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Research Report

Electrophysiological signatures of resting state networks predict cognitive deficits in stroke

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ABSTRACT

Localized damage to different brain regions can cause specific cognitive deficits. However, stroke lesions can also induce modifications in the functional connectivity of intrinsic brain networks, which could be responsible for the behavioral impairment. Though resting state networks (RSNs) are typically mapped using fMRI, it has been recently shown that they can also be detected from high-density EEG. We build on a state-of-the-art approach to extract RSNs from 64-channels EEG activity in a group of right stroke patients and to identify neural predictors of their cognitive performance. Fourteen RSNs previously found in fMRI and high-density EEG studies on healthy participants were successfully reconstructed from our patients' EEG recordings. We then correlated EEG-RSNs functional connectivity with neuropsychological scores, first considering a wide frequency band (1–80 Hz) and then specific frequency ranges in order to examine the association between each EEG rhythm and the behavioral impairment. We found that visuo-spatial and motor impairments were primarily associated with the dorsal attention network, with contribution dependent on the specific EEG band. These findings are in line with the hypothesis that there is a core system of brain networks involved in specific cognitive domains. Moreover, our results pave the way for low-cost EEG-based monitoring of intrinsic brain networks' functioning in neurological patients to complement clinical-behavioral measures.

1. Introduction

The conception of the brain as a collection of organized neuronal networks has important implications for understanding the relationship between brain structure and function (Friston, 2002; Park & Friston, 2013): although we know a fair amount of details about a specific brain region, information processing is mediated by long–range interactions with other regions (Varela, Lachaux, Rodriguez, & Martinerie, 2001). A deeper understanding of how brain

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areas cooperate is important to elucidate the link between functional connectivity (FC) and human behavior, with the potential to also clarify how network organization can be altered or disrupted in neurological and neuropsychiatric diseases (Baldassarre et al., 2014; Bullmore & Sporns, 2009; Greicius, 2008). Indeed, although localized brain damage can cause specific behavioral impairments, it has long been known that even the function of brain areas far from the lesion site can be modified after a stroke insult (Beis et al., 2004; Carrera & Tononi, 2014; Carter et al., 2010; Hillis et al., 2002; Perani et al., 1987). Interestingly, these physiological transformations show a strong relation with the behavioral deficits caused by a stroke, supporting the view that neuropsychological disorders should be interpreted by also considering the large-scale organization of the brain (Baldassarre et al., 2014; He et al., 2007; Hillis et al., 2002; Park et al., 2011; Wang et al., 2010).

It is now widely believed that resting state FC provides a window into the effects of stroke on brain networks organization and the consequent behavioral deficits (Carter, Shulman, & Corbetta, 2012; Fox, 2018; Siegel et al., 2016). For example, resting state FC abnormalities are strongly associated with both attentional and motor impairments following stroke (Carter et al., 2010; Carter, Patel, et al., 2012; Chen & Schlaug, 2013; Park et al., 2011; Wang et al., 2010; Yin et al., 2012). Attentional deficits have been linked to dysfunctions within the dorsal attention network (Carter et al., 2010; He et al., 2007) and more generally to a pattern of FC that is distinct from that related to motor deficits (Baldassarre et al., 2016). In a study on patients with hemispatial neglect, Baldassarre et al. (2014) observed a reduction in the magnitude of interhemispheric FC within dorsal attention, fronto-parietal, motor and auditory networks. Visual attention impairments also correlated with a loss of segregation between networks in the right hemisphere. Overall, these studies support the idea that physiological dysfunctions at the level of specific brain networks underlie specific behavioral deficits. This is revolutionizing the way of thinking about post-stroke deficits, because they do not only depend on lesion site.

Though resting state networks (RSNs) are typically mapped using functional Magnetic Resonance Imaging (fMRI) (e.g., Baldassarre et al., 2014, 2016; Siegel et al., 2016, for studies on stroke patients), the study of the neural organization has also been supported by other techniques, such as magnetoencephalography and electroencephalography (EEG). Patterns of altered alpha and beta interhemispheric FC, measured at sensors level, were found to be associated with cognitive impairments (Kawano et al., 2017; Wu et al., 2011). However, the activity extracted from single or groups of sensors cannot be attributed to specific brain regions and thus this method does not allow the study of RSNs' activity. In contrast, despite the poor spatial resolution compared to fMRI, source localization is a convenient approach for computing measures of FC from EEG signals (Dubovik et al., 2013; Guggisberg et al., 2011; Nicolo et al., 2015) and for the investigation of RSNs dynamics (Liu, Farahibozorg, Porcaro, Wenderoth, & Mantini, 2017; Marino et al., 2018; Porcaro, Liu, Mantini, Farahibozorg, & Wenderoth, 2017; Samogin, Liu, Marino, Wenderoth, & Mantini, 2019). A key contribution has been provided by the study of Mantini and collaborators (Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007), who investigated the correspondence between neuronal oscillatory processes in different EEG frequency bands and fMRI fluctuations. Their analysis showed that each network was characterized by a specific combination of EEG frequency rhythms. Recently, Liu and collaborators (Liu et al., 2017) provided the first empirical evidence that large-scale brain networks can be detected even by only relying on the EEG signal recorded in resting state (also see Liu, Ganzetti, Wenderoth, & Mantini, 2018; Marino et al., 2018; Samogin et al., 2019).

The study of RSNs has provided important insights into the functioning and the organization of the brain when cognitive tasks are not required. However, there is growing evidence that FC properties of RSNs can also be used to predict behavioral outcome in stroke (Carter et al., 2010; Ktena et al., 2019; Park et al., 2011; Siegel et al., 2016), thereby motivating the development of a low-cost method based on resting state EEG and dispensing with the complexity of patient fMRI data-analysis (Carter, Shulman, et al., 2012).

The first and crucial aim of our study was to validate the EEG-RSNs detection method of Liu and colleagues (Liu et al., 2017) in a clinical setting and with a more limited number of electrodes. The second and complementary aim was to identify neural markers of specific cognitive impairments in the intrinsic activity of the EEG-RSNs. The correlation analysis between EEG-RSNs and neuropsychological scores was initially carried out considering a wide frequency interval (1–80 Hz). However, FC analysis was also performed over specific frequency ranges to examine the contribution of each EEG rhythm in predicting the impairments, thereby providing information that is not captured by fMRI.

2. Methods

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. *Participants*

Thirty right hemisphere damaged (RHD) patients took part in the study. All participants (mean age = 64.1 years ± 10.49; mean education level = 10.3 years ± 4.54) were admitted to the San Camillo Hospital (Venice-Lido, Italy) to receive neurocognitive rehabilitation. All patients were in sub-acute/chronic phase (minimum time from onset: 46 days, see Table 1). An approximation of the sample size was determined based on previous studies that applied the method for the EEG-RSNs detection and that showed a successful maps reconstruction in a group of minimum 19 participants (Liu et al., 2017, 2018; Marino et al., 2018; Samogin et al., 2019, 2020). According to a standard questionnaire (Oldfield, 1971) all participants were right-handed. Inclusion criteria for the study were: a) presence of unilateral brain lesion (first ever event); b) absence of history of neurodegenerative disorders and/or of substance abuse. The study was approved by the regional Ethics Committee (Comitato Etico per la Sperimentazione Clinica della Provincia di Venezia e IRCCS San

Table 1 – Demographical and neurological data.

Patient	Age	Gender	Education	Etiology	Lesion Site	Lesion size (mm^3)	Time since stroke (days)
1	56	M	13	I	C; T	37,179	93
2	68	F	5	H	C	7009	133
3	79	F	5	I	C	8718	82
4	43	F	8	H	C	34,827	173
5	60	M	13	H	F; T	53,429	2240
6	64	F	13	H	T; P	109,487	3647
7	72	M	13	H	C	2421	93
8	59	M	16	I	O; P	118,574	259
9	67	M	13	I	MCA	185,846	160
10	69	M	13	I	MCA	154,505	84
11	65	F	17	H	T; Ta	479,447	697
12	50	M	13	I	C; T	17,857	46
13	50	M	8	H	BG	20,499	111
14	80	M	5	I	Pu	1260	472
15	57	M	8	I	F; P	112,932	101
16	73	F	5	H	F; P	73,069	160
17	74	M	5	H	BG; F	39,357	126
18	69	M	18	I	P; O	126,242	71
19	59	M	17	I	MCA; T; P	231,265	70
20	57	F	18	I	MCA	167,011	187
21	57	M	8	H	T; P	67,965	130
22	75	M	13	I	I; T; P	54,875	107
23	68	M	13	I	T; BG	108,370	1294
24	66	F	5	H	Pu	8629	2991
25	63	F	5	I	C; F	291,589	208
26	48	F	13	I	F; P; O; T	n.a.	699
27	81	F	5	I	C; I	37,165	221
28	45	M	8	H	C	7572	90
29	72	M	8	H	C	23,422	99
30	77	M	5	I	P	27,139	140

Gender: M = male, F = female; Etiology: I = ischemic, H = hemorrhagic; Lesion site: C = capsule; T = temporal; F = frontal; Ta = thalamus; O = occipital; P = parietal; MCA = middle cerebral artery; BG = basal ganglia; I = Insula; Pu = putamen; n.a.: data not available.

Camillo; protocol n. 2014.09 and n. 2018.04). All participants gave their written informed consent to take part in the study, which was conducted in accordance to the principles of the Declaration of Helsinki. No part of the study procedure was pre-registered prior to the research being conducted.

2.2. *Neuropsychological assessment*

All patients underwent neuropsychological assessment. The Functional Independence Measure (FIM) (Linacre, Heinemann, Wright, Granger, & Hamilton, 1994) was administered to quantify the severity of disability. The battery consists of 18 items and provides two clinical indices: a motor index and a cognitive index, which were scored separately. The motor scale comprises 13 items on seven-levels scales referring to severe disability in case of complete dependency (i.e., 1 = “total assistance” and 2 = ”maximal assistance” with autonomy less than 50%) to independency in case of good functional autonomy (i.e., 6 = “modified independence” and 7 = “complete independence”). The cognitive scale consists of 5 items on seven-levels scales (the same used for the motor scale). In order to assess visuo-spatial abilities the conventional part of the Behavioral Inattention Test (BIT) (Wilson, Cockburn, & Halligan, 1987) was administered. The evaluation included 6 subtests (lines, letters, and stars cancellation; line bisection; figure copy and spontaneous drawing) that are used to compute the overall BIT score. Attentional matrices (Spinnler & Tognoni, 1987) were also administered to assess selective attention deficits. This task is a digit cancellation test consisting of three different matrices. Patients had 45 sec to cross out the digit(s) printed at the top of each matrix (1 target in the first matrix, 2 targets in the second matrix and 3 targets in the last matrix). Raven’s progressive matrices test (Carlesimo, Caltagirone, & Gainotti, 1996) was also administered to assess the overall cognitive functioning of our patients. This test investigates abstract, relatively culture-free non-verbal reasoning abilities and was not considered in the statistical analyses. Neuropsychological data are displayed in Table 2.

2.3. *Brain lesion segmentation*

CT or MRI were available for 29 out of 30 patients. MRI data were not acquired for patient 26 due to severe claustrophobia. An automated brain lesions segmentation was performed using the Lesion Identification with Neighborhood Data Analysis software (Pustina et al., 2016) and the resulting lesion mask was visually inspected at least by two researchers under the supervision of a neurologist. Whenever necessary, lesion masks were manually corrected using ITK-snap software (Yushkevich et al., 2006). Individual scans were reoriented and then normalized to an age-appropriate template brain by

Table 2 – Neuropsychological assessment.

Patient	BIT Cut off: >130	FIM motor index (max 91)	FIM cognitive index (max 35)	Attentional matrices Cut-off: >30	Raven Cut-off: >18.96
1	142	64	31	40.5	30.3
2	143	53	27	51	38.9
3	98[a]	21	19	27[a]	15.2[a]
4	140	26	21	27.75[a]	36
5	144	81	35	43.5	21.5
6	140	57	32	50.75	26.4
7	138	58	26	43.75	33.2
8	124[a]	29	27	22[a]	25.2
9	118[a]	26	29	25.25[a]	20.4
10	142	66	31	49.75	33.1
11	102[a]	40	33	14.25[a]	24.7
12	145	91	27	41.25	28.1
13	143	75	29	43	30.3
14	137	43	26	39.75	22
15	66[a]	58	30	17.5[a]	27.8
16	71[a]	51	29	20.5[a]	21.5
17	125[a]	84	27	37.25	31.2
18	132	72	31	20.75[a]	18.4[a]
19	107[a]	23	30	28[a]	26.2
20	144	49	35	49	29.6
21	141	42	32	33.5	28.8
22	139	28	28	24.25[a]	24.8
23	141	30	35	42.25	31.1
24	146	77	35	56	33.9
25	102[a]	52	29	37.2	27
26	140	61	29	41.8	26.3
27	136	32	26	44.25	23
28	133	16	21	27.25[a]	28.8
29	140	60	31	32.25	31.8
30	137	26	26	55.25	31.2

BIT Behavioural Inattention Test (Wilson et al., 1987): global scores. FIM Functional Independence Measure (Linacre et al., 1994): raw scores for motor and cognitive indices. Attentional matrices (Splinner e Tognoni, 1987): age and education corrected scores. Raven's progressive matrices (Carlesimo et al., 1996): age and education corrected scores.

[a] Performance below cut-off.

means of the SPM Clinical Toolbox (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) using enantiomorphic normalization. The maximal overlap (23 patients) occurred in the white matter adjacent to putamen (MNI: X = 29, Y = − 20, Z = 12) (see Fig. S1 – Supplementary Materials).

2.4. EEG data collection

Electrophysiological data were collected at the San Camillo Hospital in a dedicated lab. Resting state EEG was recorded for 10 min. Data were acquired using an elastic cap with 64 pre-amplified electrodes (Acticap, BrainProducts) mounted according to the International 10–20 system (Oostenveld & Praamstra, 2001). The sampling rate was set at 500 Hz and the impedance was kept below 5 kΩ. During the EEG recording, patients were asked to keep their eyes open and to fixate the center of a computer monitor in order to reduce eye movements.

2.5. EEG-RSNs detection

We employed the method of Liu et al. (2017) (also see, Liu et al., 2018; Marino et al., 2018; Porcaro et al., 2017; Samogin et al., 2019, 2020) for EEG-RSNs detection. The pipeline of analysis consists of four steps (see Supplementary Materials for details): 1) data preprocessing; 2) volume conduction model creation; 3) brain activity reconstruction; 4) temporal independent component analysis (ICA) for RSN mapping. Specifically, a time-frequency decomposition of the reconstructed neural signal for each voxel was performed using the spectrogram method. The power time-courses were computed for the classic frequency bands (delta: 1–4 Hz, theta: 4–8 Hz, alpha: 8–13 Hz, beta: 13–30 Hz, gamma: 30–80 Hz) and for the full 1–80 Hz band. Temporal ICA (Calhoun, Adali, Pearlson, & Pekar, 2001) was applied only on the full band (1–80 Hz) power envelopes to ensure an unbiased detection of EEG-RSNs (Liu et al., 2017). The ICA output consists of a number of ICs, each comprising a spatial map and an associated time-course (Brookes et al., 2011; Liu et al., 2017; Mantini et al., 2007). For EEG-RSNs detection, a template-matching procedure based on similarity with RSNs derived from fMRI data was used (Mantini, Corbetta, Romani, Orban, & Vanduffel, 2013). Each IC can be associated only to one template. The fMRI templates consisted of 14 networks: default mode network (DMN), dorsal attention network (DAN), ventral attention network (VAN), right fronto-parietal network (rFPN), left fronto-parietal network (lFPN), language network (LN), cingulo-opercular network (CON), auditory network (AN), ventral somatomotor network (VSN), dorsal somatomotor network (DSN), visual foveal network (VFN), visual peripheral network (VPN), medial prefrontal network (MPN), and lateral prefrontal network (LPN). After the identification of the IC associated with a specific network, the spatial maps for delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–80 Hz) bands, respectively, were obtained by correlating the power envelopes of the source-reconstructed EEG data with the band-limited power envelope of the selected IC.

2.6. *Statistical analyses*

Brain-behavior correlation analyses were carried out using the SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/). Linear regressions were performed considering each EEG-RSN connectivity as predictor and the neuropsychological indices [BIT; motor index of FIM; cognitive index of FIM and Attentional matrices (corrected scores)] as dependent variables. The predictor is an index of FC expressing, for each voxel, the correlation between the EEG power and the specific time course associated with each RSN (that is, a measure of voxel integration within the network). Lesion size (standardized value) was included in the regression model as variable of no interest. For patient 26 the average group lesion size was used. The first analysis was performed on the wide frequency band (1–80 Hz), producing a correlation map expressed in terms of T-scores. Local clusters were then identified by only considering regions at least 1 cm^3 in size, showing a significant correlation ($p \leq .05$, FDR-corrected for multiple comparisons). For each cluster identified within a particular network for the band 1–80 Hz, linear regressions were repeated by separately considering the contribution of each of the five EEG frequency bands.

In order to explore the possible influence of other neurological variables (i.e., time from stroke and stroke etiology), we also performed supplementary analyses by creating subgroups of patients with more homogeneous neurological characteristics. The latter results are only reported in the Supplementary Materials and should be taken with caution due to the smaller number of patients (see Supplementary Methods and Analyses and Tab. S4).

No part of the study analyses was pre-registered prior to the research being conducted.

3. Results

The Results section is organized as follow. First, behavioral performance at neuropsychological tests and their correlation with neurological variables are presented. Second, EEG-RSN maps obtained using temporal ICA in the wide frequency band (1–80 Hz) are presented. Then, correlation analyses between EEG-RSNs and neuropsychological scores are presented, showing the significant clusters of voxels identified for each EEG-RSN and their correlation with neuropsychological indices. T-scores and corrected probability levels are reported for each significant result.

3.1. *Behavioral performance*

Overall cognitive functioning was good, as measured by Raven's test (mean = 27.56, ± 5.32), with only two patients scoring below the cut-off. The evaluation of visuo-spatial abilities using the BIT yielded poor performance (overall score < 130) for 9 out of 30 patients (mean = 128.53, ± 21.39). The attentional matrices test (mean = 36.22, ± 11.73) showed pathological scores for 11 out of 30 patients. Motor autonomy in everyday life was measured by the motor index of FIM (scores range: 13–91). The performance of our patients was heterogeneous with a minimum score of 16 and high scores (>78) only for 2 patients (mean = 49.70, ± 21.02). We also administered the cognitive scale of FIM in order to assess the general cognitive performance in daily situations (scores range = 5–35). We found a general good performance with a minimum score of 19 and high scores (≥30) for 13 out of 30 patients (mean = 28.90, ± = 4.05).

Spearman correlations (with *p*-values adjusted for multiple comparisons using Holm's method) were computed in order to investigate potential relations between neurological characteristics and patients' performance at neuropsychological tests. The correlation results are provided in the Supplemental materials (see Tab. S1). We found a significant correlation between BIT and Attentional matrices test ($r = .71$, $p = .0001$), showing that the two attentional measures were highly correlated in our patients' sample. The correlation between Lesion size and FIM cognitive index also reached significance ($r = .52$, $p = .0410$), but its sign went in the unexpected direction (i.e., larger lesion size associated to better performance). However, it is worth noting that the FIM cognitive scores were in the high range for many patients. No other significant correlations emerged. In particular, time from stroke was not associated with any of the behavioral measures.

3.2. *EEG-RSN maps*

Temporal ICA was applied to reconstruct RSN maps in the full frequency band (1–80 Hz). While spatial ICA is commonly preferred in fMRI studies, temporal ICA is a convenient approach in case of EEG/MEG connectivity analysis (Brookes et al., 2011). Fig. 1 displays the 14 RSNs detected in the group of 30 RHD patients. Dice Similarity (DS) analysis was performed to quantify the correspondence between EEG and fMRI RSNs maps. Results are reported in the Supplementary Materials (see Supplementary Methods and Analyses and Tab. S2), showing an overall good match between EEG and fMRI maps.

3.3. *Correlation between EEG-RSNs and neuropsychological indices*

3.3.1. *Dorsal attention network (DAN) – attentional matrices*

The analysis carried out on the Attentional matrices score showed a significant positive correlation with a cluster that is part of the DAN ($t = 2.5241$, $p = .0087$) when the wide EEG band (1–80 Hz) was considered. This cluster was located in the inferior division of the lateral occipital cortex (left hemisphere, X = - 47; Y = - 65; Z = - 10) (Fig. 2, panel a). Moreover,

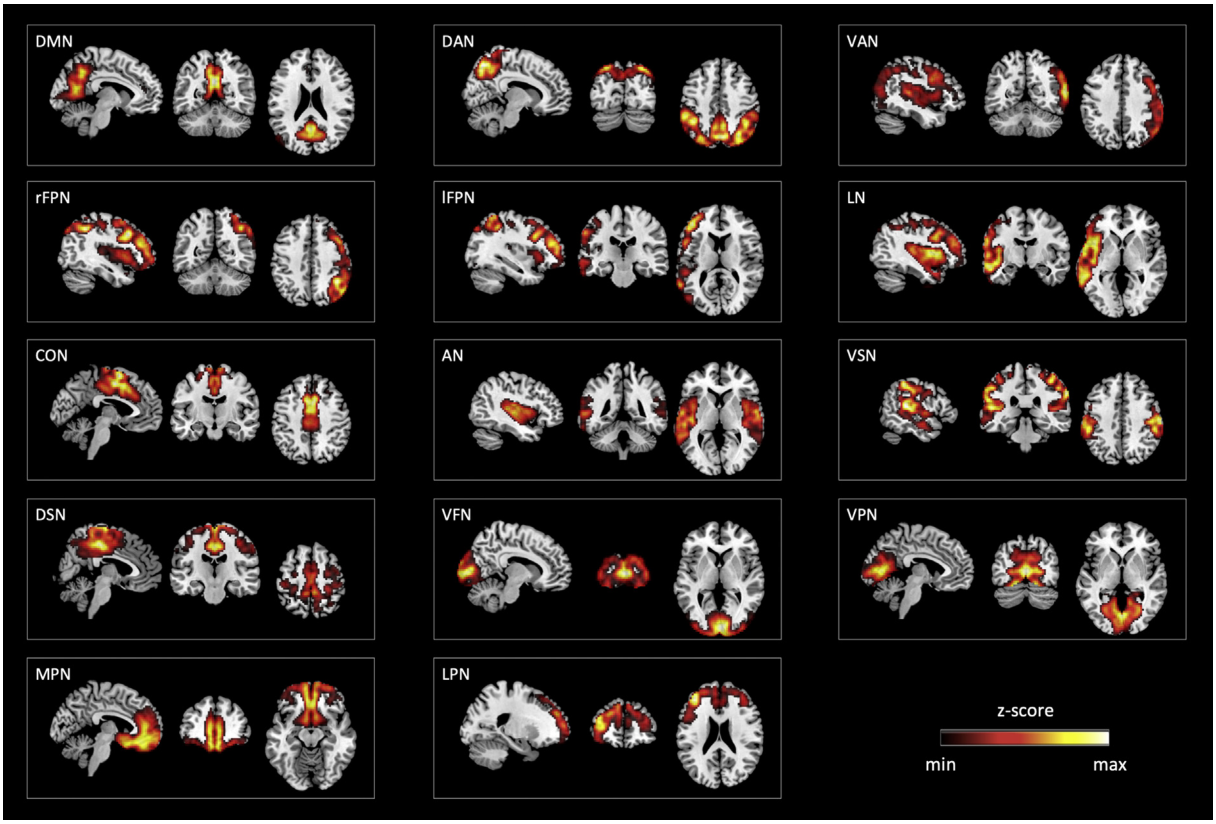

Fig. 1 — RSNs reconstructed using temporal ICA from wide-band EEG signals (64 channels). EEG RSNs were selected on the basis of the spatial overlap with fMRI-RSN: DMN, DAN, VAN, rFPN, lFPN, LN, CON, AN, VSN, DSN, VFN, VPN, MPN and LPN. Group-level maps (N = 30) were thresholded at z > 2 for visualization purpose.

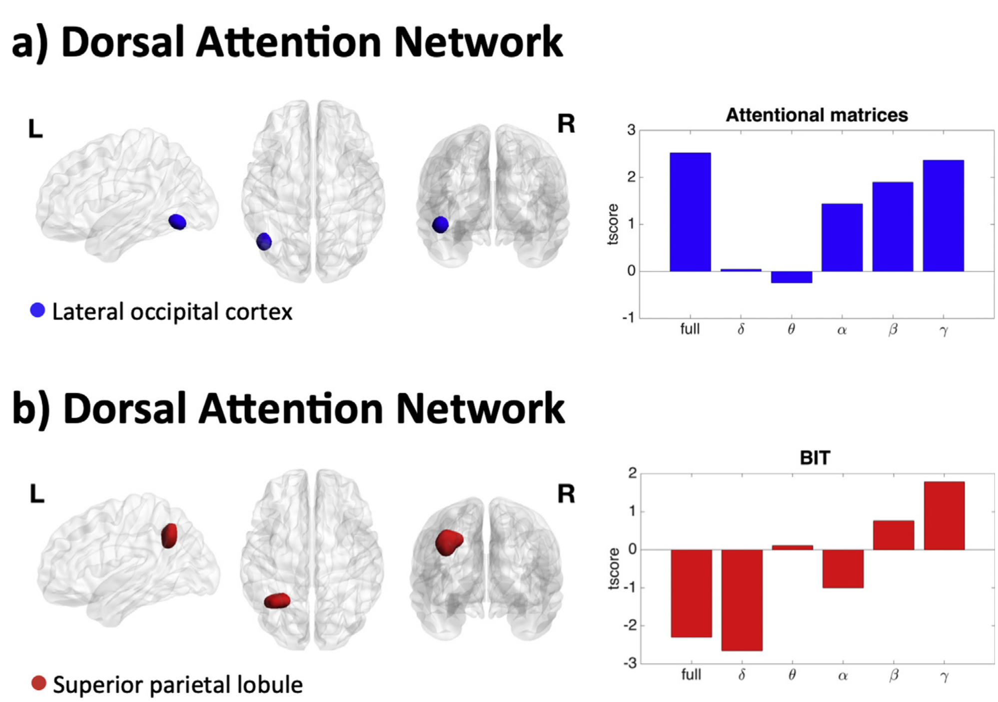

Fig. 2 — Correlation between DAN and Attentional matrices/BIT. The figure shows significant clusters of voxels ($p \leq .05$) within DAN and their correlation with Attentional matrices (panel a) and BIT scores (panel b).

when individual EEG frequency bands were considered, this positive correlation was also found in the beta rhythm ($t = 1.8973$, $p = .0339$) and in the gamma rhythm ($t = 2.3694$, $p = .0123$). These results show that lower integration of this cluster within DAN is associated to lower scores at attentional matrices test and that the beta and gamma bands play a prominent role in driving this association.

3.3.2. *Dorsal attention network (DAN) – BIT*

The analysis carried out on the BIT battery revealed a negative correlation in a cluster that is part of the DAN ($t = -2.3001$, $p = .0144$) within the wide frequency range. The specific cluster was located in the superior parietal lobule (left hemisphere, X = - 33; Y = - 57; Z = 39) (Fig. 2, panel b). A negative correlation was also found when the delta band was analyzed ($t = -2.6582$, $p = .0063$) and a positive correlation emerged when the gamma band was analyzed ($t = 1.7850$, $p = .0424$). These results suggest that worse performance at visuo-spatial tasks is predicted by higher integration of superior parietal lobule within DAN in slow delta rhythm and by lower integration of the same cluster in high gamma rhythm.

3.3.3. *Dorsal attention network (DAN) – FIM motor index*

The analysis carried out on the motor index of FIM showed positive correlations with three clusters that are part of DAN ($t = 2.5986$, $p = .0073$; $t = 2.5146$, $p = .0089$ and $t = 2.6673$, $p = .0062$, respectively). The nodes identified corresponded to the inferior temporal gyrus (temporo-occipital division) (right hemisphere, X = 57; Y = - 57; Z = - 10); to the precentral gyrus (left hemisphere, X = - 28; Y = - 10; Z = 62) and to the superior frontal gyrus (right hemisphere, X = 26; Y = −1; Z = 64) (Fig. 3, panel a). This effect was observed in the full EEG frequency range (1–80 Hz), in the delta rhythm for the first and third clusters ($t = 2.1699$, $p = .0192$ and $t = 2.2823$, $p = .0150$, respectively) and in the theta rhythm for the second cluster ($t = 1.7355$, $p = .0466$). More specifically, when the delta/theta EEG bands are considered, lower integration of these three regions within DAN is associated with lower levels of motor ability as assessed by FIM.

3.3.4. *Language network (LN) – FIM motor index*

The analysis carried out on the motor index of FIM showed the presence of a negative correlation with a cluster in the LN ($t = -2.1514$, $p = .0200$), considering the wide frequency band. The cluster was located in the precentral gyrus (left hemisphere, X = - 51; Y = 8; Z = 25) (Fig. 3, panel b). Considering individual EEG rhythms, negative correlations were also found within delta ($t = -2.2517$, $p = .0160$), beta ($t = -2.2562$, $p = .0159$) and gamma ($t = -2.4163$, $p = .0111$) frequency bands. The results suggest that, both for full, delta, beta and gamma bands higher integration of this region within LN is associated to lower score in the motor index of FIM.

3.3.5. *Medial prefrontal network (MPN) – FIM cognitive index*

The analysis carried out on the cognitive index of FIM revealed a negative correlation with a cluster that is part of MPN ($t = -2.4938$, $p = .0093$). The region corresponded to the anterior division of the middle temporal gyrus (right hemisphere, X = 48; Y = 4; Z = - 29) (Fig. 3, panel c). This negative correlation emerged considering the wide EEG band, but also when the theta band was analyzed ($t = -2.0902$, $p = .0227$). These results

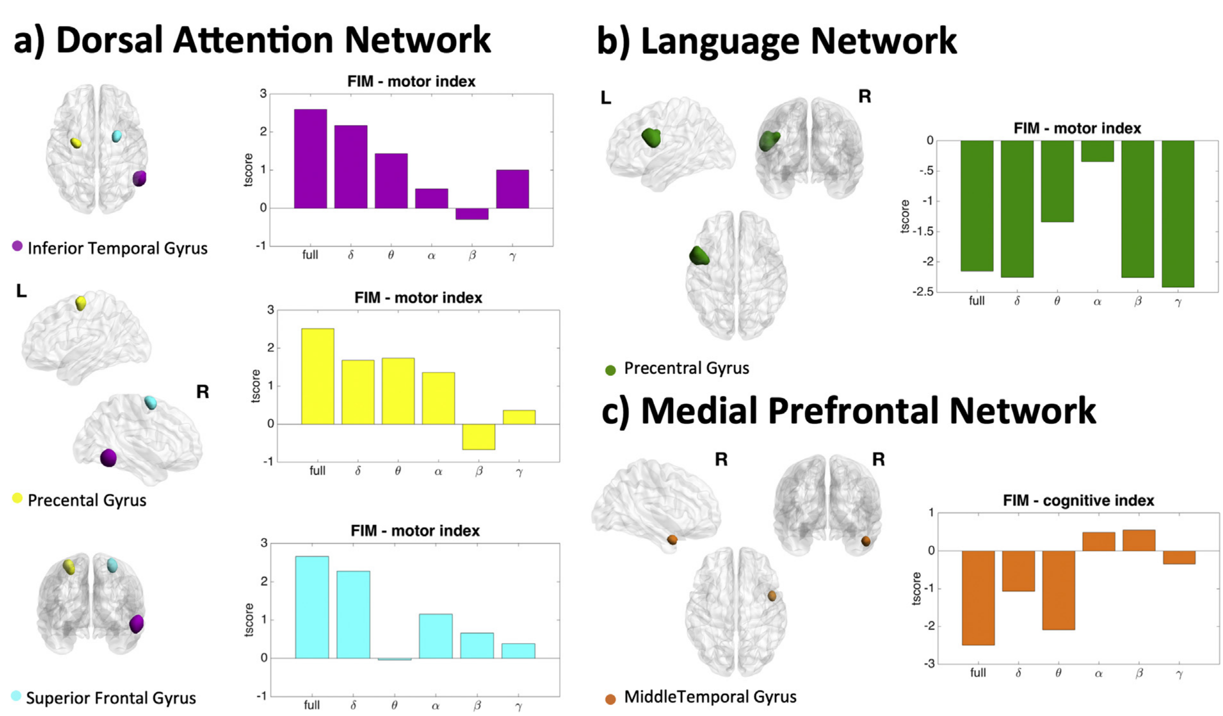

Fig. 3 – Correlation between DAN, LN, MPN and FIM. The figure shows significant clusters of voxels ($p \le .05$) within DAN (panel a)/LN (panel b) and their correlation with FIM motor index. Panel c shows clusters within MPN and their correlation with FIM cognitive index.

suggest that greater integration of the middle temporal gyrus within the MPN is associated to lower levels of cognitive independence, in particular within the theta frequency range.

A complete table including all the significant correlations between EEG-RSNs and neuropsychological indices is provided in the Supplementary Materials (see Tab. S3).

No significant correlations emerged for the other EEG-RSNs.

4. Discussion

Recent studies suggest that the disruption of RSN connectivity underlies the presence of behavioral deficits following stroke (Baldassarre et al., 2016, 2014; Carter et al., 2010; Ktena et al., 2019; Park et al., 2011; Siegel et al., 2016). Though fMRI techniques are usually employed to detect brain networks at rest, recent studies have shown that RSNs can be reconstructed from high-density EEG signals (Liu et al, 2017, 2018; Marino et al., 2018; Samogin et al., 2019). The present study attempted the first validation of the EEG-RSNs detection method in a neurological population, and further investigated the link between intrinsic brain activity and behavior, first considering a wide frequency band and then narrowing the focus on the contribution of different EEG rhythms. The main purpose was to examine whether EEG-RSNs organization could be predictive of cognitive deficits, thereby providing a new assessment tool based on EEG markers that could complement classical paper-and-pencil neuropsychological measures.

Once the spatial maps were obtained and the time-courses for each EEG-RSNs were extracted, our analysis aimed at exploring their correlation with neuropsychological indices. Overall, our patients showed good general cognitive functioning as assessed by Raven's test and FIM cognitive index, while attentional, visuo-spatial and motor impairments were frequent across patients, as typically observed in heterogeneous samples of RHD patients. A first important result is that correlations were found only between a subset of EEG-RSNs and specific behavioral indices. In particular, impaired performance was mostly associated with functional connectivity within, DAN, LN and MPN, in line with the hypothesis that there is a core system of brain networks involved in specific cognitive domains (Baldassarre et al., 2016; Fox, 2018; He et al., 2007). The significant results are discussed in the following sections, with particular emphasis on the interhemispheric imbalance in DAN activity and on the interplay between visuo-spatial attention and motor planning.

4.1. *Interhemispheric imbalance in dorsal attention network activity*

Two clusters within the DAN showed a significant correlation with the Attentional matrices and the BIT scores, two neuropsychological tests assessing selective attention and visuo-spatial deficits (i.e., neglect). Studies on healthy participants suggest that the fronto-parietal regions within DAN play a crucial role in mechanisms of selective attention that allow the suppression of irrelevant and the detection of salient information (Corbetta & Shulman, 2002; Lanssens, Pizzamiglio, Mantini, & Gillebert, 2020). The dorsal system is also involved in preparing an attentional set necessary for stimulus processing and for planning goal-directed responses (Corbetta & Shulman, 2002).

The role and functioning of DAN following stroke has been widely investigated in neuroimaging studies (Baldassarre et al, 2014, 2016; Carter et al., 2010; Corbetta & Shulman, 2011; He et al., 2007; Ptak & Schnider, 2010; Siegel et al., 2016). A common view is that attentional deficits (i.e., neglect) stem from alterations in large-scale distributed networks (Corbetta & Shulman, 2011). In the acute/subacute phase, right hemisphere damaged patients with spatial impairments show abnormal interhemispheric DAN activity that correlates with the behavioral deficit (Baldassarre et al., 2014, 2016). Interestingly, dysfunction in both left and right DAN regions were found to be related to patients' performance, suggesting that neglect might be caused by imbalanced DAN activity (Baldassarre et al, 2014, 2016; Carter et al., 2010; He et al., 2007). Corbetta, Kincade, Lewis, Snyder, and Sapir (2005) observed a correlation between spatial impairments and functional imbalance patterns, consisting in hyper-activation in the left and hypo-activation in the right dorsal parietal cortex in patients with right hemisphere damage. Notably, these regions were structurally intact and the recovery of attention deficits was related to the restoration of activity in these areas. These results are in agreement with the hypothesis that neglect is caused by a mechanism of interhemispheric inhibition (Kinsbourne, 1987) and with the more recent hypothesis that disruption of interhemispheric functional connectivity is associated with spatial deficits (Baldassarre et al., 2014).

In our study, we observed correlations between DAN and patients' attentional performance. On one hand, lower integration of a region in the left lateral occipital cortex within DAN in high beta and gamma rhythms was associated with poor selective attention ability. On the other hand, visuo-spatial impairments were predicted by higher integration of left superior parietal lobule within DAN in slow delta rhythm and by lower integration of the same cluster in fast gamma rhythm.

Several EEG studies showed that poor cognitive outcome is predicted by increased delta activity and depression of faster alpha or beta activity in the ischemic hemisphere (Assenza, Zappasodi, Pasqualetti, Vernieri, & Tecchio, 2013; Finnigan & van Putten, 2013; Finnigan, Wong, & Read, 2016), and that stroke patients generally present greater slow EEG power both in the affected and unaffected hemisphere compared to healthy controls (Assenza et al., 2013; Dubovik et al., 2012). However, there is also evidence that interhemispheric synchronization in faster EEG bands (i.e., alpha/beta) is a sensitive marker of patients' outcome (Dubovik et al., 2012; Kawano et al., 2017; Nicolo et al., 2015; Wu et al., 2011). With respect to RSNs, it has been shown that each network is characterized by a specific combination of different brain rhythms in healthy brains (Mantini et al., 2007). Moreover, cognitive networks (including DMN, DAN, VAN) show greater power spectrum density in low frequency bands compared to perceptual networks (Marino et al., 2018). In contrast, greater power spectrum in gamma frequency is prevalent in perceptual networks (i.e., somatomotor, auditory and visual networks). These findings are in line with the idea that slower fluctuations promote information exchange on larger spatial scale, while faster fluctuations support local processing (Canolty et al., 2006).

Our findings could be explained in terms of imbalanced activation of DAN regions. In particular, stroke might cause a deactivation of fronto-parietal regions in the affected hemisphere and a hyper-activation of unaffected contralesional areas. This alteration might consequently hinder the control of attentional focus, the ability to plan actions and the visuo-spatial awareness. Note that we found a strong correlation between behavioral performance at Attentional matrices and BIT, suggesting that both deficits might be associated to the alteration of the same neural substrate. In line with previous evidence (Baldassarre et al., 2016; Carter et al., 2010; Corbetta et al., 2005), we suggest that attentional deficits might be associated with abnormal interhemispheric activity and recovery might be linked to a rebalancing of the bilaterally distributed dorsal network.

4.2. *DAN and motor planning*

We also examined the resting state FC associated with functional independence, assessed by the FIM battery. Our results showed a positive correlation between neural organization within DAN and the motor scale of FIM. Recent studies suggested that DAN is critically involved in executive control (Kim, 2010; Mantini et al., 2007) and selective attention, especially in the visuo-spatial domain (Baldassarre et al., 2014; Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). Visuo-spatial attention influences the selection of sensory information relevant to the movement goal (Goldberg & Segraves, 1987; Peters, Handy, Lakhani, Boyd, & Garland, 2015) and activates neural circuitry also used during motor planning (Casarotti, Lisi, Umiltà, & Zorzi, 2012; Craighero & Rizzolatti, 2005); in this respect, brain damage could alter visuo-spatial/motor attention, which in turn influences motor planning (Peters et al., 2015). This is also in agreement with the finding that the severity of motor deficit is associated with resting state fMRI FC both within DAN and somato-motor networks (Siegel et al., 2016). In our study, the motor deficits emerging in everyday life activities were associated with lower integration of three clusters within the DAN, exclusively for slow EEG rhythms (i.e., delta/theta bands). In accordance with the above-presented theories, we suggest that the functional motor outcome after stroke is influenced by the dorsal-attentional system.

4.3. *LN and motor control*

We also found a correlation between the precentral gyrus (LN) and the FIM motor score. It has been proposed that motor control could be strictly related to speech representation (Hodgson & Hudson, 2018). In particular, there is evidence that both language and fine motor control share neural regions localized in the left hemisphere and involved in action planning and sequential processing (Hodgson & Hudson, 2018; Verstynen, Diedrichsen, Albert, Aparicio, & Ivry, 2005). In our study higher integration of precentral gyrus was associated with low FIM motor scores. A possible explanation is that activity in resting state condition within regions part of the language network could be crucial for an efficient planning of sequential actions. Altered communication between these regions might therefore contribute to the difficulty in the execution of common daily activities and more generally in the motor representation process. Although the dominance of the left hemisphere for motor skills has been observed in previous studies, there is also evidence of right-hemisphere specialization in goal-directed actions (Serrien, Ivry, & Swinnen, 2006). In this perspective, the dynamics occurring following unilateral stroke need further investigations, as well as the role of slow and fast frequency activity within areas associated with impairment.

4.4. *Functional cognitive independence*

The relation between FC dynamics and functional cognitive independence was also investigated. FIM cognitive scale includes the assessment of patient's capability to communicate, interact with other people, solve problems and memorize information in daily activities. Given the complexity of these tasks, it is conceivable that modifications within the MPN might alter the recruitment of resources required for processing stimuli in the environment and manipulating information in autonomy. In particular, our findings suggest that cognitive functioning impairments in everyday life might be related to resting state FC alteration within a brain region implicated in the multimodal integration of information (anterior middle temporal gyrus) (Visser, Jefferies, Embleton, & Ralph, 2012). In line with previous fMRI studies (Baldassarre et al., 2014; He et al., 2007), we propose that FC dysfunctions at rest can set up abnormal interactions during active tasks. Note that the higher integration within MPN was associated with lower cognitive independence only within theta band. In this respect, future investigation should clarify the possible relation between slow ipsilesional activity and general cognitive functioning also including patients with severe disruption of autonomy.

5. Conclusions and limitations

The current study investigated the relationship between EEG signatures of intrinsic brain networks' activity and behavior following stroke. Our results show that RSNs can be successfully mapped from data recorded with a 64 channels system. Thus, although information extracted from a high-density (128–256 channels) system is certainly more accurate, our results show that this methodology allows network reconstruction using a relatively small number of electrodes, which is a more typical context in clinical settings. Crucially, previous studies on EEG-RSNs involved only healthy participants, whereas our study provides a proof-of-concept for the application to neurological patients. Our EEG-RSNs approach is particularly convenient both in terms of time and costs. Indeed, this method only requires 10 min of EEG recording during rest condition: this is particularly effective in a clinical context, where patient's collaboration is not always guaranteed, and it appears very suitable for monitoring changes in FC during neurorehabilitation. EEG, compared to fMRI, is more comfortable, less contaminated by head and body movements and it is a potentially bed-side system. Furthermore, typical MRI exclusion criteria (e.g., metal plates, pace-makers, claustrophobia, etc.) do not apply to EEG. Finally, it is worth nothing that this approach also examines the role of individual EEG bands in predicting the impairments. Several studies encourage the employment of electrical brain stimulation as a potential treatment to improve neurorehabilitation after stroke (de Aguiar, Paolazzi, & Miceli, 2015; Hummel & Cohen, 2006; Marquez, van Vliet, Mcelduff, Lagopoulos, & Parsons, 2015; Nowak, Grefkes, Ameli, & Fink, 2009). In line with this new perspective for cognitive recovery, our analysis provides precious information about the EEG band associated with the impairments, highlighting which frequency range should be prioritized for transcranial electrical brain stimulation.

As a next step, it would be interesting to systematically compare altered functional dynamics of RSNs in EEG and fMRI on the same patient sample. Moreover, though the current study focused on the relation between RSNs dynamics and attentional/motor impairments, the same method could be used to examine the association to other cognitive functions and also consider computerized assessment tasks that show higher sensitivity compared to paper-and-pencil tests (see Blini et al., 2016; Bonato et al., 2019; Bonato, Priftis, Umiltà, & Zorzi, 2013). Finally, the EEG-RSN method is well suited for longitudinal studies, which would permit to track changes in network activity during recovery from stroke and examine how different types and doses of rehabilitation modulate the RSNs–behavioral relationship.

One limitation of the current study is that it did not include a group of age-matched controls, thereby preventing the possibility to directly relate changes in networks activity to the stroke. A second limitation is the use of the univariate statistical approach, but this choice was primarily motivated by the relatively small sample size. Indeed, a multivariate approach could be implemented in future work to further investigate the EEG-RSNs dynamics associated to behavioral impairments in a larger sample of stroke patients, also in relation to lesion topography. Indeed, previous studies have shown that some cognitive deficits are better predicted by fMRI FC (i.e., attention, visual and verbal memory), while others are better predicted by lesion location (i.e., motor, visual) (see, Salvalaggio, De Filippo De Grazia, Zorzi, De Schotten, & Corbetta, 2020; Siegel et al., 2016).

In conclusion, as previously proposed in the context of fMRI studies, our results support the idea that the presence of alterations in spontaneous network dynamics can be predictive of specific neuropsychological deficits. A cost-effective monitoring of RSNs functioning might have a great impact on clinical diagnosis and on the development of stroke rehabilitation programs.

6. Data and analysis code availability

The data that support the findings of this study are available on request from the corresponding author, subject to the fulfillment of a formal data agreement. The data are not publicly available, due to privacy or ethical restrictions. Copyright restrictions also prevent public archiving of the various neuropsychological tests and instruments used in this study, which can be obtained from copyright holders in the cited references.

Legal restrictions that are beyond our control prevent us from publicly archiving the analysis scripts used in this research. Specifically, for commercial use, these can be obtained through licensing agreement with KU Leuven Research and Development. These digital materials will, however, be shared freely on request with research groups and non-profit making organizations provided they agree in writing not to share them with commercial parties or use them for profit.

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Author contributions

Zaira Romeo: Conceptualization, Methodology, Software, Data curation, Formal analysis, Writing- Original draft preparation; **Dante Mantini**: Conceptualization, Methodology, Software, Writing - Review & Editing, Funding acquisition; **Eugenia Durgoni**: Data curation, Investigation; **Laura Passarini**: Data curation, Investigation; **Francesca Meneghello:** Conceptualization, Project administration; **Marco Zorzi**: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Funding acquisition, Project administration.

Declaration of Competing Interest

The authors report no competing interests.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2021.01.019.

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