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Summary

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Psychotic disorders are one of the leading causes worldwide of long-term disability. It is a psychiatric syndrome consisting of perceptual, cognitive, emotional and behavioural symptoms. The prevalence rate is relatively low (±3% for the broader psychosis spectrum) and remission can be achieved for the majority of the patients. However, a reasonable proportion of patients with a psychotic disorder experience persisting social and professional impairments in daily life. The cost for psychotic disorders is still enormous, estimated almost 94 billion euros in 2010 in Europe, although the ratio of societal cost per patient to 2015 gross domestic product per capita varies from 37% in Switzerland to 214% in the UK [1]. Expenses are related to long-term unemployment, and high costs of chronic use of treatment and support. The etiology of the disease is still largely unknown and the current treatment is not curative, merely focused on attenuating the primary symptoms [2, 3].

Science: new diffusion parameters, replication and other environmental risk factors

The presented studies in this thesis yielded several insights on the course of white matter (WM) integrity in patients with a psychotic disorder and their genetically related healthy siblings. One of the studies of this thesis showed widespread cross-sectional patient-control differences in fractional anisotropy (FA), while siblings of patients revealed intermediate FA values, although not significant from the control group. These findings teach us that these WM alterations may reflect illness, or treatment related effects rather than a genetic risk. Future studies examining WM integrity should implement new diffusion methods as 'Free Water Imaging (FWI)' and the 'Permeability Diffusivity Index (PDI) to investigate the nature of these alterations in WM microstructure in more detail [4].

For the first time, a small, but statistically significant FA decline in the right cingulum over a 3-year time period was found in healthy siblings compared to controls. This earlier-than-expected by age WM decline in siblings without any (subclinical) psychotic symptoms may point to an aberrant WM development curvature and a potential WM intermediate phenotype. Replication of these results is needed, preferably including siblings at different age stages to acquire a more complete WM age-trajectory of this higher-than-average risk group.

The WM trajectory in the 3-year timeframe in patients with a psychotic disorder was rather stable, but appeared conditional on the level of cannabis use, the degree of childhood trauma experiences and exposure to antipsychotic (AP) medication. These findings provide evidence for an early neurodevelopmental cause of WM alterations in the pathology of psychotic disorder with a potential influence of (early) environ-

mental factors and AP medication on WM development later in life. It is worthwhile to examine other environmental risk factors for psychotic disorder, such as pre-or perinatal birth defects, urban upbringing, and social exclusion, in relation to WM structure. This may help us to identify children at a young age with an increased risk of developing a psychotic disorder. Medical, psychological as well as societal precautions can then be taken to minimize the risk for psychosis as much as possible.

Clinic: prevention, diagnostic and prognostic marker

Diffusion tensor imaging has, despite numerous pitfalls [5], proven to be a useful research tool for *in vivo* investigation of structural brain abnormalities in psychotic disorder. However, the above-mentioned findings are all based upon group differences and are not applicable to the individual patient in daily clinical practice. The presented data in this thesis may entail however promising new insights for daily and future clinical practice.

Present tense

(i) Although a clear causal relation between cannabis and trauma associated WM alterations over time and long-term prognosis in patients with psychotic disorder has not been established, physicians as well as patients should be aware of the potential impact of these environmental factors on cerebral vulnerability. This should not lead to negativism and determinism but to realistic information on resiliency and plasticity, thereby contributing to empowerment of patients and preventing professional stigmatization.

(ii) Society must be informed about adolescent cannabis use and childhood trauma as risk factors for the development of psychotic symptoms and the potential adverse effect on long-term WM brain development. Prevention campaigns should warn young adolescents not to experiment with or use cannabis, at least until their brains are fully matured. Evidence-based treatment programs for cannabis addiction (e.g. motivational interviewing) should be applied at an early phase in the treatment of first-episode patients with comorbid cannabis abuse.

(iii) Neighbours, primary school teachers, general practitioners and mental health workers should signal family problems at an earlier stage to prevent cases of childhood abuse. Youth services should be sufficiently funded to support dysfunctional families or placing children into foster families if necessary, to prevent potential childhood traumas.

(near) Future

(iv) There is still a considerable diagnostic delay for the diagnosis of psychotic disorder, which has serious consequences for the patient and his recovery. Patients may drop out of school, alienate from their families and friends, become vulnerable for drug abuse, and have an increased suicide risk [3]. This delay is partly the result of the fact that patients with a psychiatric syndrome are diagnosed by thorough anamnesis and that in the prodromal or pre-psychotic phase the main symptoms can be vague and *non-specific*. An objective biological (imaging) marker is still missing, but would be very useful for diagnostic purposes, classification, staging of the disease, or prediction of the outcome [6]. The present thesis showed that longitudinal change in potential WM biomarkers might be relevant to further exploration, since the degree of exposure to an environmental stressor as well as the level of exposure to antipsychotic medication revealed different slopes of FA decline over time in patients with psychotic disorder. However, more specific and reliable WM measures are warranted in view of the disadvantages of the common applied diffusion indices (see below). Combining the clinical presentation of a patient with fixed interval WM measurements of specific regional WM tracts may provide us with information on the (positive or negative) effects of medication or drug use and finally, a long-term prognosis of the disease. However, whether a negative or positive WM slope is associated with worsening or amelioration of symptoms or a worse or better long-term outcome has not yet been established and needs further investigation.

(v) Given the overlapping FA findings in a various psychiatric disorders and the fact that diffusion data appears to be highly sensitive to common artifacts [7], diffusion imaging falls short when applied for etiological, diagnostic and prognostic purposes in psychiatry. However, a network analysis in which the patients' symptoms, his functional and structural brain abnormalities, and his predisposed and current environmental stressors are combined in a mathematical algorithm, may be a more promising diagnostic tool in the near future [8, 9].

Summary

In conclusion, the presented results in this thesis have several implications, on a scientific level, as well as on clinical reasoning and intervention level. The longitudinal results on the WM course in healthy siblings and the childhood trauma and cannabis associated WM alterations in patients with a psychotic disorder warrant further replication. Understanding the timing and effect of environmental risk factors on neuronal brain matter is crucial, as well as the age-related trajectory of brain tissue. Whether it is static, worsens over time or ameliorates throughout a recovery process is essen-

tial in the improvement of knowledge of psychosis outcome and for planning future therapeutic strategies. Therefore, these presented results should be disseminated through peer reviewed journals and presentations on national and international (schizophrenia) conferences, and also made accessible to patients and family members.
Although the clinical implications of this work are hitherto limited, the presented results in this thesis may play a supporting role in the implementation of public prevention programs (through e.g. television, social media). The general public must be aware of the detrimental effects of childhood trauma exposure and adolescent cannabis use on the developing brain, resulting in an increased risk for psychiatric disorders.

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