Editorial

for the special issue "Resting-state fMRI and Cognition" in Brain and Cognition

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Research in cognitive neuroscience employing resting-state functional magnetic resonance imaging (rs-fMRI) has experienced an exponential boom since Biswal et al.'s pioneering work in the mid-nineties of the last century, when it was demonstrated that rs-fMRI is capable to reveal enhanced functional connectivity within functional subsystems of the human brain (Biswal et al., 1995, 1997). Rs-fMRI derives its name from the fact that hemodynamic activity is recorded while participants lie in the MR scanner without any experimental task. Instead, participants are usually instructed to let their minds wander freely and not fall asleep. Under these conditions, the body obviously is in a "resting position"; the brain, however, is never at rest but rather enters a so-called default mode involving increased activity in a set of brain areas that are usually deactivated during externally structured tasks (Gusnard & Raichle, 2001; Raichle et al. 2001; Shulman et al., 1997).

In the absence of experimentally or otherwise defined extraneous events under such "resting" conditions, which precludes the traditional analysis approach to task-fMRI data, research has focused on the spontaneous low-frequency fluctuations (typically $f < 0.1$ Hz) of the blood oxygenation level–dependent (BOLD) signal (Fox & Raichle, 2007). These continuous fluctuations offer a means to assess interregional functional connectivity (FC) defined as the temporal co-occurrence of spatially distinct neurophysiological events. In particular, brain regions are considered to be functionally connected if their fluctuations over time are positively correlated.

Using this approach, interhemispheric FC was first described for the two primary motor cortices (Biswal et al., 1995). In seed-based approaches like this, correlation coefficients representing pairwise FC between voxels or sets of voxels are typically transformed into Fisher's Z-scores (to approximate a normal distribution) for hypothesis-driven statistical comparisons of FC values between seed regions (Bzdok et al., 2013) and/or participant groups such as patients and healthy controls (Biswal et al., 1998), or young and older adults (Langner et al., 2015). Later applications of this approach used resting-state FC as a means for characterizing individual voxels and forming clusters of voxels with similar whole-brain FC patterns in order to further subdivide macroanatomical brain regions or even the entire cortex (connectivity-based parcellation; see, e.g., Genon et al., 2018; Schaefer et al., 2018). For a historic overview of the first steps and advances in rs-fMRI research, the interested reader is referred to Biswal (2012).

A different, data-driven approach to resting-state BOLD signal fluctuations is investigating differences and similarities across the frequency spectrum of oscillations between areas; an approach usually performed by coherence analysis (He et al., 2007). The currently most frequently used evaluation strategy is independent component analysis (ICA), which splits the signal (all voxels' time series) into independent coherent components. This allows for the data-driven definition of spatially distributed networks consisting of voxels that show coherent spontaneous activity fluctuations (Beckmann et al., 2005). One of the first brain systems described in detail using ICA was the default-mode network (DMN), in which the anteromedial prefrontal cortex forms one of the central hubs (Raichle et al., 2001; Greicius et al., 2003). Further research has shown that whole-brain ICA reliably separates roughly ten large-scale functional systems (e.g., van Djik et al., 2010; Smith et al., 2009): DMN, medial and lateral visual networks, dorsal and ventral attention networks, the fronto-parietal task control (or: executive control) network, including language regions in the left hemisphere, the cingulo-opercular (or: salience) network, the auditory network, the somato-motor network, the medial parietal network, and the cerebellar network. Interestingly, these networks are largely comparable to those identified with task-based fMRI (Cordes et al., 2000; Smith et al., 2009). Recent advances in automatized ICA approaches achieved a precision that may allow using this strategy also for presurgical mapping of, for instance, the language network in individual patients (Lu et al., 2017).

Furthermore, graph-theoretic approaches to resting-state FC data have propelled the network-science view of the human brain, yielding large advances in our understanding of the brain's intrinsic connectional architecture (i.e., the "connectome"; see, e.g., Bullmore & Sporns, 2009, 2012; van den Heuvel and Sporns, 2013). For instance, nodal degree maps have been calculated, which, for any given location in the brain, indicate the extent of information sharing with the rest of the brain. Using this approach identified a "small-world structure," which describes an optimal organization of local specifications and global integration with minimal costs of integration (van den Heuvel et al., 2010). Such graph-theoretic measures are now applied for characterizing the connectomes of different groups of individuals, for instance those who are sensitive to developing chronic pain disease (Mansour, et al., 2016).

When briefly sketching the development over the last decades seen in rs-fMRI research, we should not forget to mention that there are also shortcuts and controversies about this method (for reviews, see Buckner et al., 2013; Murphy et al., 2013). Especially, different approaches to measurement and artifact reduction have been discussed controversially among the research community. For instance, there has always been a dispute on the interpretation of resting-state fluctuations of brain activity since the cognitive and affective processes and the behavior of the participant in the scanner are not controlled for. Furthermore, how can one get rid of physiological noise from respiration and heart rate if the main BOLD signal oscillation is near the resting respiration rate? Birn et al. (2006) proposed an elegant method for regressing cardiac and respiratory variance out of the rs-fMRI BOLD signal, but this has not become a standard approach. Also, may it even be necessary to record an electroencephalogram to monitor vigilance fluctuations up to falling asleep?

In addition, there is an ongoing debate on the optimal preprocessing of rs-fMRI data: For example, most authors use confound regressors for noise reduction before statistical evaluation such as the mean-centered global or tissue-specific signal intensities and the head motion parameters from image realignment (Satterthwaite et al. 2013). In contrast, some apply an adjustment based on the first five components of a principal component analysis (first suggested by Behzadi et al., 2007) or apply temporal ICA-based artefact removal (Griffanti et al., 2015). Further, some authors use band-pass filtering between 0.01 and 0.08 Hz, whereas others only apply a high-pass filter ($f > 0.01$ Hz). Finally, the modeling methods (no experimental manipulations that could be modeled with a given onset) are also under discussion. However, despite the tremendous analytical flexibility, it is appealing and reassuring that rs-fMRI (i) reveals characteristic FC differences between pathological and physiological brain states (e.g., Biswal et al., 1998), (ii) shows a considerable reproducibility in long-term measurements of healthy participants (e.g., Poldrack et al., 2015), and (iii) is associated with structural connectivity between functional areas (Greicius et al., 2009).

Based on a symposium on relationships between resting-state FC and cognition held at a congress for clinical neurophysiology and neuroimaging in Düsseldorf, Germany, we asked researches studying resting-state FC in a number of different fields to contribute to this special issue. In one contribution the authors (Pfannmöller & Lotze, 2018) detail the application of recent methodological advances in identifying individuals with a high risk for developing an illness (such as a chronic pain disease) out of a cohort of healthy participants. This might be highly relevant for the development of biomarkers in general. These authors provide an overview on that field predominantly driven by the results obtained by Apkarian and collaborators from Chicago, USA.

Another highly interesting issue is the diagnostic value of rs-fMRI in evaluating different levels of impairment of consciousness. The data of a group from Liége, Belgium, pointed to the importance of an intact DMN for assessing consciousness (Vanhaudenhuyse et al., 2010). The group around Boris Kotchoubey from Tübingen, Germany, has been working since decades with these patients and compared the usefulness of rs-fMRI with activation fMRI after the presentation of emotional or lexical stimuli (Sitaram et al., 2018).

Dorothee Saur and colleagues from Leipzig, Germany, have performed groundbreaking longitudinal research on the restitution of language functions in patients suffering from aphasia after stroke using word mismatch tasks (Saur et al., 2006) and also showed how damage to different structural connections between language areas have an impact on the recovery and symptoms of aphasia (Kümmerer et al., 2013). Here they investigated the role of rs-fMRI in understanding network pathology in post-stroke aphasia (Klingbeil et al., 2018).

It is conceivable that stroke or hypoxia may heavily disturb large-scale functional networks. What about obese people? How do they differ in their resting-state FC, and how can aerobic training modulate these pathologies? The group of Agnes Flöel in Greifswald, Germany, has focused on this issue in their contribution (Prehn et al., 2018). They investigated 29 older overweight healthy participants with normal to elevated fasting glucose levels and divided the group in one with aerobic fitness training and one with stretching training over 6 months. Not only the task switching ability improved over time only in the aerobic training group but also the rs-FC increased between bilateral dorsolateral prefrontal cortex and the bilateral precuneus.

The group around Vaibhav Diwadkar (Ravishankar et al., 2019) from Detroit, USA, investigated a more active role resting-state FC may play for memory consolidation: they examined how FC between cortical-hippocampal networks is modulated during rest phases of a paired-associate learning paradigm, in which rehearsal is assumed to take place. Indeed, memorization success was found to be associated with particular modulations in FC during these phases, which the authors interpreted as evidence of an active and constructive resting state in the brain.

Florian Zepf from Perth, Australia, and his collaborators examined resting-state FC aberrations in adolescent ADHD in a meta-analytically defined network subserving sustained attention and observed that network architecture was selectively altered in ADHD, with several aberrant connections being linked to ADHD-related traits such as impulsivity.

Susanne Weis and colleagues from Durham, UK, examined the stability of resting-state networks and their susceptibility to menstrual-cycle effects. It was found that FC in the DMN, other than in the auditory network, showed cycle-dependent modulations in women, while being stable in men, suggesting that earlier findings of hormone-related differences in task-evoked brain activity might in fact be partly due to cycle-related differences in ongoing spontaneous activity, especially in frontal brain regions.

The contribution of Robert Langner et al. examined the FC profiles of two bilateral brain regions, posterior midtemporal gyrus and collateral sulcus, involved in skilled visual object and pattern recognition in chess, respectively. Their results show differences and some overlap in the functional networks linked to each seed region, having implications for how visual expertise with movable objects in complex, social situations is mediated by the human brain via integrating different processing modules of ventral and ventro-dorsal visual streams.

Paige Greenwood et al. investigated maternal reading fluency and the functional connectivity between the child's future reading network. Interestingly, these children (13, aged about 4 years) engaged greater connectivity in the semantic language network with less reading ability of their mothers. The authors interpreted this finding by suggesting that children whose mothers have lower reading ability compensate for lower-quality reading exposure at home via greater engagement of the language network and regions related to language for narrative comprehension. Radek Ptak and François Lazeyras described a case study of a patient with failure to retrieve meaning from shape in visual object agnosia and pure alexia and compared rs-fMRI to 4 healthy age-matched controls. Not suprisingly, the patient exhibited reduced FC between the lesioned left and the intact right cortex areas. The authors interpreted the findings that focal damage to the lateral occipital cortex may have global effects on representations of objects in bilateral occipito-temporal cortex, thus supporting the view that bilaterally distributed coding is necessary for the retrieval of associative knowledge from shape.

Here is a list of all ten contributions of this special issue:

1. Jörg Pfannmöller & Martin Lotze: Resting-state biomarkers for chronic pain – a network view
2. Ranganatha Sitaram et al.: Spatial characteristics of spontaneous and stimuli-induced individual functional connectivity networks in severe disorders of consciousness
3. Julian Klingbeil et al.: Resting-state functional connectivity: an emerging method for the study of language networks in post-stroke aphasia
4. Kristin Prehn et al.: Using resting-state fMRI to assess the effect of aerobic exercise on functional connectivity of the DLPFC in older overweight adults
5. Mathura Ravishankar et al.: Cortical-hippocampal functional connectivity during covert consolidation sub-serves associative learning: Evidence for an active "rest" state
6. Florian Zepf et al.: Functional connectivity of the vigilant-attention network in children and adolescents with attention-deficit/hyperactivity disorder
7. Susanne Weis et al.: Sex differences and menstrual cycle effects in cognitive and sensory resting state networks
8. Robert Langner et al.: A network view on brain regions involved in experts' object and pattern recognition: Implications for the neural mechanisms of skilled visual perception
9. Paige Greenwood et al.: Maternal reading fluency is positively associated with greater functional connectivity between the child's future reading network and regions related to executive functions and language processing in preschool-age children
10. Radek Ptak and François Lazeyras: Functional connectivity and the failure to retrieve meaning from shape in visual object agnosia

We hope that this special edition of Brain and Cognition provides a current and broad view on the possibilities, usefulness as well as limitations of applying rs-fMRI in the fields of cognitive and clinical neuroscience.

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