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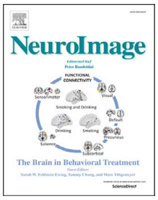

Definition and characterization of an extended multiple-demand network

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ABSTRACT

Neuroimaging evidence suggests that executive functions (EF) depend on brain regions that are not closely tied to specific cognitive demands but rather to a wide range of behaviors. A multiple-demand (MD) system has been proposed, consisting of regions showing conjoint activation across multiple demands. Additionally, a number of studies defining networks specific to certain cognitive tasks suggest that the MD system may be composed of a number of sub-networks each subserving specific roles within the system. We here provide a robust definition of an extended MDN (eMDN) based on task-dependent and task-independent functional connectivity analyses seeded from regions previously shown to be convergently recruited across neuroimaging studies probing working memory, attention and inhibition, i.e., the proposed key components of EF. Additionally, we investigated potential sub-networks within the eMDN based on their connectional and functional similarities. We propose an eMDN network consisting of a core whose integrity should be crucial to performance of most operations that are considered higher cognitive or EF. This then recruits additional areas depending on specific demands.

1. Introduction

Executive functioning is central to coordinated, goal-directed behavior and thought to play a major role in a wide range of different psychiatric and neurological diseases (Zelazo and Müller, 2002). However, despite its significance and the consequent effort directed towards investigating it, the true nature of executive abilities remains rather elusive. One of the main reasons for this is that executive functioning is probably not a single process but should be rather regarded as a “macro-construct” that includes different aspects of mental functioning (Zelazo et al., 1997). Moreover, the lack of a clear formal definition of executive functioning is also due to the nature of the aspects that constitute it, the relationship among these and their contribution to the overall concept (Lezak, 1982). Mirroring this lack of formal definition of executive functioning, several brain regions and networks have been implicated as the brain's underpinning of executive functioning. In this perspective, the network aspect is particularly important, as there is a growing consensus that higher cognitive, including “executive”, functions depend on distributed networks rather than any particular region in isolation (Corbetta and Shulman, 2002). In addition, it has been shown that “executive networks” seem to sustain a wide range of cognitive functions (Fedorenko et al., 2013; Cabeza and Nyberg, 2000), prompting the term multiple-demand network (MD; Duncan and Owen, 2000; Duncan, 2010). Unfortunately, different perspectives, operationalizations and traditions have resulted in a rather diverse co-existence of labels for brain networks associated with executive control. One is the aforementioned multiple-demand network as defined by convergent activation across multiple cognitive tasks in fMRI (Duncan, 2010). A very similar example is the cognitive control network, which has been described as a network that includes a set of cortical regions that are consistently co-active during cognitive control tasks (Cole and Schneider, 2007). Other comparable networks include the fronto-parietal control system (Vincent et al., 2008), the superordinate cognitive control network (Niendam et al., 2012), the task-positive network (Fox et al., 2005), and the extrinsic mode network (Hugdahl et al., 2015). In addition, there seems to be some convergence with concepts such as the salience network (Seeley et al., 2007), the ventral attention network (VAN) (Vossel et al., 2014; Japee et al., 2015) and the dorsal attention

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network (DAN) (Corbetta et al., 2008; Corbetta and Shulman, 2002), besides other functional networks such as the working memory network (Rottschy et al., 2012), the vigilant attention network (Langner and Eickhoff, 2013), and the inhibitory control network (Cieslik et al., 2015).

Inspecting these various networks, it quickly becomes evident, that virtually all of them indicate the posterior-medial frontal cortex [pre-supplementary motor area and adjacent middle cingulate cortex (pre-SMA/MCC)], the bilateral anterior insula (aINS), intraparietal sulcus (IPS), and posterior inferior frontal sulcus (IFS) as regions contributing to executive processing. Interestingly, these regions were suggested as part of a multiple-demand network (MDN) by Duncan (2010) and emerged from a recent integration (Müller et al., 2015) of three large-scale neuroimaging meta-analyses on working memory (Rottschy et al., 2012), vigilant attention (Langner and Eickhoff, 2013), and inhibitory control (Cieslik et al., 2015).

In turn, there are also several brain regions not included in these rather conservative definitions of regions of the MDN but can nevertheless be found in several of the aforementioned networks. These include, e.g., the basal ganglia and thalamus, the more anterior IFS/dorsolateral prefrontal cortex, or the dorsal premotor cortex. In addition, the MDN as suggested by Duncan (2010) or Müller et al. (2015) are based on the (most robust) convergence of activation data and do not directly consider the perspective of a distributed neural network. In light of these two observations, it seems likely that the previously established regions of the MDN entertains close interactions with several other regions that may be considered as an extended MDN (eMDN) complementing the original regions.

Mapping and characterizing this broader MDN is the core aim of this study. In more detail, this entails the computation of robust connectivity maps for each original MDN region by combining task-free and task-based functional connectivity analyses. The eMDN is then identified by convergence across multiple of these robust connectivity maps for the seed regions. Next, we functionally characterize the ensuing eMDN regions by an objective analysis of experimental paradigms that evoke activation of these regions. Finally, we investigate potential cliques of regions within the extended MDN based on similarities in connectional and functional profiles.

2. Methods

2.1. Seed definition

The seed regions for this work were based on the meta-analytically defined multiple-demand network of Müller et al. (2015), which was defined by performing a conjunction across three large-scale neuroimaging meta-analyses on working memory (Rottschy et al., 2012, covering e.g., n-back, Sternberg or delayed match-to sample tasks), vigilant attention (Langner and Eickhoff, 2013, covering e.g., stimulus detection or simple reaction tasks), and inhibitory control (Cieslik et al., 2015; covering, e.g., Stroop, Simon or Flanker tasks). The regions present in the resulting conjunction consist of the bilateral anterior insula, bilateral inferior frontal junction/gyrus, right middle frontal gyrus, right intraparietal sulcus and the posterior medial frontal cortex extending from the midcingulate cortex to the (pre-) supplementary motor area.

To ensure that the functional connectivity analyses of all seed regions were based on the same number of voxels, in spite of unequal cluster sizes, we represented each seed by a 5 mm sphere around its center of gravity. The only exception to this approach was the posterior medial frontal cortex cluster whose center of gravity was located between MCC and pre-SMA. Given the presence of distinct peaks within both MCC and pre-SMA, both of these were retained as seed coordinates. Thus, eight seed coordinates (Fig. 1; Table 1) were used for whole-brain resting-state and meta-analytic connectivity modeling analyses that were intersected to define the robust, state-independent connectivity map for each seed.

2.2. Resting-state functional connectivity

Seed-based RS analysis was used to investigate the task-independent functional connectivity of each original MDN region. Resting-state fMRI images of 192 healthy volunteers were obtained from the Enhanced Nathan Kline Institute – Rockland Sample (Nooner et al., 2012). The local ethics committee of the Heinrich-Heine University in Düsseldorf approved re-analysis of the data. During RS acquisition, subjects were instructed to look at a fixation cross, not think about anything in particular and not to fall asleep. Images were acquired on a Siemens TimTrio 3T scanner using BOLD contrast [gradient-echo EPI pulse sequence, TR = 1.4 s, TE = 30 ms, flip angle = 65°, voxel size = 2.0 mm × 2.0 mm × 2.0 mm, 64 slices]. Physiological and movement artifacts were removed from the RS data by using FIX (FMRIB's ICA-based Xnoiseifier, version 1.061 as implemented in FSL 5.0.9; Salimi-Khorshidi et al., 2014; Griffanti et al., 2014), which decomposes the data into independent components (ICs) and identifies noise components using a large number of distinct spatial and temporal features via pattern classification. Unique variance related to the identified artefactual ICs is then regressed from the data together with 24 movement parameters (including derivatives and 2nd order effects as previously described and evaluated; cf. Satterthwaite et al., 2013). Data were further preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, London) and in-house Matlab scripts. The first four scans were excluded prior to further analyses, the remaining EPI images corrected for head movement using a two-pass (alignment to the initial volume followed by alignment to the mean after the first pass) affine registration. The mean EPI image for each subject was then spatially

Table 1
Seed coordinates derived from the meta-analytically defined multiple-demand network by Müller et al. (2015).

	x	y	z
Right aINS	38	22	−2
Left aINS	−36	18	−2
Right IFJ/IFG	48	10	28
Left IFJ/IFG	−48	10	30
Right MFG	44	38	20
Right IPC/IPS	44	−44	46
MCC	4	20	44
pre-SMA	−2	6	58

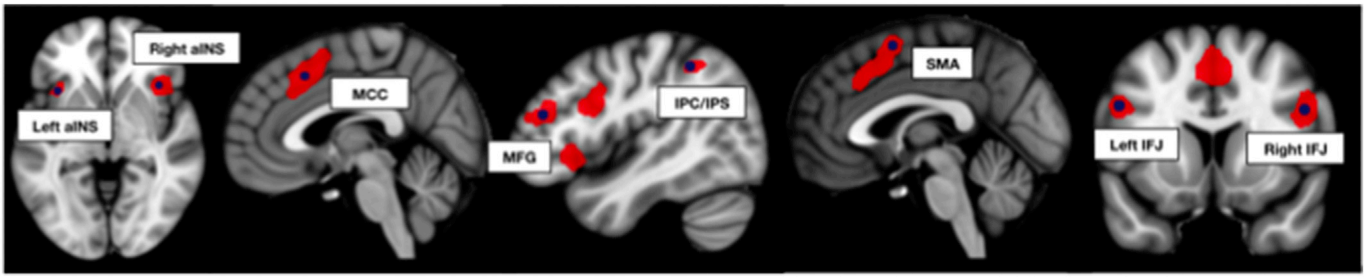

Fig. 1. Seed regions (shown in dark blue) derived from the meta-analytically defined multiple-demand network by Müller et al., (2015) (shown in red).