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6.2 MICROSTRUCTURAL IMAGING WITH ADVANCED DIFFUSION MRI METHODS – WHAT IS GAINED AND WHAT IS LOST?

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Background: Diffusion MRI is one of the important technological advances that played a crucial role in the discovery of abnormalities related to schizophrenia. While other imaging modalities focused on volumetric changes, and on functional changes (e.g., metabolic, and vascular) diffusion MRI introduced the ability to study microstructural changes. Most diffusion MRI studies focused especially on the white matter, where the diffusion tensor imaging (DTI) analysis, which by now is considered widely available and conventional, provided unique microstructural contrasts. The most important parameter has been the fractional anisotropy (FA), which was perceived as a white matter integrity measure, and sometimes as a myelin integrity measure. The simplicity of the DTI model, and its growing availability on clinical scanners resulted with a considerable body of work demonstrating reduced FA in schizophrenia, leading to new clinical hypotheses, suggesting that mental disorders may involve white matter deficiency, which in turn would lead to mis-wiring, and connectivity issues that may explain some of the unusual symptoms associated with schizophrenia. However, even though DTI measures, and specifically FA, appear to be very sensitive to subtle brain changes, these measures are not specific to any pathology. In fact, while clinical studies attempted to relate DTI measures with white matter and myelin integrity, methodological studies provided clearer evidence that such a relationship is not warranted, since DTI measures could be affected by multitude of sources. This methodological complication raised the need for more advanced microstructural imaging, which could provide superior specificity to underlying pathologies, and especially to pathologies that are related to white matter integrity and connectivity.

Methods: In the recent years advanced diffusion acquisition and modeling approaches became available, leading to a significant number of studies that have applied these new tools on psychosis populations. Tools include biological model-based approaches such as free-water imaging, NODDI and permeability-diffusivity index. Other tools select model free approaches such as Kurtosis imaging, Q-space imaging, Diffusion spectrum imaging, and Generalized FA. The advanced methods provide new ways to characterize abnormalities, but at the same time, as the models become more complicated, so are the acquisitions, their length, and their sensitivity to noise. This talk will review findings from advanced diffusion MRI methods and will compare them with those obtained by the conventional DTI approach.

Results: The comparison shows that while the sensitivity to identify abnormalities is not necessarily increased by the advanced methods, the fact that in some of these approaches the specificity is improved provides new insights into the nature of the underlying abnormalities. Nevertheless, even though specificity is improved, care must be taken with the interpretation of the result given the fact that diffusion MRI is an indirect measure of microstructure, limited by the assumption embedded in each model.

Discussion: The emerging results present dependency on the stage of the psychosis (e.g., first episode, chronic) as well as on the age and gender of the subjects, suggesting that care must be taken in the study design, as well as in the statistical analyses performed. The findings also promote the use of multi-modal acquisitions, as well as the collection of biological, clinical and cognitive parameters. The combined information of these different domains is more likely to truly characterize the underlying abnormalities.

6.3 EEG AS A TOOL FOR PSYCHOSIS RESEARCH: CHALLENGES, PITFALLS AND NEW OPPORTUNITIES

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Background: Electroencephalography (EEG) as the oldest technique currently in use for the analysis of brain function has strong advantages not offered by other techniques: it is a direct measurement of neuronal activity and offers a high temporal resolution. Accordingly, it is very useful for the investigation of neuronal oscillations which are related to disturbed core mechanisms of schizophrenia such as NMDA-receptor dysfunction or E/I imbalance and alterations in connectivity.

Methods: On the other hand, the method has also strong limitations, e.g. the difficulty of precise localization, which is due to the inverse problem and also its blindness to subcortical structures that are highly relevant for psychosis research, such as the ventral striatum.

Results: Uncritical use of this technique has created widespread skepticism, leading probably to some degree of underestimation of the unique opportunities offered. In this talk, limitations of the technique will be addressed as well as current strategies of proper usage such as the combination of EEG and fMRI.

Discussion: Simultaneous EEG-fMRI offers the best from both modalities, that is high temporal and high spatial resolution, but here, too, methodological challenges have to be addressed. Finally, the development of new noninvasive tools for brain stimulation such as transcranial alternating current stimulation (tACS) with the opportunity of frequency-specific modulation of neuronal oscillations (“entrainment”) for both brain research and therapy makes detailed information about disturbed oscillations patterns in psychosis even more relevant.

6.4 BRAIN FUNCTIONAL CONNECTOMICS BASED ON RESTING STATE FMRI: FROM NODES TO NETWORKS

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Background: Emerging evidence suggests that psychosis arises from disrupted communication between distributed neural networks. In the past decade, network-sensitive neuroimaging methods have made it possible to examine vulnerable brain networks in living humans. Previous work has demonstrated that distinct functional intrinsic connectivity networks can be mapped in the healthy brain with task-free or “resting-state” functional magnetic resonance imaging (fMRI). Instead of the changes evoked by specific stimuli, resting state fMRI captures the spontaneous low frequency blood-oxygenation-level-dependent signal fluctuations at rest. Regions showing synchronized spontaneous activities are usually functionally connected and are often supporting highly relevant brain functions.

Being more applicable in patients, recent resting state fMRI studies in psychosis have reported widespread functional dysconnectivity, targeting multiple neural systems that include the default mode network, the salience network, the auditory network, and fronto-striato-thalamic circuits. Such functional connectivity disruptions are also associated with more severe symptoms and more cognitive impairments in patients.

Methods: In this talk, I will cover four primary methods for deriving functional connectivity from resting state fMRI data and discuss their pros and cons in the context of schizophrenia. 1) Seed-based approach: correlation between signals of a seed region to other target regions or with the rest of the brain. 2) Independent component analysis: decompose the fMRI data of all brain voxels into spatially non-overlapping and temporally coherent networks. 3) Brain parcellation-based connectivity matrices: based on a set of predefined regions of interest covering the whole brain, the functional connectivity between all pairs of regions are computed and the individual-level connectivity matrices are compared. Lastly, 4) graph theoretical approach is highly useful in capturing and visualizing complex brain interactions embedded in these high dimensional matrices. In a brain graph, each ROI is a node and the functional connectivity between a pair of ROIs is an edge. Graph theoretical measures can then capture the brain functional topology such as functional segregation or modularity at nodal, network, and whole-brain levels.