The use of resting state data in an integrative approach to studying neurocognitive ageing – Commentary on Campbell and Schacter (2016)

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Abstract

This is a commentary on Campbell and Schacter (2016), 'Ageing and the Resting State: Is Cognition Obsolete?'. Campbell and Schacter argue that resting state data have a limited ability to contribute to the study of neurocognitive ageing and that the field should focus more on results from carefully controlled experimental designs. In this commentary, we argue for a different perspective on future research directions in neurocognitive ageing. Specifically for the need to use a more integrative approach; combining rest and task data as well as information from different modalities to obtain a better understanding of the neural mechanisms that underlie healthy cognitive ageing. Potential benefits of this integrative approach are illustrated with a number of examples. In addition, we discuss some of the advantages of using resting state data as part of this integrative approach.

The field of neurocognitive ageing is aimed at identifying the neural mechanisms behind the effects of ageing on cognitive functioning. The most popular methods to investigate this include task and resting state functional magnetic resonance imaging (fMRI). The opinion paper reported in this issue of "Language, Cognition and Neuroscience", by Campbell and Schacter (2016), claims that the resting state approach only has a limited ability to contribute to the study of neurocognitive ageing. As an alternative, Campbell and Schacter argue for more emphasis on carefully controlled experimental designs, where individual differences in task performance can be linked to differences in regional activity and connectivity.

In this reply, we argue for a different alternative - while both rest and task states provide means to study neuronal activity, separately they offer a limited characterisation of the effects of ageing on neurocognitive processes. The approach proposed here is based on established research practices in neuroscience (Cicchetti & Blender, 2006; Grillner, Kozlov, & Kotaleski, 2005; Poznanski, 2002), where various imaging data are integrated in order to improve our understanding of the neural mechanisms shaping age-related decline as well as preservation of cognitive function. The focus of this paper is on integration of

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resting state with task based fMRI data and on the benefits of integrating structural and functional data. There are many other ways in which an integrative approach could benefit neurocognitive ageing research which will not be discussed here, such as the integration of resting electrophysiological and fMRI measurements in order to combine different spatio-temporal scales and understand individual differences (Betzel & Bassett, 2016; Hipp & Siegel, 2015; Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009) and age differences in cortical neurodynamics (Balsters et al., 2013; Cicchetti & Blender, 2006; Voytek & Knight, 2015). We start by providing examples of this integrative approach, combining rest and task data as well as structural and functional data. Next, we illustrate a number of important benefits of using resting state data within this integrative framework. Finally, we will discuss some of the specific issues mentioned by Campbell and Schacter (2016).

One of the most significant findings in neurocognitive ageing research, is the finding of "compensation"; the observation that age-related over activation of specific (frontal) brain regions during task execution is associated with improved performance (Cabeza, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Park & Reuter-Lorenz, 2009). This finding has sparked a lot of interest in the field and suggests that higher levels of activation can be used to counter the effects of challenges to the neural system, such as those imposed by age-related declines in gray and white matter integrity (Park & Reuter-Lorenz, 2009). However, over-activations are not consistently associated with better performance, and appear to be a sign of age-related cognitive decline in some other studies (Grady, 2012). More importantly, such observations do not lead to a mechanistic understanding of the neural processes underlying successful neurocognitive ageing. Even if we know that the activation of certain regions is associated with higher level of cognitive performance, there are still many unknowns. Why are these regions more active in some people than others? What is causing these higher levels of activation, and does this reflect a domain-general or a domain-specific mechanism? Such questions have led to increasing demands for more sophisticated interpretation of fMRI data (Morcom & Johnson, 2015), such as a shift away from localization (the study of regionally specific activity), towards functional integration (the study of brain connectivity) (Razi & Friston, 2016). However, a shift from activity to connectivity is not sufficient to obtain a mechanistic understanding of age-related changes in cognition. It is therefore important to move towards a more integrative approach in which we aim to answer such questions by combining dataset and data features from different modalities and cognitive states.

Integrating task and resting state functional MRI data

The combination of resting state and task data is one example of how an integrative approach can lead to a more mechanistic understanding. The study of functional networks has demonstrated age-related changes in the communication of brain regions within and between different brain networks; both during task performance and in resting state (Geerligs, Maurits, Renken, & Lorist, 2014; Salami, Pudas, & Nyberg, 2014; Spreng, Stevens, Viviano, & Schacter, 2016). Such results suggest that the phenomenon of over activations (or compensatory responses) during task performance, which are typically interpreted as a change that is linked to a specific cognitive state, could actually reflect

a more persistent change in the brain network architecture of older adults. This idea is supported by previous research, where task-related patterns of regional co-activation were shown to be highly similar to resting state networks based on functional connectivity (Toro, Fox, & Paus, 2008), and where direct associations have been found between resting state connectivity and task-evoked activity (Mennes et al., 2010; Zou et al., 2013). Moreover, an important recent study by Tavor et al. (2016) showed that individual variability in patterns of functional connectivity in resting state could be used to accurately predict individual differences in regional activity across a variety of tasks. This link between task-activations and connectivity patterns in rest has been attributed to similarities between rest and task states in the information flow between brain regions (Cole, Ito, Bassett, & Schultz, 2016).

Studies of resting state connectivity in ageing have shown an age-related increase in connectivity between specific networks, leading to a more integrated mode of information processing in older adults (Betzel et al., 2014; Chan, Park, Savalia, Petersen, & Wig, 2014; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015; Song et al., 2014). Therefore, if patterns of information flow are similar in task and rest, we would expect to see more widespread activation patterns during task performance in older adults, particularly in higher-order association areas where the age-related loss of network segregation appears to be most pronounced (Chan et al., 2014). This is in line with the results of a meta-analysis, showing that age-related over-activations are highly prevalent in fronto-parietal regions across a wide range of tasks (Li et al., 2015). If a direct association between age-related changes in task-induced activation and resting state activity or connectivity can be shown, this will change the interpretation of the age-related changes in regional activation. What is currently interpreted as a compensatory response related to a specific task may be explained by a more stable age-related change in the connectivity or information flow between different brain regions, potentially due to neuroanatomical changes.

Previous work has shown that part of the observed differences in functional connectivity between individuals reflect a stable difference in brain function (Finn et al., 2015; Geerligs, Rubinov, Cam-CAN, & Henson, 2015). These stable changes could be due to differences in the structural connectivity between brain regions, which have been shown to indirectly affect age-related changes in functional connectivity (Betzel et al., 2014). Alternatively, they could be related to changes in neurotransmitter systems (van den Brink et al., 2016), or changes in gray matter volume or differences in past experiences (Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009; Luo et al., 2012). The other aspects of observed differences in functional connectivity are associated with the specific state participants are measured in (Geerligs, Rubinov, et al., 2015). When such transient differences are associated with better task performance, this suggests that the flexibility of the functional architecture is important in maintaining high levels of functioning. Previous work has demonstrated that moving between different cognitive states, such as rest and task, is associated with widespread changes in functional connectivity. Some regions appear to be generally more flexible in their connectivity patterns, and are able to flexibly connect to other task relevant regions in order to facilitate task performance (Cole et al., 2013). Such flexible coupling may be especially important to ensure high level of cognitive functioning with advancing cognitive age (Gallen, Turner, Adnan, & Esposito, 2016; Geerligs, Saliasi, Renken, Maurits, & Lorist, 2014). State and trait aspects of functional connectivity cannot be disentangled if

we only focus on the activation or connectivity patterns that are associated with a specific task or resting state. In this context, resting state is one (of multiple) measures which can be compared to different task states to help disentangle trait and state differences in brain function.

Integrating structural and functional MRI data

Another way to investigate mechanisms behind individual differences in activity and connectivity is to directly combine functional and structural MRI data (Burzynska et al., 2013; Salami, Pudas, et al., 2014; Salami, Rieckmann, Fischer, & Bäckman, 2014). The compensation theory of neurocognitive ageing suggests that the additional activations observed in older adults offset the effects of lack of function in other brain regions, possibly due to age related structural decline in other brain regions (Park & Reuter-Lorenz, 2009). Therefore, one can argue that the association between task performance and regional activity will depend on the participants' level of structural decline; specifically in participants with high levels of structural decline we would expect to observe that performance is dependent on the recruitment of additional regions during task performance (Kalpouzos, Persson, & Nyberg, 2012).

Resting state data may also be useful in the context of integration of structural and functional data. One important question is how the ongoing communication between brain regions is shaped by the regional loss of while matter in older adults (Davis et al., 2009). Declines in white matter integrity in older adults have been shown to have direct implications for cognitive functioning in old age (Madden, Bennett, & Song, 2009; Penke et al., 2012; Salami, Eriksson, Nilsson, & Nyberg, 2012), presumably by affecting the ability of different brain regions to communicate efficiently (Hermundstad et al., 2013; Honey et al., 2009). Age-related declines in white matter have a constant impact on regional communication; not just in task situations but also in rest (Betzel et al., 2014). Therefore, resting state data may be especially appropriate to get a better understanding of how changes in white matter affect the connectivity within and between different brain networks. A follow up question would be how this affects the function of affected regions during the performance of specific cognitive tasks and how this in turn affects performance.

Measuring multidimensional age-related change

Another important reason to use a more integrative approach, instead of focusing on a single cognitive task, is that different cognitive functions are not independent. The cognitive dedifferentiation hypothesis suggests that ageing modulates the interplay between different cognitive processes (Baltes & Lindenberger, 1997; de Frias, Lövdén, Lindenberger, & Nilsson, 2007), with correlated rates of decline across different cognitive domains (Lindenberger & Ghisletta, 2009; Wilson et al., 2002). Furthermore, not all cognitive abilities decline at same rate, some remain spared or even improve in performance with increasing age (Salthouse, 2010b). The neural basis of these age-related differences and interactions remain largely unknown. The evidence for bidirectional interactions between resting state and task-based neurodynamics (Mastrovito, 2013; Northoff, Qin, & Nakao,

2010) suggests that the use of resting state in combination with multiple task states may lead to a better characterization of interacting neurocognitive processes across the lifespan.

In addition to purely focusing on the neural mechanisms behind age-related changes in cognitive functioning (Campbell and Schacter, 2016), another important question in neurocognitive ageing research is how environmental and lifestyle factors are associated with more successful cognitive ageing (Park & Reuter-Lorenz, 2009; Whalley, Deary, Appleton, & Starr, 2004). In this context, our interest is in understanding which factors (e.g. diet, smoking, vascular health, education, exercise) are important in determining age-related changes in cognition and how these changes in cognition are mediated by changes in brain structure and function (Debette et al., 2011; Gajewski & Falkenstein, 2016; Ronan et al., 2016; Sabia et al., 2012; Stern, Stern, Gurland, & Tatemichi, 1994). While some lifestyle factors may influence domain-specific functions and may be most adequately studied in the context of specific cognitive tasks; many of these factors would be expected to have broader, domain general impacts on cognitive functioning in older adults. Therefore, measures of brain health which are not associated with one specific task, such as those obtained with structural MRI and in resting-state, may be especially suitable to identify the neural correlates associated with different lifestyle factors (Smith et al., 2015).

Specific advantages of resting state data

While functional connectivity between brain regions and networks can be measured in datasets which are not collected in resting state (e.g. Cole, Bassett, Power, Braver, & Petersen, 2014), there are a number of unique advantages to using resting state as a baseline connectivity measure. For example, longitudinal task-based studies are biased by practice effects (Salthouse, 2010a), which are less problematic for resting state measurements. In addition, resting state is uniquely suited to obtain information about brain function in participants who are unable to perform certain cognitive tasks. If an older participant can no longer perform a certain task, it is questionable how informative measurements of brain activity during that task are. Will they inform the researcher about why this participant is not able to perform the task, or merely about the neural correlates of not performing the task? The work by Tavor et al. (2016) showed that it may be possible to obtain information about task-related regional activity in a wide range of domains from a single resting state scan. While resting state is typically used to study functional associations between brain regions, recent methodological advances have made it possible to examine the direction of connectivity between brain regions during resting state, using spectral DCM (Friston, Kahan, Biswal, & Razi, 2014). This technique has recently been successfully applied to investigate age- and cognition-related differences in neural connectivity, independent of age differences in neurovascular coupling (Tsvetanov et al., 2016). Finally, the most important reason for not discarding resting state data in the study of neurocognitive ageing is the unparalleled availability of resting state data. Because resting state is now being used by a large portion of fMRI researchers, there is the opportunity to integrate data across centres and participant sets (Miller et al., 2016). By pooling data in aggregate analysis we can obtain much more accurate estimates of effect sizes, both of group differences and of individual variability in relation to cognitive function (Biswal et al., 2010). This could not easily be achieved with any cognitive task, or with naturalistic stimuli which participants may respond

to differently when they are viewed repeatedly. However, we agree with Campbell and Schacter (2016) that the comparison of resting state data between groups should be a starting point instead of an end goal. Group differences should be used to develop hypothesis about effects on cognitive functioning as well as mechanistic underpinnings, which can then be tested by integrating different types of data.

Mental activities during the resting state

Campbell and Schacter (2016) mentioned two specific limitations of resting state connectivity studies, which we would like to comment on here. The first limitation is that age-related differences in resting state connectivity may be associated with age differences in mental activities at rest. Indeed, it is likely that there are systematic group differences in the nature of spontaneous thought. However, this issue of differences in mental activities may be a more general problem in the study of neurocognitive ageing which is not limited to resting state measures. With age, the amount of effort that is experienced while performing demanding cognitive tasks increases, even in the absence of age differences in performance (Hess & Ennis, 2014). In addition, older adults are more motivated to avoid errors leading to differential response strategies (Forstmann et al., 2011; Starns & Ratcliff, 2010). Such systematic differences in the approach to cognitive tasks will likely affect the observed task activation (Blumen et al., 2012; Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2010). For example, Davis at al. (2014) observed no age-related differences in the expression of the language network during natural listening conditions; age-differences in the prefrontal network only emerged after participants were asked to judge the syntax of the sentences. This suggests that it is the engagement in a task, rather than the language processing itself that leads to observed age-related differences (Davis, Zhuang, Wright, & Tyler, 2014), potentially associated with the strategies and effort invested in this task by older and younger adults. Even in the case of naturalistic stimuli, it is unclear whether older and younger adults are engaged in the same mental processes. Recently, Campbell et al. (2015) showed that the engagement in a common experience across participants (e.g. movie watching) led to highly synchronized brain responses between different individuals. Interestingly, this synchronization was much stronger in younger than older adults, which appeared to be related to age-related deficits in selective attention. Together, these findings suggest that equating mental engagement, effort and response strategies across participants is an important but challenging problem in both resting and task-based studies of ageing. This observation actually strengthens the case for incorporating both resting state and task-based studies in research on neurocognitive ageing, as the age-related differences in mental activities would probably not be consistent across rest and task contexts. Therefore, stable differences in functional connectivity that can be observed in different task conditions would be clear evidence for a trait effect which is not due to differences in mental experience.

Systematic noise in fMRI data

The second limitation that Campbell and Schacter (2016) mentioned is the susceptibility of resting state analyses to motion and physiological artefacts. In response to this, we would like to point out that this is a problem that is general to all analysis of functional connectivity, both in task and resting state. In both cases it is difficult to separate time-

dependent variations in neural activity from time-dependent artefacts due to head motion, breathing or heart rate variability (Birn, Diamond, Smith, & Bandettini, 2006; Chang et al., 2013; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). In task contexts, it is possible to contrast two different task conditions, which should reduce the impact of these nuisance variables. However, with this approach we lose the rich information about individual variations in the consistent patterns of information flow (connectivity) that are present in both task conditions. When two conditions are contrasted, the assumption is made that physiological artefacts will remain relatively constant across conditions. However, even this assumption has been shown to be invalid in specific cases. For example, task-correlated motion (Gavrilescu et al., 2004), or task-related breathing or heart rate changes can occur in tasks which are highly cognitively demanding, involve emotional stimuli or require focused or sustained attention (Birn, Murphy, Handwerker, & Bandettini, 2009; Hillenbrand, Ivry, & Schlerf, 2016). Therefore continued efforts to improve functional connectivity pipelines, so that connectivity estimates are less affected by a variety of physiological and mechanical artefacts, are critical for this field.

Related to the issue non-neural physiological signals in fMRI studies of ageing is also the concern that differences in activity of task-based fMRI signal may partly reflect differences in vascular health (Logothetis, 2008), which may not be related to underlying differences in neural connectivity (Balsters et al., 2013). Without careful correction for age differences in vasculature, differences in task fMRI activity can be erroneously regarded as neuronal differences. Recently, a method using resting state fMRI data was proposed (Kannurpatti & Biswal, 2008) and validated (Tsvetanov et al., 2015) as a way to correct for these vascular differences, without the need for separate scans with breath holding or hypercapnia (Liu, Glover, Mueller, Greve, & Brown, 2012). This illustrates that there are different ways in which rest and task data can be integrated effectively in the study of neurocognitive ageing.

Conclusions

In conclusion, it is important to start moving beyond traditional resting state or task-based analyses. In order to gain better insights in the brain mechanisms underlying cognitive change in relation to age, we need to adapt a more integrative approach, combining multiple data features across modalities and cognitive states to allow more robust inferences about cognitive ageing in terms of functional reorganisation of brain-behaviour relations and their underlying neurobiological mechanisms. To optimally move from the results of such integrated studies to mechanistic interpretations, it will be important to extend current theoretical models of neurocognitive ageing to generate predictions about different imaging modalities and cognitive states.

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