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Research report

Cognitive stimulation of the default-mode network modulates functional connectivity in healthy aging

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ABSTRACT

A cognitive-stimulation tool was created to regulate functional connectivity within the brain Default-Mode Network (DMN). Computerized exercises were designed based on the hypothesis that repeated task-dependent coactivation of multiple DMN regions would translate into regulation of resting-state network connectivity.

Forty seniors (mean age: 65.90 years; SD: 8.53) were recruited and assigned either to an experimental group ($n=21$) who received one month of intensive cognitive stimulation, or to a control group ($n=19$) who maintained a regime of daily-life activities explicitly focused on social interactions. An MRI protocol and a battery of neuropsychological tests were administered at baseline and at the end of the study. Changes in the DMN (measured via functional connectivity of posterior-cingulate seeds), in brain volumes, and in cognitive performance were measured with mixed models assessing group-by-timepoint interactions. Moreover, regression models were run to test gray-matter correlates of the various stimulation tasks.

Significant associations were found between task performance and gray-matter volume of multiple DMN core regions. Training-dependent up-regulation of functional connectivity was found in the posterior DMN component. This interaction was driven by a pattern of increased connectivity in the training group, while little or no up-regulation was seen in the control group. Minimal changes in brain volumes were found, but there was no change in cognitive performance.

The training-dependent regulation of functional connectivity within the posterior DMN component suggests that this stimulation program might exert a beneficial impact in the prevention and treatment of early AD neurodegeneration, in which this neurofunctional pathway is progressively affected by the disease.

1. Introduction

A specific pattern of change in brain function is observed when individuals disengage from attending to overt cognitive tasks and are “at rest” (Greicius et al., 2003). During this mental state the brain is free to engage in undisturbed, spontaneous, “self-projecting” cognitive computations, such as autobiographical remembering, envisioning of the future, theory of mind, or spatial navigation imagery (Buckner and Carroll, 2007). The circuit of areas showing increased activity during these states was labelled Default Mode Network (DMN) (Raichle et al., 2001) and includes the posterior cingulate cortex, the medial prefrontal cortex, the inferior parietal lobule, the lateral temporal cortex, and the hippocampal formation (Buckner et al., 2008). The precuneus has also been recognized by some authors as part of the DMN (Utevsky et al., 2014), as well as a midline cerebellar lobule (Habas et al., 2009). Statistical evidence has demonstrated that this network is not a unitary entity, but is most likely the combination of distinct sub-systems. Andrews-Hanna et al. (2010) used graph-analytical techniques and clustering analysis and were able to assign the various hubs of the DMN to a core kernel consisting of the posterior cingulate and the anterior medial prefrontal cortex, and to two sub-systems, one

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encompassing the temporal hubs and the dorsomedial prefrontal cortex, and one including retrosplenial, ventromedial prefrontal, inferior parietal and mediotemporal cortices. This statistical separation appears to reflect a functional dissociation, as each of the two sub-systems was found to sustain its preferential set of spontaneous cognitive processes (Andrews-Hanna et al., 2010). The use of independent component analysis has then revealed the existence of another type of statistical dissociation. The DMN is very often estimated as two distinct components, namely an anterior and a posterior one (Uddin et al., 2009). Aside from its statistical properties, this sub-divison appears to be relevant in the description of neurodegeneration caused by Alzheimer's disease (AD). In fact, the evidence collected in some investigations suggests that, in clinically estabilished AD, the posterior DMN is pathologically down-regulated, while the anterior DMN is pathologically up-regulated (Damoiseaux et al., 2012; Jones et al., 2011). In addition to that, AD is associated with a progressive disconnection between the anterior and posterior hubs of the DMN. This has been found using independent component analysis (Song et al., 2013) and graph theory (Santz-Arigita et al., 2010), and it has also been suggested by the analysis of low frequency fluctuations in BOLD signal (Wang et al., 2007).

The hierarchical sub-division of the DMN into separate sub-systems and the identification of the effects of AD on each sub-system is particularly relevant for the creation of preventive and therapeutic instruments. It has been suggested that the framework describing modifications in functional connectivity generated by AD could be an optimal model to develop and assess the efficacy of new pharmacological treatments (Hampel et al., 2011). At the moment, the most recognized form of pharmacological treatment in AD is based on the enhancement of cholinergic neurotransmission. Enhanced neurotransmission at a synaptic level should reflect regulation of circuital connectivity at a systemic level. Based on this principle, some teams investigated changes in connectivity within the DMN after treatment with donepezil (Solé-Padullés et al., 2013) and memantine (Lorenzi et al., 2011). In a similar way, it was recently suggested that even cognitive interventions for AD could be designed and assessed based on the DMN framework (De Marco et al., 2014).

It has been indicated that increased resting-state functional connectivity displayed by a set of areas would be the result of frequent co-activation of those areas during goal-directed brain function (Martínez et al., 2013). This principle would resemble the Hebbian paradigm "Neurons that fire together, wire together", not applied to single cells connections, but to a larger scale of multiple-neuron network (Cheng et al., 2012). Although a number of experimental trials have investigated the impact of cognitive stimulation on functional connectivity in healthy adults (e.g. Jolles et al., 2013; Martínez et al., 2013; Takeuchi et al., 2011a; Voss et al., 2012), no study has specifically tested a program of exercises, the conceptualization of which is focused on the DMN.

We created a set of computerized tasks with multiple cognitive demands to induce co-activation of different DMN regions. We then administered a 20-session protocol of these network-based tasks to elderly adults without cognitive impairment. We hypothesized that this program would up-regulate functional connectivity within the posterior DMN, and would also up-regulate connectivity between the anterior and posterior components. The main goal of the study was to test the efficacy of such model of intervention in healthy aging in order to justify its application in a clinical population with AD in its prodromal stage. The multi-dimensional process of healthy aging features decrease of functional connectivity within the DMN components in a qualitatively similar, yet non pathological form as that observed along the severity stages of AD (e.g. Jones et al., 2011; Koch et al., 2010; Mevel et al., 2013; Mowinckel et al., 2012; Wu et al., 2011). For this reason, testing the efficacy of the treatment in healthy elderly adults would represent the ideal proof of concept for this type of cognitive stimulation.

In addition, construct validity of the tasks included in the program was assessed with voxel-based correlational methodology (Tyler et al., 2005).

2. Material and methods

2.1. Participants

Adults older than 50 years without subjective cognitive complaints were enrolled from the population of the Venetian archipelago. A complete neurological screening led by a senior clinical neurologist was carried out on all candidates in order to rule out the presence of exclusion criteria, which were set as follows: cognitive impairment, significant pharmacological treatments with psychotropic medications, cholinesterase inhibitors, memantine, drugs for research purposes or with toxic effects to internal organs, a significant disease at clinical level, a previous history of transient ischemic attacks, a diagnosis of severe vascular pathology, a baseline structural MRI revealing a major diagnostic entity, presence/diagnosis of uncontrolled seizures, peptic ulcer, cardiovascular disease, sick sinus syndrome, neuropathy with conduction difficulties, significant disabilities, evidence of abnormal baseline levels of folates, vitamin B12 or thyroid stimulating hormone, significant depression/anxiety or other psychiatric conditions. A full neuropsychological-test battery was administered to determine absence of cognitive impairment. The scores obtained on the various cognitive tests were used for diagnostic purposes as well as baseline scores for the analysis of concurrent changes in cognitive abilities induced by cognitive stimulation.

All participants were invited to take part in the study and assigned to either the experimental or control groups. Forty-six individuals were enrolled, 27 of whom were allocated to the experimental condition. The anamnestic notes of all 19 participants assigned to the control condition were examined to ascertain that all carried out a stimulating lifestyle characterized by intense social contact. All these participants were, in fact, either still employed or engaged daily in organizational activities or voluntary work within the same setting where the experiment took place.

2.2. Network-based cognitive stimulation

A program of cognitive exercises was devised for the purpose of targeting aspects of connectivity which are down-regulated in healthy aging and, to a pathological level, in the early stages of AD. This resulted in the selection of specific cognitive domains, the coactivation of which would result into a strengthening of the patterns of functional connectivity of interest. Semantic processing, memory retrieval, logical reasoning, and executive processing were identified as computational domains adequate for the purpose and, at the same time, suitable for implementation into computerized exercises. Visuospatial and verbal materials were used to create computational activities which would rely on multiple cognitive abilities. As the main objective of each task was to tap distant hubs of the DMN concurrently, specific cognitive operations suitable for being combined in one task were selected. Although the design of a single stimulation task would have been sufficient to test the experimental hypothesis and, at the same time, would have allowed a "transparent" control of the mechanism by which engaging in the trials translates into regulation of functional connectivity, we decided to create multiple tasks. This choice was made both to confer a treatment-like aspect to the intervention, and to minimize the degree of potential monotony and boredom caused by the constant repetition of a single task for multiple sessions.