHinting-Task = 0.95, p<0.05). DSST and FERT performances did not change the association between LON and Hinting Task performance. Taken together, ToM deficits are transdiagnostically associated with social dysfunction and this is partly related to reduced information processing speed.

18) Szerman et al. (2022). **Is there such a thing as gambling dual disorder? Preliminary evidence and clinical profiles.** *European Neuropsychopharmacology.*

Patients with gambling disorder (GD) frequently present other mental disorders, such as substance use disorder (SUDs), attention deficit/hyperactivity disorder (ADHD), mood disorders, and impulse-control disorders. We propose that GD should not be conceptualized as a single nosological entity, but rather as a gambling dual disorder (GDD). This study aims to provide further evidence of the co-occurrence of GD and other mental disorders in routine clinical practice and to identify different clinical profiles of severity. This descriptive, cross-sectional, and observational study included 116 patients with GD who were undergoing treatment in a specialized center. The MULTICAGE-CAD 4 and South Oaks gambling screen questionnaires confirmed the presence of GD in 97.4% and 100% of the patients, respectively. Other addictive behaviors such as compulsive spending, Internet, video games, or SUD (59.5%, 27.6%, 11.2%, and 13.8%, respectively) were also identified. The most used substances were tobacco (42.2%) and alcohol (5.2%). Half of the patients suffered from ADHD, 30.2% showed moderate or severe depression, and 17.2% suffered from a social anxiety problem. The majority (76.7%) also presented a phenotype with high impulsiveness. The cluster analysis identified two different clinical profiles of severity in patients with GDD. One profile showed higher severity of other mental disorders (ADHD, depression, anxiety, SUD, or insomnia), impulsivity, general psychopathological burden, and disability. In conclusion, our study provides further evidence on the co-occurrence of GD and other mental disorders supporting the GDD existence, shows impulsiveness as a vulnerability factor for GD, and identifies two clinical severity profiles.

Conclusion

A lot of the PRISM 2 main findings are already published. But there will be more publications, these 3 data analyses are already finalised and will be published soon:

- Objective: DMN functional connectivity in the rostromedial prefrontal cortex (rmPFC) on rsfMRI is negatively associated with social functioning in patients with schizophrenia (SZ), Alzheimer's Disease (AD) and in Healthy Control (HC) participants. Responsible partners: 08 SBG + 06 VUMC

- Objective: Correlation of SFS self-report social functioning scales with Behapp measurements of social functioning. Responsible partner: 01 RUG

- Objective: To demonstrate that the relationship of comparatively lower DMN functional connectivity in the rmPFC predicts worse social functioning in SZ, AD, and HC applies to patients with Major Depressive Disorder (MDD). Responsible partners: 08 SBG + 06 VUMC

And the data analyses below are in their final stages:

- Objective: High Behapp social functioning scores are associated with high resting state EEG connectivity index scores in the DMN of patients with AD, SZ, and in HC, independent of their diagnostic labels. Responsible partners: 07 Biotrial + 01 RUG

- Objective: To demonstrate that the finding of higher Behapp social functioning scores predicts higher resting state EEG functional connectivity in the DMN applies to patients with MDD. Responsible partners: 07 Biotrial + 01 RUG

- Objective: To determine whether speech-based endpoints measured from a variety of speech elicitation tasks are related to social dysfunction in participants with SZ, AD, MDD and HC participants. Responsible partner:13 BI

- Objective: To determine whether EEG DMN connectivity index scores (in response to emotional valent faces) are associated with social dysfunction in patients with SZ, AD, MDD, and in HC participants. Responsible partner: 07 Biotrial

- Objective: High Behapp social functioning scores are associated with high DTI fractional anisotropy (FA) or mean diffusivity (MD) in the Inferior Frontotemporal Fasciculus (IFF), uncinate fasciculus (UF), and forceps minor (FM) functioning in patients with SZ, AD, MDD, and in HC independent of diagnostic labels. Responsible partners: 01 RUG + 08 SBG

Please see also for more details: D3.5Manuscript(s) on the outcomes linked to the primary objectives of the deep phenotyping study: reproducibility and generalisability of PRISM 1 findings observed in PRISM 2.

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