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Resting-state connectivity in neurodegenerative disorders: Is there potential for an imaging biomarker?

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ABSTRACT

Biomarkers in whichever modality are tremendously important in diagnosing of disease, tracking disease progression and clinical trials. This applies in particular for disorders with a long disease course including presymptomatic stages, in which only subtle signs of clinical progression can be observed. Magnetic resonance imaging (MRI) biomarkers hold particular promise due to their relative ease of use, cost-effectiveness and non-invasivity. Studies measuring resting-state functional MR connectivity have become increasingly common during recent years and are well established in neuroscience and related fields. Its increasing application does of course also include clinical settings and therein neurodegenerative diseases. In the present review, we critically summarise the state of the literature on resting-state functional connectivity as measured with functional MRI in neurodegenerative disorders. In addition to an overview of the results, we briefly outline the methods applied to the concept of resting-state functional connectivity.

While there are many different neurodegenerative disorders cumulatively affecting a substantial number of patients, for most of them studies on resting-state fMRI are lacking. Plentiful amounts of papers are available for Alzheimer's disease (AD) and Parkinson's disease (PD), but only few works being available for the less common neurodegenerative diseases. This allows some conclusions on the potential of resting-state fMRI acting as a biomarker for the aforementioned two diseases, but only tentative statements for the others.

For AD, the literature contains a relatively strong consensus regarding an impairment of the connectivity of the default mode network compared to healthy individuals. However, for AD there is no considerable documentation on how that alteration develops longitudinally with the progression of the disease. For PD, the available research points towards alterations of connectivity mainly in limbic and motor related regions and networks, but drawing conclusions for PD has to be done with caution due to a relative heterogeneity of the disease. For rare neurodegenerative diseases, no clear conclusions can be drawn due to the few published results. Nevertheless, summarising available data points towards characteristic connectivity alterations in Huntington's disease, frontotemporal dementia, dementia with Lewy bodies, multiple systems atrophy and the spinocerebellar ataxias.

Overall at this point in time, the data on AD are most promising towards the eventual use of resting-state fMRI as an imaging biomarker, although there remain issues such as reproducibility of results and a lack of data demonstrating longitudinal changes. Improved methods providing more precise classifications as well as resting-state network changes that are sensitive to disease progression or therapeutic intervention are highly desirable, before routine clinical use could eventually become a reality.

1. Introduction

A biomarker is a usually indirect measure that accurately and reproducibly allows for an objective classification of a biological or pathogenic process or a pharmacological response (Strimbu and Tavel, 2011). There are also biomarker-surrogates, which have the same aims as a regular biomarker, but are an even less direct measure that is oftentimes easier to obtain that a *true* biomarker.

Resting-state fMRI connectivity can be seen as biomarker-surrogate, as while it does not directly capture neuronal processes and their connectivity it allows for insight in such characteristics. In general biomarkers should not only be able to identify the presence of e.g., a

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disease, but also should allow for tracking progression, severity and, importantly, treatment effects. This requirement holds particularly true for clinical trials studying neurodegenerative diseases, as their (usually) long courses complicate monitoring of clinical end-points and the often very long pre-clinical phases of these diseases hinder it entirely. As there is more and more evidence that interventions in neurodegenerative disorders need to be applied in very early or even pre-symptomatic phases of the respective disorder(s), monitoring of disease progression based on clinical features becomes well-nigh impossible, thus merely enforcing the need for reliable and easy-to-track biomarkers in this field. The usual measures of quality of an instrument, namely objectivity, reliability and validity apply to biomarkers as well (Strimbu and Tavel, 2011). In addition, the biomarker in question should be measurable easily and preferably non-invasively, should not require the cooperation of the patient (such as complying in highly demanding cognitive tasks, seeing that we are dealing with disorders of the brain) and should be widely available. Therefore, resting-state functional magnetic resonance imaging (fMRI) seems like an attractive choice, as it fulfils many of these requirements and available evidence so far points to it potentially being suitable for application as biomarker (Pievani et al., 2014).

Resting-state describes a task-free situation that is additionally characterised by very low levels of sensory stimulation. The concept itself is far from new and has been applied in neuroscience for a long time, although it may not always having been called explicitly *resting-state* (Snyder and Raichle, 2012). Not too long after the introduction of fMRI and the blood oxygen level dependant (BOLD) contrast (Ogawa et al., 1990), the combination of fMRI and the resting-state was used to assess connectivity of the brain (Biswal et al., 1995). Since then it has grown to become a popular and commonly used method in neuroscience and has of course also been applied within research on neurodegenerative diseases.

The question we here need to address when evaluating imaging (bio)markers is, if resting-state fMRI enables (i) to detect disease-specific changes compared to controls, (ii) these alterations are sensitive to disease progression and responsive to therapeutic intervention, and (iii) finally are reproducible and thus reliable.

In principle, resting-state data can be gathered with functional methods different than fMRI, such as electroencephalography (EEG), magnetic encephalography (MEG) (van Diessen et al., 2015) and functional near infrared spectroscopy (fNRIS) (Niu and He, 2014). Due to the fact that it is now widely available, the cost manageable, the method being non-invasive and the spatial resolution of imaging very high, fMRI is by far the most common method used to collect resting-state datasets and the number of published papers employing it rose fast during recent years and remains high (Fig. 1).

In contrast to task-based approaches it could be argued that resting-state measurements provide a more neutral setting, as they do not elicit specific task-based activation. The neutrality of the resting-state condition comes with certain challenges, though. Besides numerous sources of error that might confound the data (Murphy et al., 2013), there is also considerable sensitivity of the measurement against the specific implementation of the resting condition such as eyes being closed, open or fixated (Patriat et al., 2013). Wandering of the mind should also be considered a source of variation of the data gathered (Mason et al., 2007), but that variation might be averaged out given a certain amount of data.

To characterise connectivity as measured with resting-state fMRI a wide variety of methods is available. An approach that is rather common is to correlate time series of brain regions (Biswal et al., 1995; Shehzad et al., 2009) and regard positive correlations as connectivity, while negative correlations (also called *anti-correlations*) have an unclear role. Similarly, common is the usage of independent component analysis (ICA) to identify brain networks. It aims to identify components of a data set by reducing statistical dependence between them, thus delineating data from different sources (Comon, 1994). It has been shown that the components identified by data correspond very closely to regions typically activated by task-based fMRI (Smith et al., 2009), are consistently measurable across healthy subjects (Damoiseaux et al., 2006) and show good test-retest reliability (Zuo et al., 2010). Further techniques to characterise connectivity based on resting-state fMRI include graph-theoretical approaches (Wang et al., 2010); Granger causality (Seth et al., 2015), as well as short-distance measures such as amplitudes of low-frequency fluctuations (ALFF) (Yang et al., 2007; Zang et al., 2007) and regional homogeneity (ReHo) (Zang et al., 2004). Of these measures, Granger causality is a measure of effective connectivity, while ALFF characterises features of individual regions. The here described methods are only a subset of techniques available for analysis of resting-state fMRI data and thus it is not surprising that integration of results is not without difficulties. Cole (2010) describes available methods and open questions regarding them in greater detail.

Despite the large amount of analysis methods and difficulties in summarising results, a set of resting state networks in the brain have been identified and replicated many times in the literature. These networks are sets of brain regions that are interconnected serving a specific purpose. The most prominent example here is likely the *default mode network* encompassing the posterior cingulate, precuneus, inferior parietal cortex, orbitofrontal cortex, medial prefrontal cortex, ventral anterior cingulate, left dorsolateral prefrontal cortex, left parahippocampus, inferior temporal cortex, nucleus accumbens and the midbrain (Greicius et al., 2003; Raichle et al., 2001). It is believed to provide a baseline state of the brain that represents self-reference, emotional processing, memory as well as spontaneous cognition and aspects of consciousness (Raichle, 2015). Further networks include the *frontoparietal networks* – associated with numerous aspects of cognition and language processing (Smith et al., 2009; Zuo et al., 2010); the *sensorimotor network* relevant for motor execution and somatosensory components (Biswal et al., 1995; Smith et al., 2009); the two dorsal and ventral *attention networks* with the former associated with voluntary orientation and the latter linked to detection of salient targets (Corbetta and Shulman, 2002; Fox et al., 2006). Finally, the *salience network* is associated with the identification of relevant targets from the inputs the brain receives (Downar et al., 2000; Seeley et al., 2007), while the *executive control network's* main function is directing attention on such targets (Seeley et al., 2007). The location of these networks is visualised in Fig. 2.

If resting-state fMRI measurements could achieve similar quality in clinical practice, this would allow for rather fast and non-invasive diagnosis and tracking of progression in neurodegenerative disease and possibly beyond. Earlier reviews on this matter provide promising results and first evidence for potentially disease-specific patterns in connectivity alterations (Pievani et al., 2014). However as research is constantly expanding and methods are being developed, it should be reassessed whether more light could be shed on these disease-specific patterns. Thus, we summarise the current state of the literature on functional resting-state-based results in neurodegenerative disorders in this review. The overall aim is to answer the question whether resting-state based data can serve as a non-invasive biomarker to diagnose and differentiate diseases.

2. Methods

Searches on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) were conducted for the following neurodegenerative diseases: Alzheimer's Disease (AD); Parkinson's Disease (PD); Huntington's Disease (HD); Multiple System Atrophy (MSA); Dementia with Lewy Bodies (DLB); Frontotemporal Lobar Degeneration (FTD); Amyotrophic Lateral Sclerosis (ALS); Creutzfeld-Jacob-Disease (CJD); Friedreich Ataxia (FRDA); and the Spinocerebellar Ataxias (SCA). The query “resting state” followed either by the name of the disease or a unique part of the name (such as *Alzheimer* for Alzheimer's disease) was used, the same was repeated with the search term “functional connectivity”.