Resting-state fMRI neurodynamics in neuropsychiatric disorders

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Summary

Neuropsychiatric disorders such as schizophrenia, autism, mild cognitive impairment and depression are described as neurological conditions with psychiatric symptoms. An important issue in these diseases is the lack of brain biomarkers, which causes diagnostic uncertainty and lack of treatment navigation. Finding these neurobiomarkers by means of neuroimaging techniques, such as functional MRI, is the core of psychoradiology—a relatively new field of research.

In this thesis we attempt to contribute to this research field by investigating new ways of assessing brain dynamics using resting-state functional MRI (rs-fMRI). More specifically, three methods to assess neurodynamics are evaluated: the Granger causality (measure of effective connectivity), the wavelet coherence (spectro-temporal analysis), and the evolutionary game theory approach on networks. Neuropsychiatry is a vast field of research, thus, in order to narrow the focus, these novel approaches to brain dynamics assessment are tested on two neuropsychiatric disorders: the accelerated cognitive ageing (ACA) observed in elderly with epilepsy, and the autism spectrum disorder (ASD).

The main goals of this research on discovering new biomarkers for neuropsychiatric disorders and the utility of brain dynamics in rs-fMRI are introduced in Chapter 1. This introductory chapter also contains a review of the state-of-the-art of the current solutions for finding these fMRI-based neurobiomarkers and the description of the three novel abovementioned dynamics methods.

In Chapter 2, static functional connectivity (sFC) between large-scale resting-state networks (RSNs) is measured in ACA and compared to age- and education-level-matched healthy elderly in two resting-state fMRI sessions (pre- and post-task). Within the lateralised executive networks, i.e. fronto-parietal networks, the static connectivity was slightly weakened in both resting states. Regarding the between-network sFC analysis, the default mode network (DMN) had a weaker and anti-correlated connectivity with the ventral attention network (VAN) in ACA patients as compared to the control group in the pre-task resting state. At post-task, i.e. after a cognitively demanding task, the strength of the connectivity between the salience network (SN) and the dorsal attention network (DAN) was also decreased, whereas the DMN connectivity with the VAN increased and was not significantly different from the DMN-VAN connectivity in controls anymore. In general, the network functional connectivity amount networks tended to change more in ACA than in healthy controls, where the emphasis was shifted to connectivity between the DMN and the cognitive-control networks (FPR, VAN, DAN and SN). In this chapter we conclude that the switching of activity between the DMN, SN and executive network appears less efficient or delayed in ACA patients, which might be an echo of a loss of segregation. This loss of segregation also appears naturally in 'healthy' ageing, which corroborates the idea of a faster cognitive decline in our patients with ACA.

After investigating the sFC between large-scale cognitive networks, we explore the effective connectivity, i.e. the directed causal influences between the networks in terms of Granger causality in Chapter 3. This is performed on the same ACA patients and healthy controls. In addition, the correlation between the causality values and the deterioration in IQ scores is assessed. As seen with static connectivity, the GC from executive control and attention networks are also challenged in ACA patients. More specifically the directed connectivity from the cingulate cortex towards

the DAN, fronto-parietal right and the SN is stronger in the patients as compared to the control group in the pre-task rs-fMRI. After the task, this tendency of over-recruitment is reduced and statistically non-significant. When we assessed the association between GC and the cognitive decline measurements, our main findings reveal that in both rs-fMRI scans (pre- and post-task) the stronger GC from the DMN to the VAN is correlated with a stronger decline in perceptual reasoning index (most deficient IQ scores in ACA patients, related to fluid intelligence). These results are corroborated by the CRUNCH[1] and PASA[2] models of brain ageing. Hence, these findings are in line with our accelerated cognitive ageing hypothesis.

In Chapter 4, the effective connectivity between large-scale cognitive and limbic (emotion-related) RSNs is measured in ASD and compared to age- and IQ-matched healthy adolescents in two resting-state fMRI sessions. First, the within-network sFC, i.e. the spatial distribution and strength of activation of the RSNs are not different between patients with ASD and controls. However, the between-network causality shows discrepancies. The adolescents display also different results in GC when comparing the two resting-states sessions. Indeed, our results suggest that the dynamic causal measurement from the ventral attention network towards the executive-salience network is weakened in ASD patients, after an emotional task is performed, i.e. after triggering, or challenging, the brain cognitive state of the patients prior to the resting-state evaluation. These networks are known to be involved in emotion processing as well as involuntary cognitive processing, which are usually impaired for patients with autism.

A novel dynamics metric derived from wavelet-coherence maps is investigated in the adolescents with autism in Chapter 5. In this chapter we aim at designing methodology for objective diagnosis of autism. This metric is coined the time of in-phase coherence, which provides an indication of how long two RSNs are synchronized with each other. Classifiers for autism diagnosis are then trained with these times of in-phase coherence features. Leave-one-out cross validation is applied for performance evaluation. To assess inter-site robustness, we also trained our classifiers on the in-house data, and tested them on an independent rs-fMRI dataset from Leuven University. We distinguished ASD from non-ASD adolescents in both independent datasets at more than 86% accuracy. In the second experiment, classifying the Leuven dataset with classifiers trained with our in-house data, resulted in 80% accuracy (100% sensitivity, 66.7% specificity). This study shows that synchronicities between the VAN and the two fronto-parietal networks are biomarkers of ASD, and wavelet coherence-based classifiers lead to robust results and could be used as an objective diagnostic tool for ASD.

Chapter 6 implements the evolutionary game theory approach on networks (EGN) onto activity time series of the ACA patients and the (age- and education-matched) controls. Here, we also tested classifiers with features based on a novel dynamics metric derived from the EGN model: the emulative powers of the networks. We compared these EGN-based classifiers with classifiers trained on GC, time of coherence, and static functional connectivity (sFC) features. Results show that features extracted from the EGN approach—the emulative powers—are the best descriptors of the ACA condition, using dynamics associated with the DMN and the DAN. With these dynamics markers, linear discriminant analysis could identify ACA at 82.9% accuracy. Using wavelet-coherence (WCoh) features with decision-tree algorithm, and sFC features with support vector machine (SVM), ACA could be identified at 77.1% and 77.9% accuracy respectively. GC fell short of being a relevant biomarker with best classifiers having an average accuracy of 67.9%. Combining EGN-, WCoh-, GC-, and sFC-based features increased the classification performance up to 95.8% accuracy using SVMThe dynamics of the networks that lead to the best classifier performances are known to be challenged in elderly, and the results are in line with the idea of ACA patients having an accelerated cognitive decline. These findings allow us to localise the functional

[1]Compensation-Related Utilization of Neural Circuits Hypothesis
[2]Posterior-Anterior Shift in Aging

networks affected by ACA, which in turns could lead to targeted treatment. This classification pipeline is also promising and could help diagnosing other neuropsychiatric disorders, and contribute to the field of psychoradiology.

Because of the weak discriminative power of GC, as shown in the previous paragraph, Chapter 7 investigates an alternative method for measuring effective connectivity between large-scale RSNs: the Bayesian search for effective connectivity topology. The Bayesian search is first compared to Granger causality with simulated times series. After showing the benefit of the new method in theory, we applied the Bayesian search algorithm on RSN time series of healthy young adults; and we were able to show the effect of intensive music listening sessions on the dynamic connectivity of cognitive networks.

Finally, Chapter 8 draws conclusions about neurodynamics in neuropsychiatric disorders, based on the results obtained in this research, and discusses the limitations but also the contributions and application prospects of these new tools in psychoradiology. Future work for this field of research is also discussed. For instance, the use of multi-modal approaches to improve classification performances is mentioned; or refining our dynamics models at different levels of abstraction (in the top-down and bottom-up brain processes) and tailored to the specificities of neuropsychiatric disorders could also be an avenue to explore. These new explorations could further help developing robust biomarkers of mental disorders, which could improve not only automated diagnostic tools, but also provide advances in prognosis—in terms of disease progression or treatment responses.