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Neuronal Networks Observed with Resting State Functional Magnetic Resonance Imaging in Clinical Populations

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1. Introduction

Functional Magnetic resonance imaging (fMRI, (Ogawa et al., 1990)) in the absence of experimental tasks and behavioral responses, performed with the patient in a relaxed "resting" state (rs-fMRI), takes advantage of the neural origin of spontaneous blood-oxygen-level-dependent (BOLD) signal fluctuations (Biswal et al., 1995) to represent the rate and timing of activity synchronization across the entire brain (Damoiseaux et al., 2006; Mantini et al., 2007; van de Ven et al., 2004).

Independent component analysis (ICA) (Hyvarinen et al., 2001), when applied to whole-brain rs-fMRI, allows extracting from each individual patient data set a series of activation images describing the BOLD signal temporal correlations within and between functionally connected brain regions, forming highly reproducible neural networks called resting state networks (RSN) (Damoiseaux et al., 2006; Mantini et al., 2007). Particularly, ICA transforms individual patient rs-fMRI data sets into series of RSN maps, allowing for a voxel-based population analysis of whole-brain functional connectivity without the need to specify "a priori" the regions of interest constituting the layout of the neural network (McKeown et al., 1998; van de Ven et al., 2004).

In normal volunteers there are at least six RSNs consistently found whose neurological significance has been established according to the functional specialization and anatomical connectivity of the constituent regions (Greicius et al., 2009; van den Heuvel et al., 2009) as well as to the possible association with neuro-electrical rhythms (Mantini et al., 2007). Altogether the functional connectivity of these RSNs represents a basic physiological condition of the human resting brain (Gusnard & Raichle, 2001).

While the number, role, meaning and potential of RSNs in representing and interpreting the functional architecture of the human brain is still debated and sometimes controversial (Morcom & Fletcher, 2007), a number of voxel-based population rs-fMRI studies have uncovered significant differences between normal and clinical populations in various neurological disorders, and a particular attention has been given to cognitive decline as a primary or secondary aspect of neurodegeneration (Bonavita et al., 2011; Cherkassky et al., 2006; Greicius et al., 2007; Greicius et al., 2004; Mohammadi et al., 2009; Nakamura et al., 2009; Rocca et al., 2010; Rombouts et al., 2005; Roosendaal et al., 2010; Sorg et al., 2007; Sorg et al., 2009; Tedeschi et al., 2010).

In this chapter we will review the physiological and technical background of resting state neural networks and the ICA methodology currently used for observing and analyzing RSNs in normal and clinical populations. The main physiological RSNs will be illustrated and discussed with special emphasis to those exhibiting functional abnormalities in neurological disorders. In addition, two clinical applications will be presented, where this methodology showed pathological changes in amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) patients in comparison to normal subjects.

2. Physiology and anatomy of the resting-state networks

In a functional connectivity study, the active human brain is conveniently represented in terms of independent functional networks of mutually interacting regions (Friston et al., 1996). Anatomically, these regions can be either distant from each other or result from a fine segregation of bigger into smaller neuronal assemblies. Functionally, two imaging voxels or regions exhibiting neural signals highly correlated in time (synchronized) are conceptually part of the same network.

When measuring the brain with fMRI over prolonged intervals of time (e. g. from two to ten minutes), it is possible to detect throughout the brain characteristic spontaneous fluctuations in the BOLD signal which occur at relatively low frequencies (<0.1 Hz) and are not of technical (artifactual) origin (Biswal et al., 1995; Damoiseaux et al., 2006; Mantini et al., 2007; Smith et al., 1999; van de Ven et al., 2004). When assessing the functional connectivity of these fluctuations across regions, a series of networks can be built, that clearly resemble the same functional networks activated during the performance of active tasks, even if the participant is not performing any specific task and is simply instructed to remain still, with eyes closed and without thinking to anything specific. In other words, under simple resting conditions, the brain is engaged in spontaneous activity which is not attributable to specific inputs or to the generation of specific output, but is intrinsically originated.

A possible link between functional connectivity and spontaneous synchrony of brain signals was already proposed in early electroencephalography (EEG) studies (French & Beaumont, 1984), suggesting that long-range EEG coherencies across cortical regions and between hemispheres could be originated from a relatively small number of interacting regions and processes (see, also, e.g., (Koenig et al., 2005; Locatelli et al., 1998)). Even if EEG and fMRI signals have very different spatial and temporal scales, it has been later demonstrated that a tight correspondence exists between the spatial distribution of low-frequency BOLD signal fluctuations and the main EEG rhythms, for at least six reproducible RSNs (Mantini et al., 2007), in line with the idea that the two modalities share a common neurophysiological origin, represented by the local field potential (LFP) (Logothetis & Pfeuffer, 2004). More specifically, it has been hypothesized that the low-frequency BOLD signal fluctuations are themselves due to low-frequency LFPs or to low frequency modulations of high-frequency LFPs (Raichle, 2010).

The most frequently and consistently reported RSNs, which are also correlated with EEG rhythms, include the default-mode network (DMN), functionally connecting the posterior and anterior cingulate cortex (PCC and ACC) and, bilaterally, the inferior parietal lobules

(Greicius et al., 2003; Raichle et al., 2001); the visual network (VIS) involving bilaterally the retinotopic occipital cortex up to the temporal-occipital junctions and middle temporal gyri (Lowe et al., 1998; Wang et al., 2008); the fronto-parietal network (FPN) including, bilaterally, the intra-parietal cortex and the superior-lateral frontal cortex (Corbetta & Shulman, 2002); the sensori-motor network (SMN) involving, bilaterally, the pre- and post-central gyri, the medial frontal gyrus, the primary and supplementary motor and the primary and secondary sensory areas (Biswal et al., 1995); the auditory network (AUD), involving, bilaterally, the superior and middle temporal cortex (Seifritz et al., 2002) and the self-referential network (SRN) involving the ventro-medial prefrontal cortex and the perigenual anterior cingulate cortex (D'Argembeau et al., 2007). The brain maps of these six typical RSNs in a normal population are exemplarily shown in figure 1 using different colors for the different networks.

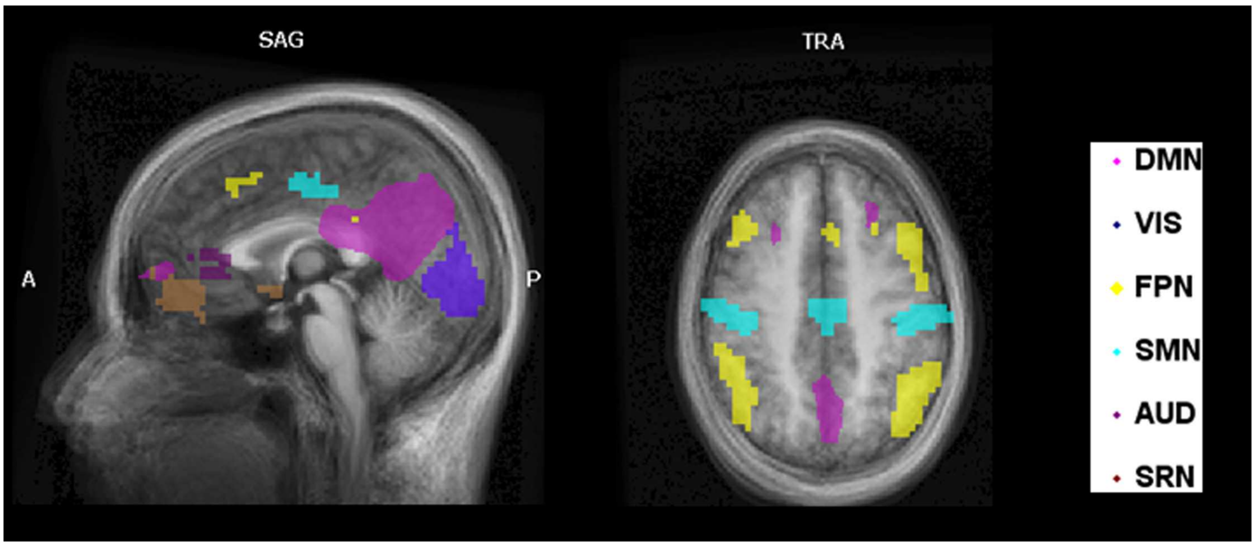

Fig. 1. Typical RSN maps. Visual network (VIS), default-mode network (DMN), fronto-parietal network (FPN), sensori-motor network (SMN), auditory network (AUD) self-referential (SRN) network.

As anticipated (and exemplified in figure 1), all the RSNs consist of anatomically separated, but functionally connected regions, sharing and supporting the same sensitive, motor or cognitive functions (Cordes et al., 2000). The RSNs reported in the normative literature have generally resulted to be quite consistent across studies, despite some differences in data acquisition and analysis techniques that partially account for the variability observed in the number and lay out of the networks. For instance, the DMN has been sometimes distinguished into two separate subnetworks, the anterior and posterior DMN (see, e. g., (Damoiseaux et al., 2008)), and the FPN as two lateralized networks (right and left FPNs, RFPN and LFPN) (see, e. g., (Damoiseaux et al., 2006; Tedeschi et al., 2010)). The auditory and visual networks have been presented in terms of a one single network (see, e. g., (Mantini et al., 2007)), two (see, e. g., (Damoiseaux et al., 2006)) or even three (see, e. g., (Rocca et al., 2011)) subnetworks.

Understanding the functional correlate of a given RSN under normal physiological conditions is crucial to correctly address any possible link between altered rs-fMRI patterns and behavioral and clinical variables. However, it should also be recognized that cytoarchitectonically distinct brain regions are kept functionally connected by white matter connections that directly (monosynaptically) or indirectly (multisynaptically) make the ongoing communication physically possible (Greicius et al., 2009; van den Heuvel et al., 2009). Thereby, it is equally important to clarify whether the observed RSN functional connectivity is mediated by direct or indirect structural connections, e. g. by combining rs-fMRI with diffusion tensor imaging (DTI), an MRI technique that allows the study of white matter fiber bundles.

By far, the most studied RSN in the clinical and research neuroimaging community is the DMN (Greicius et al., 2003; Raichle et al., 2001). This network has attracted considerable interest in the neuroscience community for its possible role as the baseline cognitive state of a subject and its link to memory and executive functions in normal and pathological conditions. In fact, the DMN normally includes the ACC and PCC regions, known to be involved in attention-related processes (Badgaiyan & Posner, 1998) and often detectable as transiently or consistently deactivated during many different types of cognitive tasks (McKiernan et al., 2003). For this reason, Raichle et al. (2001), who first targeted this type of brain activity with positron emission tomography (PET) imaging, have introduced the concept of "default-mode" activity and attempted to differentiate a "cognitive" baseline state from a "general" resting state in human brain. Thereafter (Greicius et al., 2003) the DMN has been often conceptualized as a "stand-alone" function or system to be analyzed with data models specifically oriented to functional connectivity (Bullmore et al., 1996). Within the DMN, the PCC node, one of the most intensively interconnected regions in the whole brain (Cavanna & Trimble, 2006; Hagmann et al., 2008), seems to mediate all the intrinsic functional connectivity of the brain (Fransson & Marrelec, 2008). Indeed, the PCC plays an essential role in all types of introspective mental activity, ranging from immediate suppressing of distracting thoughts to avoid mistakes (Li et al., 2007; Weissman et al., 2006) up to modulating rethinking about the past to imagine the future and awareness (Buckner et al., 2008).

The VIS network involves regions in the striate, peri-striate and extra-striate visual cortex, which are normally activated by a visual task. This network extends from the lingual and fusiform gyri (i. e. V1 to V4) up to the occipito- and middle temporal regions (i. e. MT/V5), even if, in some reports, regions belonging to the primary and secondary visual system are shown to belong to separate visual RSNs (see, e. g., (Rocca et al., 2011)).

The fronto-parietal (or "executive-attention") network (FPN), sometimes found to be lateralized (i.e., right and left FPN), is also relevant for cognition. Particularly, the FPNs seem to be central for cognitive processing as they involve regions such as the dorsal frontal and parietal cortices potentially overlapping with the dorsal attention network which is known to mediate executive control processing (Corbetta & Shulman, 2002).

The SMN includes regions in the precentral and postcentral gyrus and in the supplementary motor area, all regions that both anatomically and functionally correspond well to motor and sensory areas, e. g. activated during a finger tapping task (Biswal et al., 1995).

The AUD network involves regions in the auditory cortex, which are normally activated by an auditory task. This network extends from the Heschl's gyrus to the superior temporal gyrus and the insula and has been also reported as one or two RSNs (see, e. g., (Damoiseaux et al., 2006)).

3. Methodology for the analysis of the resting-state networks

RSN can be observed using several functional connectivity analysis tools. A straightforward approach entails extracting the extracting the time-course of the BOLD signal from a predefined region-of-interest (ROI) and subsequently searching all regions whose time-course significantly correlates with the ROI time-course. This method produces RSN maps that are extremely simple to interpret (Fox & Raichle, 2007; Greicius et al., 2003), but has the important drawback that the resulting functional connectivity maps will depend on the location, extension and order of the "seed" regions chosen, and on how these are defined in advance of the analysis. By contrast, "component-based" statistical techniques (Andersen et al., 1999; Friston et al., 1993), that do not require a-priori assumptions on the regions involved, enable the observation of multiple neural networks from whole-brain resting state data sets, thereby avoiding the possibility of bias.

ICA (Hyvarinen et al., 2001) has been successfully applied to neuroimaging data of diverse imaging modalities for generating convenient representations of activated brain networks in single subjects and groups. Particularly, in fMRI, ICA is commonly applied in its spatial variant (Calhoun et al., 2001b; McKeown et al., 1998) where each statistically independent component process corresponds to a spatial map distributed over all voxels of the imaging slab. Besides separating many types of structured dynamic artefacts from fMRI time series (see, e. g., (De Martino et al., 2007)), spatial ICA can provide a meaningful representation of function-related BOLD signals and unravel the whole-brain distributed functional connectivity under different experimental and clinical conditions. Particularly, spatial ICA is commonly applied in rs-fMRI to model the spontaneous low-frequency BOLD signals in terms of whole-brain distributed maps (Mantini et al., 2007).

When exploring fMRI data with spatial ICA, it is always necessary to decide how many ICA components to extract and, among these, select those components that can be consistently and reliably associated with functional connectivity networks of interest for a given application. The number of components is basically a "free choice" parameter (Calhoun et al., 2009), typically ranging between 20 and 60, even if potential changes in the layout of certain ICA generated RSN maps, such as splitting of a network into multiple networks, may result from the extraction of substantially more components than the minimum needed for a stable decomposition (Abou-Elseoud et al., 2010; Kiviniemi et al., 2009).

After fMRI data preparation and preprocessing, a group statistical analysis is typically required to summarize RSN functional connectivity in one or more populations of interest and to search for possible regional differences between populations within selected RSNs.

In many cases, population-level studies based on ICA use a two-level approach, first running single-subject ICA and then combining the components into a second-level group (random effects) analysis; in order to match components between subjects clustering and spatial correlation techniques are used (Esposito et al., 2005; Schopf et al., 2011; Wang & Peterson, 2008). This strategy provides maximal power to model subject-level structured noise (Cole et al., 2010) and has the important advantage of capturing unique spatial and temporal features of the subjects' data set even if the signal to noise ratio (SNR) is substantially lower in some subjects compared to other subjects. The disadvantage of this approach is that the components that are matched across subjects are not necessarily extracted in the same way for each subject of a group (Erhardt et al., 2010).

As an alternative to clustering, temporal (Calhoun et al., 2001a; Varoquaux et al., 2010) and spatial (Svensen et al., 2002) concatenation as well as "tensorial" (Beckmann & Smith, 2005; Guo & Pagnoni, 2008) data aggregation schemes have been previously examined to perform only one ICA decomposition, thereby circumventing the problem of a "first-level" component matching. The most used aggregate group ICA approaches (Calhoun et al., 2001a; Zuo et al., 2010) are based on temporal concatenation and assume "common" ICA maps for all subjects in the first level analysis. A population analysis is then performed retrospectively determining the individual ICA components from the group ICA components. Thereby, all these methods implicitly assume that a given component is really present with exactly the same layout in all the subjects.

4. Resting state networks in clinical populations

The observational study of RSN functional connectivity in normal and clinical populations allows generating a comprehensive picture of brain functions and dysfunctions by the sole analysis of resting state fMRI activity, i. e. without relying on an active performance or engagement of the patient. This aspect is particularly attractive when studying uncooperative populations, but is generally suited to all cases where behaviors and performances are pathologically impaired. For this reason many research groups have studied RSN functional connectivity in different neurological and psychiatry disorders, detected differences between patients and controls and correlated these measures to clinical variables.

The largest numbers of studies and the most consistent results have been obtained for disorders like Alzheimer disease (AD) (Greicius et al., 2004; Petrella et al., 2011; Rombouts et al., 2005; Sorg et al., 2007; Supekar et al., 2008; Wang et al., 2007; Wang et al., 2006; Zhang et al., 2010; Zhang et al., 2009) and schizophrenia (Bates et al., 2009; Bluhm et al., 2007; Foucher et al., 2005; Greicius, 2008; Hoptman et al., 2010; Jang et al., 2011; Lagioia et al., 2010; Lynall et al., 2010; Mannell et al., ; Ongur et al., 2010; Repovs et al., 2011; Rotarska-Jagiela et al., 2010; Shen et al., ; Skudlarski et al., ; van den Heuvel & Hulshoff Pol, ; Woodward et al., 2011; Zhou et al., 2008). In this chapter, we present two examples of clinical RSN study, applied to ALS and MS.

4.1 Resting state networks in Amyotrophic Lateral Sclerosis

ALS is a chronic progressive disease that predominantly affects the motor system (Turner et al., 2009b), but neurodegeneration may also extend beyond motor areas (Geser et al., 2008; Geser et al., 2009; Murphy et al., 2007; Turner et al., 2009a). In fact, ALS patients often exhibit variable degrees of cognitive impairment with rather typical involvement of frontal executive functions (Grossman et al., 2008; Murphy et al., 2007). Thereby, studying the SMN, but also the DMN and the FPN, is crucially important to elucidate both motor and extra-motor involvement in ALS, to examine the possible interaction between physiologically sensitive and disease modified rs-fMRI parameters and to compare these functional measures with the clinical and MRI structural aspects of the neurodegenerative process.

The fact that rs-fMRI allows exploring whole-brain functional connectivity in all these RSNs with minimal bias towards a specific motor or cognitive function is particularly attractive for studying ALS patients, whose degree of cooperation normally introduces substantial variability in their performances.

The rs-FMRI fluctuations within the SMN network are reduced or even suppressed in ALS patients compared to age- and sex-matched normal controls (Mohammadi et al., 2009; Tedeschi et al., 2010). For instance, comparing the SMN maps on a voxel by voxel basis has shown statistically significant group differences bilaterally in the primary motor cortex (PMC) (figure 2).

ALS has long been characterized as a neurodegenerative disorder affecting the motor system, therefore, the observation that the coherent RS-fMRI fluctuations within the SMN are strongly reduced can be easily linked to most existing animal models of ALS explaining motor neuron degeneration both at the cellular and molecular levels (Dal Canto et al., 1995; Wong et al., 1995; Wils et al., 2010).

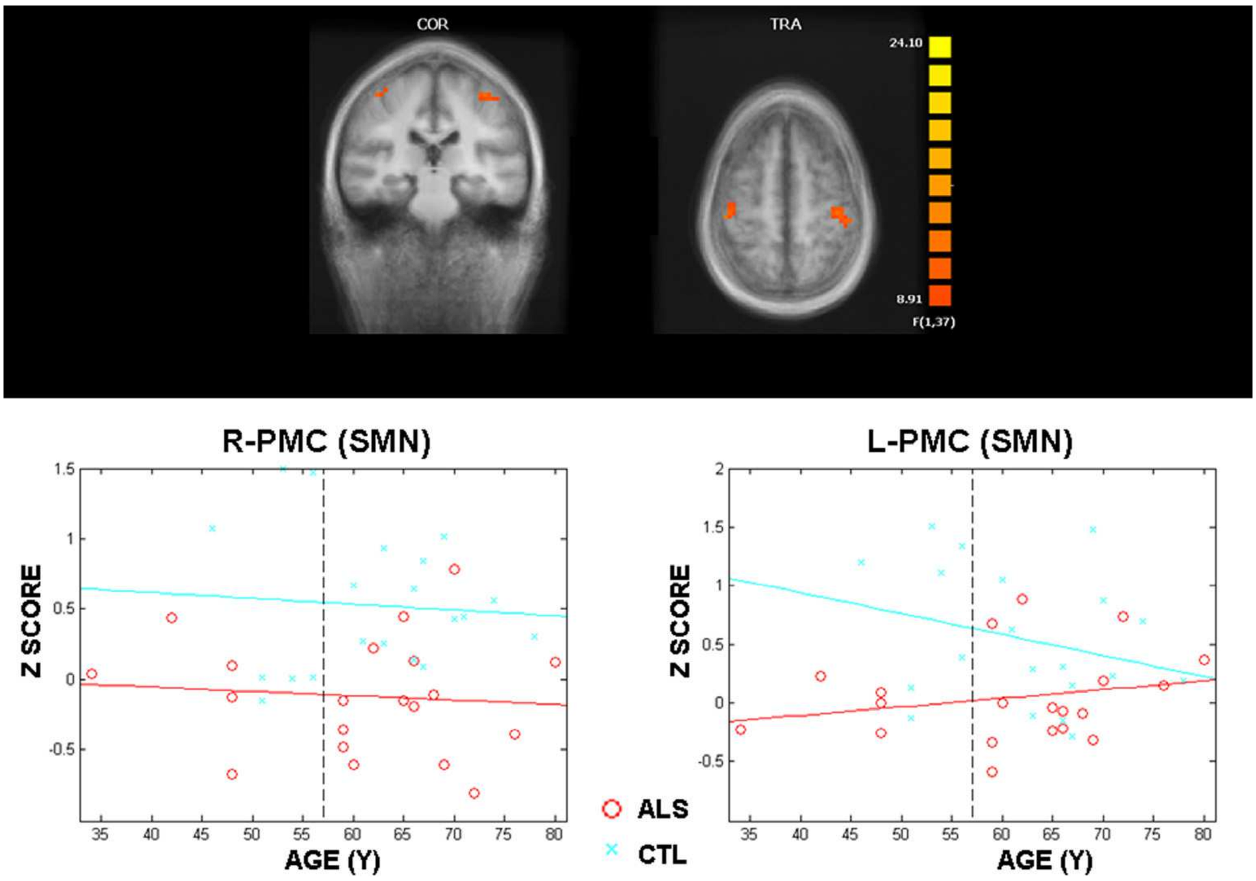

Fig. 2. ALS disease effects in the SMN. Upper panel: F-map of statistically significant disease effects within the SMN network (P=0.05, cluster-level corrected) overlaid on the average Talairach-transformed T1 image (coronal and axial cuts). Lower panel: Scatter plots of the regional ICA z-scores vs age in the R-PMC (left) and in the L-PMC (right). PMC = primary motor cortex. ALS = amyotrophic lateral sclerosis patients. CTL = control subjects.

The RFPN network is also partially suppressed in ALS patients. Figure 3 shows the localization of two regions within this network, in the superior frontal gyrus (SFG) and in the supra-marginal gyrus (SMG), where the network-specific RS-fMRI fluctuations resulted suppressed in ALS compared to controls. These effects in a cognitive executive network like the RFPN likely reflect a rather typical frontal cortex dysfunction observed in ALS patients (Abrahams et al., 1996; Hatazawa et al., 1988; Rule et al., 2010; Vercelletto et al., 1999).

Observing RSNs in ALS patients over an extended range of age has highlighted the possible interaction between aging and neurodegeneration (Tedeschi et al., 2010). Previous work has reported a significant effect of aging on DMN regions in the normal population (Esposito et al., 2008; Grady et al., 2006; Greicius et al., 2004; Koch et al., 2009; Persson et al., 2007). In ALS patients, the DMN network has shown an age-by-disease interaction effect in the PCC (figure 4), with the strength of the RS-fMRI fluctuations relatively increased rather than reduced with increasing age (and disease duration). In addition, there was also a group-by-age interaction effect in RFPN, and more precisely the middle frontal gyrus (MFG) (figure

4), further reflecting a possible attempt of the ALS brain to compensate the motor neuron degeneration by reorganizing the functional connectivity in cognitive networks within unaffected (or less affected) domains.

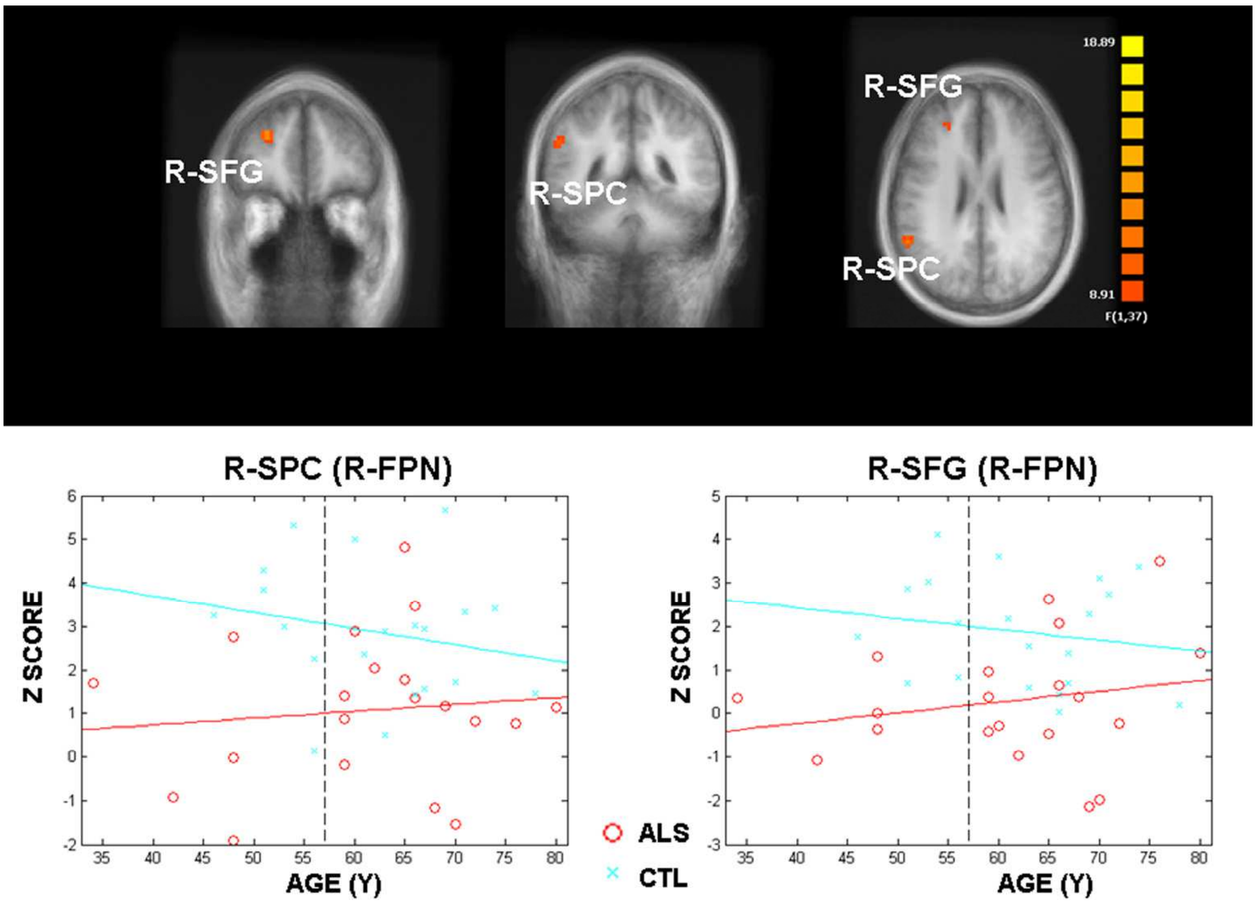

Fig. 3. ALS disease effects in the RFPN network. Upper panel: F-map of statistically significant disease effects within the R-FPN network (P=0.05, cluster-level corrected) overlaid on the average Talairach-transformed T1 image (two right sagittal cuts and one axial cut). Lower panel: Scatter plot of the regional ICA z-scores vs age in the SMG (left) and in the SFG (right). SMG = supramarginal gyrus. SFG = superior frontal gyrus. ALS = amyotrophic lateral sclerosis patients. CTL = control subjects.

This age compensatory effect on the functional connectivity can also be linked to biological processes of neuronal aging and degeneration. In fact, a few studies based on animal and cellular models of ALS pathophysiology (see, e. g., (Madeo et al., 2009)) have linked neurodegeneration and aging to specific strategies of neuroprotection by which the cell damage is contrasted with adaptive mechanisms against the physiological stress implied by aging. Thereby, these interaction patterns might represent the functional expression of the interaction between a widespread brain neurodegeneration and a physiological mechanism activated by aging. Particularly, the observed positive correlation between aging and spontaneous functional connectivity might be the result of a specific change in the default system to counteract the physiologically driven decline with age, given that ALS patients continuously alert the default system for performing any task potentially requested and made possible by the residual motor capabilities.

4.2 Default-mode network dysfunction in Multiple Sclerosis

Cognitive impairment is frequently observed in MS pathology (Benedict et al., 2006; Rao et al., 1991) and fMRI activation studies in MS patients with cognitive impairment have suggested that cerebral reorganisation (Filippi & Rocca, 2004; Mainero et al., 2004) and recruitment of non impaired cortical regions may occur as a compensatory mechanism to limit the cognitive consequences of tissue damage (Filippi & Rocca, 2004; Wishart et al., 2004).

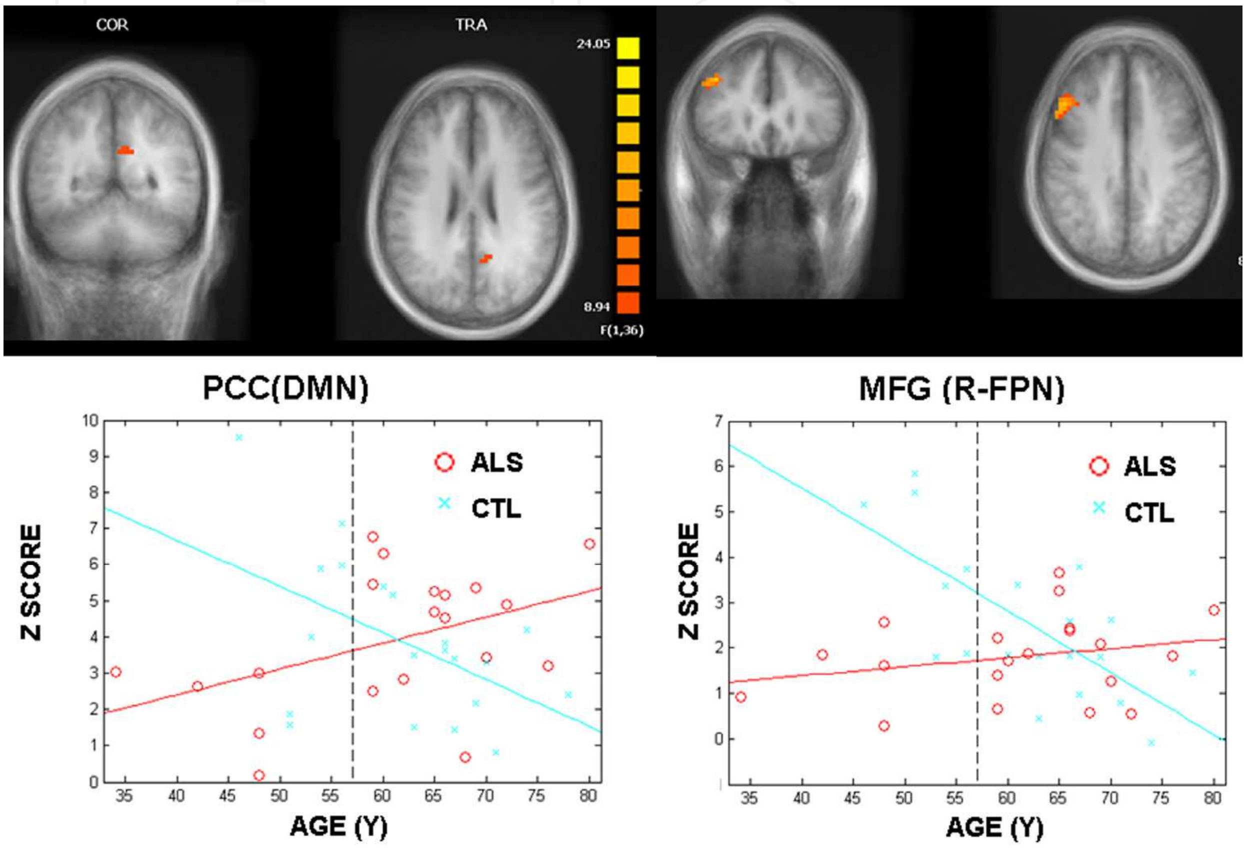

Fig. 4. ALS disease-by-age interaction in the DMN (left panel) and RFPN (right panel). Upper panels: F-map of disease by age interaction effects (P=0.05, cluster-level corrected) overlaid on the average Talairach-transformed T1 image (coronal and axial cuts). Lower panels: Regional ICA z-scores vs age in the PCC (left) and in the MFG (right).

Thereby, rs-fMRI is an attractive way to explore the spatio-temporal distribution of the spontaneous coherent fluctuations of BOLD signals within and between different regions throughout the entire human brain in different functional domains.

RS-FMRI studies have reported DMN alterations in both relapsing-remitting (RR) and progressive MS patients, when comparing MS patient groups with age and sex-matched healthy controls (Bonavita et al., 2011; Rocca et al., 2010).

The DMN connectivity distribution in RR MS patients may deviate from the control group both in the anterior node (in the ACC), that is substantially suppressed in the RR MS patient groups, and in the posterior nodes (in the PCC and, bilaterally, in the IPC), where a more distributed spatial re-organization seems to occur. Figure 5 shows a DMN comparisons map between a group of RR MS patients and a control group which clearly indicates that rs-fMRI coherent fluctuations within the DMN are reduced in RR MS patients close to the midline, both in the ACC and in the PCC, but also that, RR MS patients exhibit spots of more coherent fluctuations far from the midline, at the periphery of the PCC and toward the parieto-occipital regions of the DMN.

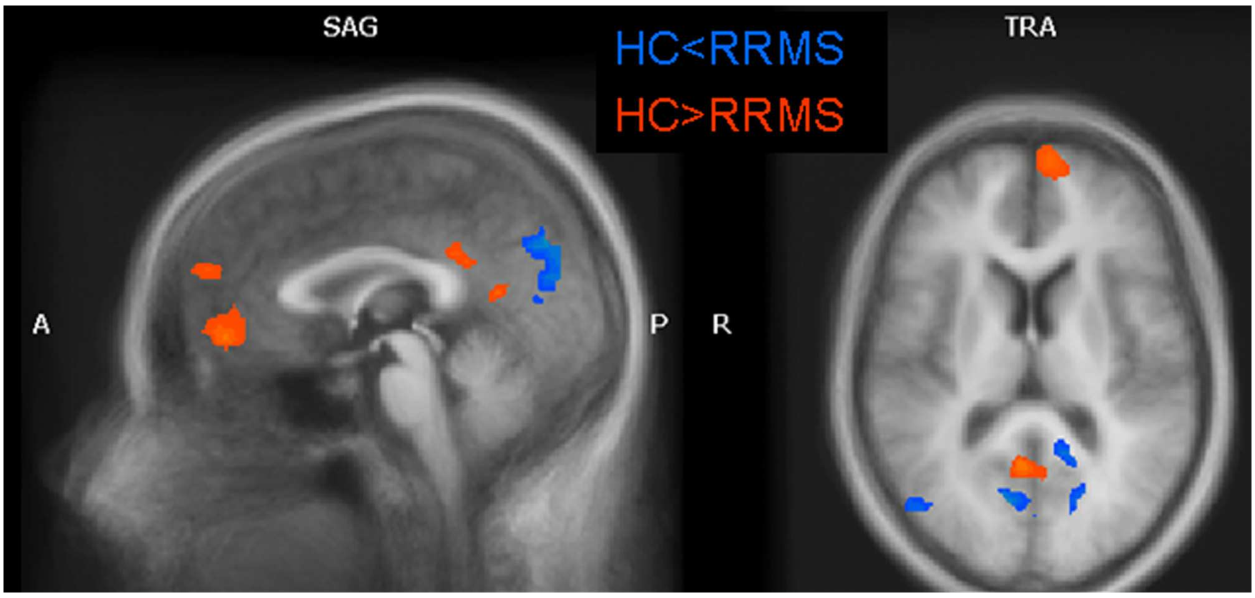

Fig. 5. Comparison between a group of RR MS patients and healthy controls (HCs). The clusters of significant differential activity are overlaid on two orthogonal slices of the averaged normalized anatomy.

A better display of the differences in the DMN functional connectivity distribution between the RR-MS and control groups is visible in figure 6, where all clusters with statistically significant differential effects are reconstructed as 3D volumes with separate colours in relation to the sign of the differences.

The comparison between RR-MS patients and normal controls becomes certainly more interesting if cognitive impaired (CI) and cognitive preserved (CP) subgroups are separately compared. Figure 7 shows this comparison and the 3D maps suggest that, while the suppression of the ACC node is a common aspect to both CI and CP RR MS patients, the re-organization of the functional connectivity in the posterior DMN can be different depending on the cognitive impairment of RR MS patients.

In summary, RR MS patients, regardless of their cognitive status exhibit a weaker DMN connectivity at the level of the ACC and the central/midline region of the PCC, together with an expanded connectivity at the level of the peripheral portions of the PCC and bilateral IPC. However, distribution changes in the posterior DMN appear with different lay outs in CI and CP patients and may thus be associated with the cognitive status of RRMS patients.

As for the other MS forms, progressive MS patients also exhibit reduced DMN connectivity, but mainly in the anterior part of the DMN (Rocca et al., 2011), where as clinically isolated syndrome (CIS) suggestive of MS seem to have increased DMN connectivity in the PCC node when compared to RR MS patients (Roosendaal et al., 2010), thus suggesting that the possible compensatory mechanism observed in the posterior DMN might be visible quite early in the disease course.

With respect to the selective involvement of the ACC in MS, one should consider that the ACC has extensive associative connections with other areas (Paus, 2001). Thereby, if cortico-cortical functional connectivity reduction is the result of axonal transection by white matter lesions, then highly connected (and distant) regions like ACC should be more vulnerable than regions with relatively fewer connections. Actually, there is evidence from histopathological studies that the cingulate gyrus shows a higher prevalence of cortical demyelinated lesions than other areas (Bo et al., 2003; Kutzelnigg & Lassmann, 2006) and therefore it is likely that these regions are intrinsically more vulnerable and more directly involved by the disease.

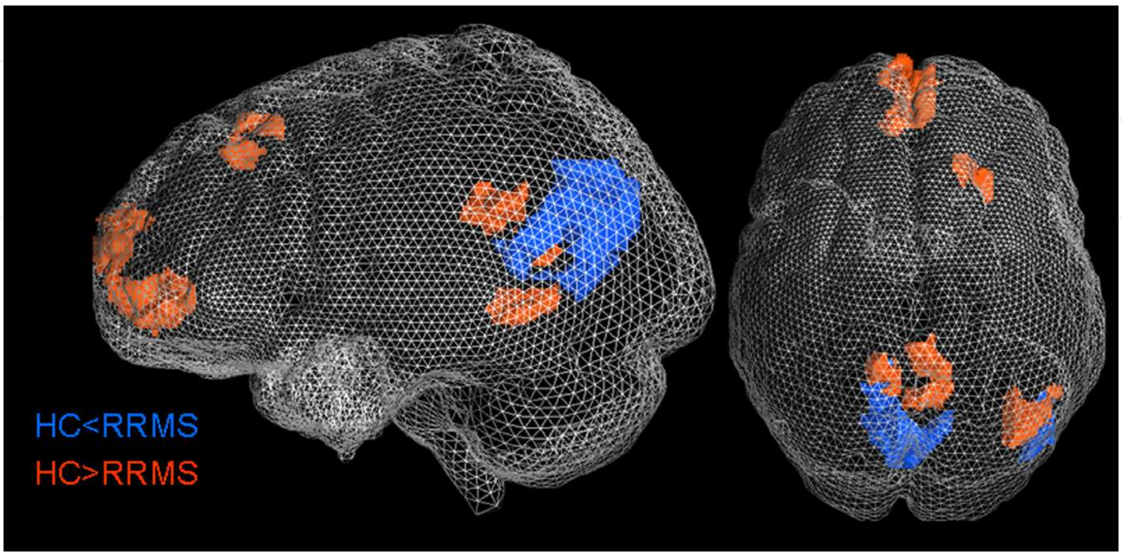

Fig. 6. Comparison between a group of RR MS patients and healthy controls (HCs). The clusters of significant differential activity are displayed as reconstructed as 3D volumes.

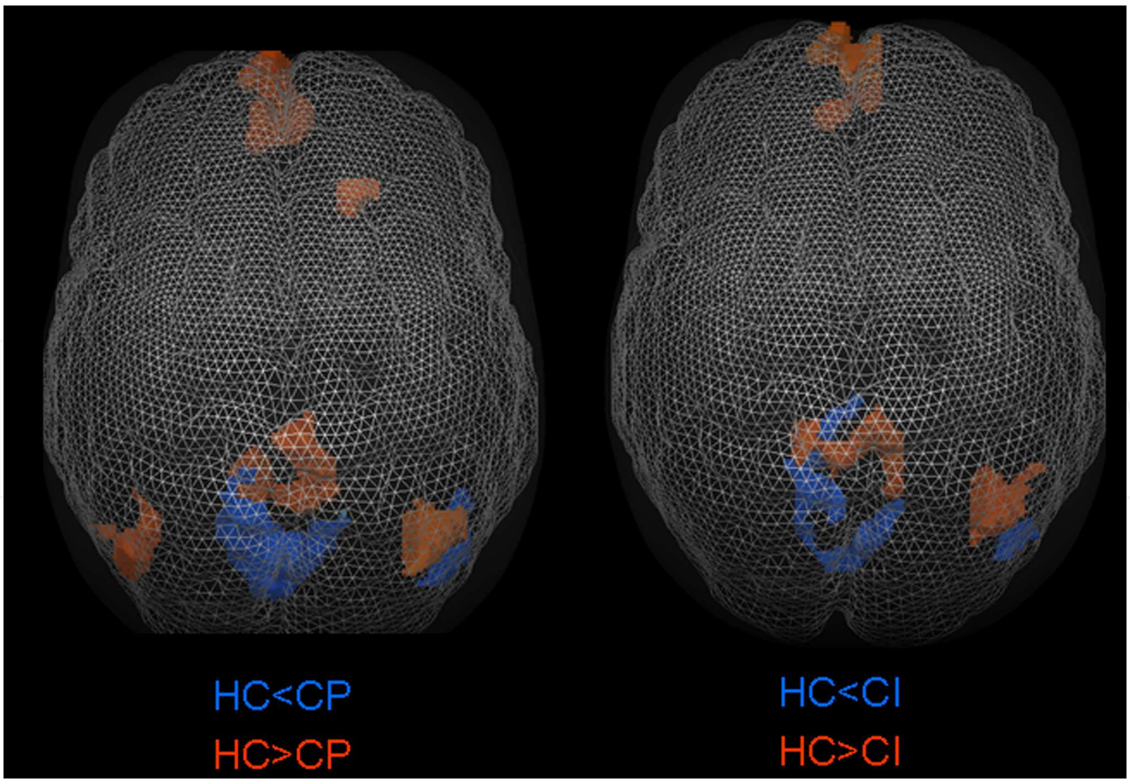

Fig. 7. Comparison between the separate groups of cognitive preserved (CP) (left) and cognitive impaired (CI) (right) RR MS patients and healthy controls (HC). The clusters of significant activity are displayed reconstructed as 3D volumes.

Van den Heuvel et al. (van den Heuvel et al., 2008) have investigated the structural connection of the DMN by combining diffusion tensor imaging and rs-fMRI data and found that the microstructural organization of the interconnecting cingulum tract, as measured by fractional anisotropy, is directly associated with the level of functional connectivity of the DMN, in particular the cingulum tract is confirmed to interconnect the PCC to the ACC of the DMN. This direct anatomical connection reflects a vast number of axonal connections between the posterior node/PCC and anterior node/ACC, responsible for the facilitation of neuronal communication between these regions. The cingulum tract is a thin white matter association bundle that is located just above and all along the corpus callosum, therefore it is expected to be frequently involved by WM lesions of MS. Thereby, if white matter MS plaques significantly contribute in determining the disconnection phenomena observed between the PCC and the ACC with the net functional loss of the ACC in the DMN of RRMS subjects, it is likely that DMN distribution changes in the posterior node represent a compensatory mechanism to sustain cognitive performances.

5. Conclusion

The present chapter has highlighted the importance of observing RSN in clinical populations in relation to both physiological and pathological factors and the potential impact of rs-fMRI as a non-invasive technique to explore whole-brain functional connectivity in neurological diseases for which the biological mechanisms are not completely understood. Particularly, since rs-fMRI does not require patient interaction, it will be possible to apply the present functional neuroimaging methodology to patients at highly advanced stages of the disease and eventually allow for longitudinal investigations.

Besides potentially shedding light on the pathological mechanisms occurring in certain neurological disorders, the clinical applications may also favor a better understanding of RSN functional connectivity in the context of brain neurophysiology, especially when the rs-fMRI patterns are carefully examined in relation to physiological and anatomical factors and to the possible interaction between these and the temporal course of a disease.

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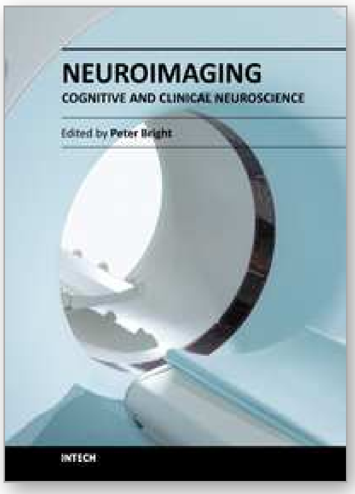

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The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

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