Two steps forward, one step back

IMPACT PARAGRAPH

This thesis studied the potential of biomarkers to be used in psychiatry, with a focus on the robustness and clinical relevance of these biomarkers. These topics are important for the development of stratified psychiatry and eventually personalized medicine. Stratified psychiatry, in this thesis considered as an interim step between the current treatment system and personalized medicine, aims to provide information on treatment success for subgroups of people who are identically diagnosed. For example, treatments for depression involve (but are not limited to) psychotherapy, pharmacological treatment, and repetitive Transcranial Magnetic Stimulation (rTMS). In stratified psychiatry, biomarkers provide information on what subgroup of depressed individuals may respond best to either of the aforementioned (or a combination of these) treatments, thereby circumventing the current trial-and-error approach. Personalized medicine goes one step further in optimizing treatment to the individual. It is a framework through which each individual reporting psychiatric complaints is assessed and treatment is allocated according to the assessed biomarkers. Biomarkers show the potential to make more informed treatment decisions and thereby increase the clinical effectiveness of psychiatric treatment. This is

important because, currently, the treatment of psychiatric disorders rests on a one-size-fits-all approach and clinical efficacy is limited.

The research presented in this thesis found that some biomarkers show the potential to be further developed as stratification tools in stratified psychiatry or personalized medicine. For example, it was found that depressed individuals with an individual alpha frequency (IAF) closer to 10 Hz respond better to 10 Hz rTMS treatment than individuals whose IAF is further away from 10 Hz. It was also found that boys reporting symptoms of attention-deficit/hyperactivity disorder (ADHD) with a low IAF respond well to QEEG-*informed* neurofeedback, whereas previous reports investigating IAF in methylphenidate treatment showed the opposite effect. In addition, spindling excessive beta (SEB), a feature observed in the electroencephalogram (EEG), is indicative of impulse control problems and this feature was similarly present in two groups who were diagnosed differently – yielding this a transdiagnostic EEG feature.

Importantly, besides developing biomarkers, this thesis focused on assessing the replicability of these biomarkers – for a biomarker that does not replicate, and thus does not show to be robust, cannot be used in clinical practice. As such, the biomarkers mentioned in the previous paragraph successfully survived replication. Yet, this thesis also identified biomarkers that could not be replicated. For example, a low IAF, more frontal theta, and a larger P300 amplitude could not be replicated as predictors of rTMS non-response. Likewise, less frontal beta/gamma activity could not be replicated as a biomarker of suicidal ideation in females reporting symptoms of depression. Also, a specific relation between SEB and sleep maintenance problems was not observed, as was reported in the original study. The importance of assessing the replicability of scientific findings is multifold. Not only does it test the existence of a finding, but it also helps establish the foundation on which future research can be based. Related to this is the importance of reporting null-findings and non-replications, as not reporting these findings can result in a skewed, unreliable representation of (the robustness of) a scientific finding. As such, performing and reporting on replication studies is vital for the progress and reliability of scientific findings.

As described before, replication research can be used to confirm or refute certain results, but its applicability to scientific practice extends beyond this dichotomy. Replication research can help explain previously contradictory findings, sculpt and refine existing work, increase methodological soundness and transparency, and establish collaborations between researchers and research facilities. These aspects are not only important for internal research groups but extend to the scientific community as a whole. For example, working together with other researchers is accompanied by different perspectives on the same topic, different ideas, and different knowledge frameworks through which a given scientific finding can be explained. This all helps in theory building and accelerating scientific progress. On a more practical level, working together with other research facilities may encourage data sharing, thereby creating larger and multi-site samples, resulting in representative datasets with high power. More so, sharing the responsibility of reporting the results of replication attempts increases the transparency and reliability of the representation of scientific findings in the literature. All these aspects are essential to consider while evaluating the results reported by scientific studies.

Another focus of this thesis has been the assessment of clinical relevance besides statistical significance. Clinical relevance is important to consider in mental health research, as the majority of the research in this research area is aimed at improving mental healthcare. Yet, many studies are based on statistical significance alone without assessing clinical relevance. This is problematic, for a statistically significant finding may not be clinically relevant. For example, clinically irrelevant findings cannot be used to base clinical decisions on or have a limited impact on the treatment or the individual seeking treatment. This thesis focused on clinical relevance by assessing the predictive value of findings and by focusing on remission rather than response. For example, it was shown that anhedonia was higher in depressed individuals who did not respond to rTMS treatment and this effect was replicated. Yet, the predictive value of this finding was relatively low – yielding a clinically irrelevant finding. Contrary, a study on the effectiveness of QEEG-*informed* neurofeedback as a treatment for ADHD reported that approximately half of the indi-

viduals achieved remission (indicative of experiencing minimal to no symptoms) after treatment. Assessing clinical relevance helps to establish the usefulness and impact of scientific findings in clinical practice and should be considered in studies focusing on improving psychiatric treatment.

This thesis has also shown that it is possible to base scientific research on heterogeneous samples. One issue of the one-size-fits-all approach is that diagnoses are primarily based on subjective reports from a patient, yet a lot of overlap in symptoms may exist between groups. Also, a lot of variation in symptom profiles within disorders exists. Individuals that are currently diagnosed with the same disorder may therefore not share similar symptoms, nor does it mean that individuals that have different diagnoses share no symptoms at all. Focusing on diagnoses and confining research to these diagnoses may result in groups that do not share similar pathological mechanisms, which may complicate research. Migrating the focus from diagnoses to shared constructs or concepts may be important for the development of robust biomarkers that correlate to behavioral profiles and transcend diagnostics. The concept of transdiagnostic research also applies to research incorporating healthy controls. Biomarkers that distinguish healthy controls from patients may not always be clinically useful, as clinical decision making rarely comes down to distinguishing a healthy control from a patient. Rather, biomarkers may help distinguish patients whose symptoms are similar, but whose diagnoses (and potentially treatment) are different (for example, in the case of unipolar and bipolar depression). Research in heterogeneous samples provides the first step in this direction, as transdiagnostic research focuses on shared constructs without being confined to one particular disorder.