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Ageing and the resting state: is cognition obsolete?

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ABSTRACT
Recent years have seen the rise in popularity of the resting-state approach to neurocognitive ageing, with many studies examining age differences in functional connectivity at rest and relating these differences to cognitive performance outside the scanner. There are many advantages to the resting state that likely contribute to its popularity and indeed, many insights have been gained from this work. However, there are also several limitations of the resting-state approach that restrict its ability to contribute to the study of neurocognitive ageing. In this opinion piece, we consider some of those limitations and argue that task-based studies are still essential to developing a mechanistic understanding of how age affects the brain in a *cognitively relevant* manner – a fundamental goal of neuroscientific research into ageing.

During the course of normal human ageing, several cognitive functions are known to decline, while others are preserved. These cognitive changes have been well documented (Burke & Shafto, 2008; Craik & Byrd, 1982; Horn & Cattell, 1967; Kausler, 1982). While several theories exist to explain this pattern of preserved and declining functions (e.g. Craik, 1983; Hasher & Zacks, 1988; Lindenberger & Mayr, 2014; Salthouse, 1996), with the advent of modern neuroimaging techniques, the question of how age affects cognition can now be addressed at a more mechanistic level by exploring how changes in brain structure and function are associated with changes in mental outputs. Functional magnetic resonance imaging (fMRI) has revolutionised the field and become the most popular technique for imaging the ageing brain *in vivo*. This method has yielded several significant advances in our understanding of neurocognitive ageing, showing that age is often accompanied by under-activation of task-relevant regions (e.g. Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Spreng, Wojtowicz, & Grady, 2010), overactivation of primarily frontal regions (for reviews, see Cabeza, 2002; Grady, 2008), and reduced deactivation of the default mode network (DMN) during tasks that require externally directed attention (e.g. Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). More recently, there has been growing interest in the effect of age on functional connectivity, or the correspondence of low-frequency fluctuations between different brain regions, with much of this work focusing on "intrinsic" connectivity observed at rest (Ferreira & Busatto, 2013).

There are several advantages to the resting-state approach that likely contribute to its popularity. First, resting-state scans are relatively easy to obtain and particularly well suited to special populations, such as children and others who may have difficulty performing experimental tasks in the scanner. While it is debatable whether older individuals fall into this category, and recent work has shown that naturalistic viewing paradigms (such as movie-watching) may be better suited to special populations as they increase compliance and minimise head motion in the scanner (Campbell et al., 2015; Vanderwal, Kelly, Eilbott, Mayes, & Castellanos, 2015), resting-state runs certainly minimise the demands placed on elderly participants. Further, because there is no specific task to perform at rest, group differences in functional connectivity are thought to reflect intrinsic or unbiased differences in underlying network organisation, rather than group differences in response to the task itself (although this assumption will be called into question below). Another advantage of the resting state comes from the popularity of the method itself. Resting-state scans are now common to most individual experiments and large-scale cohort studies and thus provide an important means for comparison across experiments and institutions, serving as a sort of baseline measure of functional brain organisation.

Despite these advantages, there are also several aspects of the resting-state approach that limit its usefulness to the study of neurocognitive ageing. This article will consider some of those limitations and argue that

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task-based studies are still essential to developing a mechanistic understanding of how age affects the brain in a cognitively relevant manner. We start by considering the objectives of neuroscientific research into ageing, followed by a discussion of how resting-state data are limited in their ability to address these goals, and finally, argue for the continued value of a task-based, cognitive neuroscience approach.

What is the goal of neuroscientific research into ageing?

Before delving into approach, we first consider a key question: What are the goals of neuroscientific research into ageing, at least at the level of analysis afforded by current neuroimaging techniques? In our view, a critical goal of this research is to determine how age-related brain changes impact cognitive function. While understanding how age affects brain structure and function in its own right can be informative, knowing the cognitive or behavioural significance of said changes is almost always desirable.

In fact, making sense of observed age-related differences in brain function can often be difficult without concurrent measures of cognition to relate those differences to. A general assumption throughout much of the literature is that neural changes that accompany ageing are in some way "bad". For instance, ageing is associated with decreased grey matter volume (Raz & Rodrigue, 2006) and loss of white matter structure (Madden et al., 2012) and, probably rightly, these changes are thought to be undesirable. However, this assumption does not always hold. For instance, the observation of increased frontal activation with age during memory retrieval or working memory tasks has, in some cases, been deemed "compensatory", in that older adults who show these overactivations tend to perform at a higher level on the task in question than those who do not (e.g. Cabeza, Anderson, Locantore, & McIntosh, 2002; Grady, McIntosh, & Craik, 2005; Reuter-Lorenz et al., 2000). This age-related increase in activation likely would have been seen as indicative of neural decline without the anchor point of cognitive performance collected at the time of scanning. Even better are paradigms that relate activation to performance on a trial-wise basis, as in subsequent memory paradigms (usually contrasting hits vs. misses; Gutchess et al., 2005; Morcom, Good, Frackowiak, & Rugg, 2003; for a recent meta-analysis, see Maillet & Rajah, 2014), response inhibition tasks (contrasting successful stop trials with go trials; e.g. Coxon et al., 2016; Sebastian et al., 2013), and verbal production tasks (e.g. contrasting successfully named famous faces with those inducing tip-of-the

tongue states; Shafto, Stamatakis, Tam, & Tyler, 2010). In all of these cases, experimental designs and accompanying tasks allowed for a greater understanding of the cognitive implications of activation differences, although some have argued that we are still a long way from understanding what age-related increases in activation actually reflect (Morcom & Johnson, 2015; Shafto & Tyler, 2014).

Studies focusing exclusively on the resting state have certainly contributed to our understanding of the brain's functional network architecture and suggested a number of ways in which this architecture may change with age. However, resting-state data alone cannot explain how these changes in network architecture affect cognition. There are several reasons for this limitation, which we turn to next.

What are some of the limitations of the resting-state approach?

We know that the brain is never truly at rest and yet, there seems to be an implicit (or sometimes explicit) sentiment in the literature that resting-state data provide a privileged view of the brain's underlying organisation. Even the term, "intrinsic connectivity", implies a sort of unbiased or pure measure, unaffected by the execution of specific cognitive operations. This view has led some to suggest that the resting state is "particularly well suited toward characterizing and understanding the complex organization of brain networks across various cohorts" (Chan, Park, Savalia, Petersen, & Wig, 2014, p. E5003). However, it has been argued that the resting state should instead be viewed as just another task state (Buckner, Krienen, & Yeo, 2013; Klein, 2014; Morcom & Fletcher, 2007), one in which the experimenter has very little control over participants' internal thoughts. Unsurprisingly, participants report engaging in a range of deliberate and explicit mental activities while lying in the scanner at rest, and the type of activity differs greatly across individuals (Fox, Spreng, Ellamil, Andrews-Hanna, & Christoff, 2015; Hurlburt, Alderson-Day, Fernyhough, & Kuhn, 2015) and relates to patterns of resting-state connectivity (Andrews-Hanna, Reidler, Huang, & Buckner, 2010; Gorgolewski et al., 2014). Given the literature on age differences in chronic thought patterns and motivations (Charles & Carstensen, 2010; Hess, 2014), as well as differences in daily responsibilities and experiences, it is not unreasonable to assume that there may be cohort differences in the types of mental activities engaged in by younger and older adults at rest (cf. Mevel et al., 2013). Recent work also suggests that older adults "mind-wander" less than younger adults, at least during active tasks, and this

reduction may reflect broader age differences in spontaneous cognition (for a recent review, see Maillet & Schacter, 2016b). Age groups may also differ in their propensity to fall asleep in the scanner, which can go unnoticed during resting-state runs. Thus, age differences in resting-state functional connectivity may at least partly reflect age differences in the type of thoughts engaged in at rest.

Another limitation of resting-state functional connectivity, which is particularly problematic in the study of ageing, is the susceptibility of these measures to motion and physiological artefact. It is now well established that differences in head motion can contribute to observed differences in functional connectivity at rest (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012), and that older adults tend to move more than younger adults (Andrews-Hanna et al., 2007). While various methods have been proposed to remove motion artefact from the data (Patel & Bullmore, 2015; Satterthwaite et al., 2013), it remains unclear whether the effects of motion can ever fully be removed or indeed, whether removing/cleaning a larger proportion of the data for one group than another is a confounding effect in its own right (Geerligs, Rubinov, Cam-CAN, & Henson, 2015). Moreover, since functional connectivity measures reflect correlated fluctuations in the blood oxygenation level dependent (BOLD) signal, any physiological factors that are known to affect the BOLD signal will also affect measures of functional connectivity (Liu, 2013; Murphy, Birn, & Bandettini, 2013). Vascular health and neurovascular coupling are known to decline with age (D'Esposito, Deouell, & Gazzaley, 2003) and despite attempts to correct for these factors, age differences in resting-state connectivity may be at least partly attributable to differences in these non-neural factors (Golestani, Kwinta, Strother, Khatamian, & Chen, 2016). Unlike rest, cognitive tasks include events of interest that can be explicitly modelled and contrasted, allowing for the decoupling of the signal of interest from that of noise and the comparison of relative differences in activation and connectivity across groups and conditions (Buckner, Snyder, Sanders, Raichle, & Morris, 2000; Henson, 2006; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). While some of the BOLD signal during task performance likely still reflects motion (Hillenbrand, Ivry, & Schlerf, 2016) and physiological artefact (Tsvetanov et al., 2015), the ability to model the signal of interest helps to obviate many of these concerns.

A final limitation of the resting-state approach is the fact that measures obtained at rest are one step removed from the cognitive phenomena that researchers attempt to relate them to. As Geerligs, Rubinov et al. (2015) recently pointed out, there seems to be a trend in the literature to use resting-state functional connectivity as a sort of trait measure – to obtain measures of connectivity during rest and then relate these measures to cognitive performance obtained offline (i.e. outside the scanner, often on a different day or time; e.g. Damoiseaux et al., 2008; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015; Onoda, Ishihara, & Yamaguchi, 2012; Wang et al., 2010). When a correlation is found, the mechanism is inferred. For instance, Chan et al. (2014) recently showed that network segregation (or the ratio of within- to between-network connectivity) decreases with age and that this decrease relates to offline measures of long-term memory. They suggested that decreased network segregation "may reflect a fundamental age-related mechanism that negatively affects cognitive function" (Chan et al., 2014, p. E5002). This conclusion may be correct, but it would be strengthened by showing that (1) decreased network segregation with age is also observed during a task relevant to long-term memory and (2) a direct relationship to concurrent task performance. While the brain's functional network architecture may be similar across rest and task (Cole, Bassett, Power, Braver, & Petersen, 2014; Krienen, Yeo, & Buckner, 2014; Tavor et al., 2016), there is reason to believe that age differences in connectivity observed at rest may not hold in all task contexts (Campbell et al., 2016; Gallen, Turner, Adnan, & D'Esposito, 2016). For instance, Geerligs, Rubinov et al. (2015) showed that despite the overlap in network architecture seen across task states (rest, movie, and low-level audiovisual task in this case), an equally large proportion of connections differed across states and, critically, the effect of age on connectivity differed substantially across tasks. Beyond ageing, this work makes the general point that resting-state connectivity should not be used as a trait measure, as it only partly reflects some stable aspect of the individual. If one is interested in the cognitive implications of individual differences in functional connectivity, as so many researchers are, then it would seem most prudent to focus on connectivity measured during the cognitive function of interest.

What should the approach be?

The view that task-based studies and measures of cognition are important may not be new, and likely few would disagree with this standpoint. But there does seem to be a worrying trend in the literature to treat cognition as an afterthought, or to shy away from task-based designs because "age effects on functional connectivity during tasks are bound to be much more varied and complex

to interpret …"(Ferreira & Busatto, 2013, p. 387). However, we would argue that in this complexity lies greater potential to advance the field. Without task data, we would not have arrived at concepts such as neural compensation (e.g. Cabeza et al., 2002; Grady et al., 1994), dedifferentiation (e.g. Dennis & Cabeza, 2011; Park et al., 2004), or the notion that older adults "max-out" frontal recruitment at lower levels of demand (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Reuter-Lorenz & Cappell, 2008). While notions of compensation have been called into question by recent work showing that frontal recruitment may simply reflect differential responding to experimental task demands (Campbell et al., 2016; Davis, Zhuang, Wright, & Tyler, 2014), none of these insights would have been possible without the use of experimental tasks.

Similarly, while resting-state data contributed to the observation that DMN connectivity declines with age (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008), task data were needed to identify the functional consequences of that decline by showing that older adults fail to suppress the DMN during externally directed attention (Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007) and that this reduced suppression predicts poorer performance on the task (Miller et al., 2008; Sambataro et al., 2010; for a recent perspective, see Maillet & Schacter, 2016a). Decreased deactivation of the DMN may reflect an inability to suppress internal thought processes, perhaps as a consequence of insufficient engagement of the frontoparietal control network (FPN) as task demands increase (e.g. Campbell, Grady, Ng, & Hasher, 2012; Grady, Sarraf, Saverino, & Campbell, 2016; Turner & Spreng, 2015). When attention needs to be directed inward (i.e. during an autobiographical planning task), older adults show preserved connectivity between the DMN and FPN, but they then fail to switch connectivity of the FPN to the dorsal attention network when attention must be redirected towards the external environment (Spreng & Schacter, 2012; see also Clapp, Rubens, Sabharwal, & Gazzaley, 2011). This latter finding was made possible by cross-task comparison, and future work may benefit from further cross-task/domain comparisons and experiments specifically designed to manipulate network recruitment and coupling.

Of course, resting-state data remain useful insofar as they serve as a point of comparison across studies and aid in the generation of new hypotheses, which then require further testing with a task-based approach (Buckner et al., 2013). For instance, Salami, Pudas, and Nyberg (2014) recently reported an age-related increase in resting-state hippocampal connectivity that was related to poorer offline episodic memory. This finding

alone would have been ambiguous in regard to mechanism, except that the authors went on to show that greater hippocampal connectivity at rest relates to under-activation and reduced hippocampal-cortical connectivity during memory encoding. While the causal direction of the relationship still cannot be determined, these findings suggest that greater chronic connectivity within the hippocampus restricts its ability to respond appropriately during active encoding. Other studies have also incorporated resting-state and task data into the same experiment (e.g. Gallen et al., 2016; Geerligs, Rubinov et al., 2015; Grady et al., 2016), showing age differences in the reconfiguration of networks moving from rest to task.

Several recent studies have started to focus on dynamic connectivity, or shifts in functional connectivity over time. This work has primarily focused on the resting state and shows that the brain's network architecture is not static, but instead dynamically reconfigures into different "brain states" across the course of a run (Allen et al., 2014; Zalesky, Fornito, Cocchi, Gollo, & Breakspear, 2014; for a review, see Hutchison et al., 2013). This work helps dispel the view, arguably promoted by the resting-state literature, that the so-called "canonical resting-state networks" have fixed identities or topographies, templates for which are readily available (e.g. Allen et al., 2011; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012). We know based on task data that these networks are not fixed, but dynamically reconfigure to meet with changing cognitive demands (e.g. Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Fornito, Harrison, Zalesky, & Simons, 2012; Leech, Kamourieh, Beckmann, & Sharp, 2011; Scott, Hellyer, Hampshire, & Leech, 2015). Going forward, future dynamic connectivity work should determine how these different brain states relate to external task events (e.g. Bassett et al., 2011). There has been some suggestion that dynamic connectivity differs with age at rest (Madhyastha & Grabowski, 2014), and it would be interesting for future work to examine this possibility within the context of a task, the structure of which would enable one to predict when dynamic shifts should occur and the implications for cognition. Potentially even more informative are recent attempts to characterise age differences in effective connectivity during task performance (e.g. Legon et al., 2015; Waring, Addis, & Kensinger, 2013). This approach allows one to develop and test several competing models specifying the direction of influence between multiple systems, and thus goes beyond observations of reduced within- or increased between-network connectivity to ask how age affects directed connectivity between systems in the service

of cognition (for a similar view, see Sala-Llonch, Bartrés-Faz, & Junqué, 2015).

How, then, should we move forward? The rise of resting-state data seems to have coincided with a shift in focus towards methods development, with higher value placed on novel/sophisticated analysis techniques than experimental design (and in some ways this is certainly justified, as imaging methods are constantly evolving and being improved upon). However, in some cases, this shift has come at the expense of decades' worth of cognitive psychology research regarding ageing. The knowledge gained from this research is valuable and should be incorporated fully into studies of neurocognitive ageing. Careful experiments designed to manipulate well-documented, known cognitive functions, rather than the mental free-for-all provided by the resting state, will help reduce unwanted noise in the data, allow for the testing of specific hypotheses, and tell us more about how the brain changes with age in a cognitively relevant way.

Conclusion

Understanding how neural function changes with age in a cognitively relevant manner is an extremely complex problem, made even more difficult by a number of confounding factors. For many, resting-state data seem to simplify this problem by removing cognition from the equation and in so doing, allowing for an unbiased measure of "intrinsic", task-free connectivity. However, as we have argued, the resting state does not provide some privileged glimpse of underlying network structure and should be viewed as just another task state – one that may introduce as many problems as it solves. If we want to know how age differences in network structure affect some cognitive function, we need experiments specifically designed to measure and manipulate that function. Indirect measures of brain function can only tell part of the story.

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