

1 Modulation of neural oscillations during 2 working memory update, maintenance, 3 and readout: an hdEEG study 4

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1 **Abstract**

2 Working memory (WM) performance is very often measured using the n-back task, in
3 which the participant is presented with a sequence of stimuli, and required to indicate
4 whether the current stimulus matches the one presented n steps earlier. In this study,
5 we used high-density electroencephalography (hdEEG) coupled to source localization
6 to obtain information on spatial distribution and temporal dynamics of neural oscillations
7 associated with WM update, maintenance and readout. Specifically, we a priori selected
8 regions from a large fronto-parietal network, including also the insula and the
9 cerebellum, and we analyzed modulation of neural oscillations by event-related
10 desynchronization and synchronization (ERD/ERS).

11 During update and readout, we found larger θ ERS and smaller β ERS respect to
12 maintenance in all the selected areas. γ_{LOW} and γ_{HIGH} bands oscillations decreased in
13 the frontal and insular cortices of the left hemisphere. In the maintenance phase we
14 observed focally decreased θ oscillations and increased β oscillations (ERS) in most of
15 the selected posterior areas and focally increased oscillations in γ_{LOW} and γ_{HIGH} bands in
16 the frontal and insular cortices of the left hemisphere. Finally, during WM readout, we
17 also found a focal modulation of the γ_{LOW} band in the left fusiform cortex and
18 cerebellum, depending on the response trial type (true positive vs. true negative).

19 Overall, our study demonstrated specific spectral signatures associated with updating of
20 memory information, WM maintenance and readout, with relatively high spatial
21 resolution.

1 **Keywords**

2 ERS/ERD, hdEEG, n-back, network, neural oscillations, working memory

3

1 **Introduction**

2 The n-back task—first described by Kirchner in 1958 (Kirchner, 1958)—is the most
3 popular task used to measure working memory (WM), relying on the presentation of
4 “rapidly, continuously changing information” to measure very short-term retention. In this
5 task, participants are presented with a series of stimuli and are asked to indicate
6 whether the current stimulus (probe) matches the stimulus presented n-stimuli back in
7 the series. A recent review highlighted that WM at n-back is associated with a cerebral
8 network that varies with stimulus type, presentation modalities and as a function of
9 processing load (Mencarelli *et al.*, 2019). Additionally, a number of evidence showed
10 that specific frequency bands of electroencephalography (EEG) oscillations are of
11 particular relevance for aspects of WM, such as the positive association between γ
12 band activity (>40 Hz) and performance at higher WM loads in healthy populations
13 (Crone *et al.*, 2006; Lachaux *et al.*, 2012; Roux *et al.*, 2012; Honkanen *et al.*, 2015;
14 Kucewicz *et al.*, 2017) and the association between θ oscillations and WM (Brookes *et al.*
15 *et al.*, 2011; Burke *et al.*, 2013; Hsieh & Ranganath, 2014). These observations have
16 recently led to the use of non-invasive brain stimulation in combination with cognitive
17 training for improving WM function (Hoy *et al.*, 2015; Hill *et al.*, 2019; Reinhart &
18 Nguyen, 2019; Jones *et al.*, 2020). Particularly, transcranial Alternating Current
19 Stimulation (tACS) (Antal & Paulus, 2013; Helfrich *et al.*, 2014) in the EEG range
20 (conventionally: 0.1–80 Hz) in the frontal cortex is believed to directly modulate cortical
21 oscillations and to impact sensory, perceptual and cognitive processes (Herrmann *et al.*,
22 2013). However, to optimize such neuromodulation approach in cognitive rehabilitation
23 of WM, we need a clear picture of the spatial distribution and temporal dynamics of

1 cortical oscillations in the cerebral network involved in WM. In this context, high-density
2 electroencephalography (hdEEG) provides us the possibility to gain information on the
3 sources of the electrical oscillations underpinning cognitive processing with an optimal
4 temporal resolution and an improved spatial resolution with respect to standard EEG
5 (Michel et al., 2012). In particular, it is also fundamental to separately analyze oscillatory
6 activity in the different phases of WM process: from the early phase of updating, i.e. the
7 stored information at stimulus presentation, up to the usage of such information to guide
8 action, going through the maintenance of information in face of other stimuli. Albeit it is
9 not easy to disentangle the classic phases of working memory process (update,
10 maintenance, readout) in the n-back task, in this study we aim to obtain information on
11 spatial location and temporal dynamics of neural activity associated with the different
12 phases. To this end, we used a custom developed pipeline for performing source
13 localization from hdEEG data. This pipeline is able to detect multiple brain networks that
14 are spatially similar to those obtained from fMRI data (Liu *et al.*, 2017; Liu *et al.*, 2018;
15 Zhao *et al.*, 2019).

16 We focused on correct update of stimuli by analyzing activity that was followed by a
17 correct press n letters after (true positive) *and* activity that was followed by a correct no-
18 press n letters after (true negative), with n being either 2 (2-back task) or 3 (3-back
19 task). Furthermore, we analyzed hdEEG activity during the maintenance and readout of
20 the n-back task. To analyze the maintenance phase, we observed the hdEEG activity in
21 the single (2-back task) or in the two (3-back task) presented letters preceding the
22 probe. Correct maintenance was identified when a correct response followed the
23 appearance of the probe on the screen and when a correct no-response followed the

1 appearance of the probe on the screen. Finally, hdEEG activity during the presentation
2 of the probe was used to analyze the readout identified by probe letters correctly
3 recognized as matching or non-matching the stimulus letter presented n-trials earlier.

4

1 **Materials and methods**

2 **Data collection**

3 We recruited 21 neurologically intact, right-handed subjects (9 females, age 30.9 ± 6.8
4 years, mean \pm SD). All subjects provided written informed consent. The study conforms
5 to the standard of the Declaration of Helsinki and was approved by the institutional
6 ethical committee (CER Liguria Ref.1293 of September 12th, 2018).

7 The behavioral task consisted in a n-back working memory (WM) task (with $n = 2, 3$) as
8 in (Hoy *et al.*, 2015). Briefly, a series of random letters (A, B, C, D, E, F, G, H, I, O) was
9 visually presented in sequence and the subject was required to respond with a button
10 press when the currently presented letter corresponded to the letter presented n trials
11 earlier (Figure 1 A). Each letter appeared on a screen for 500 ms with a 2000 ms delay
12 between stimuli presentations (Figure 1 C).

13 For hdEEG recording we used a 128 channel EEG recording system (actiCHamp, Brain
14 Products), equipped with a trigger box handling external events. We collected hdEEG
15 data at 1000 Hz sampling frequency, using the electrode FCz as physical reference. We
16 also collected horizontal and vertical electrooculograms (EOG) from the right eye for
17 further identification and removal of ocular-related artifacts.

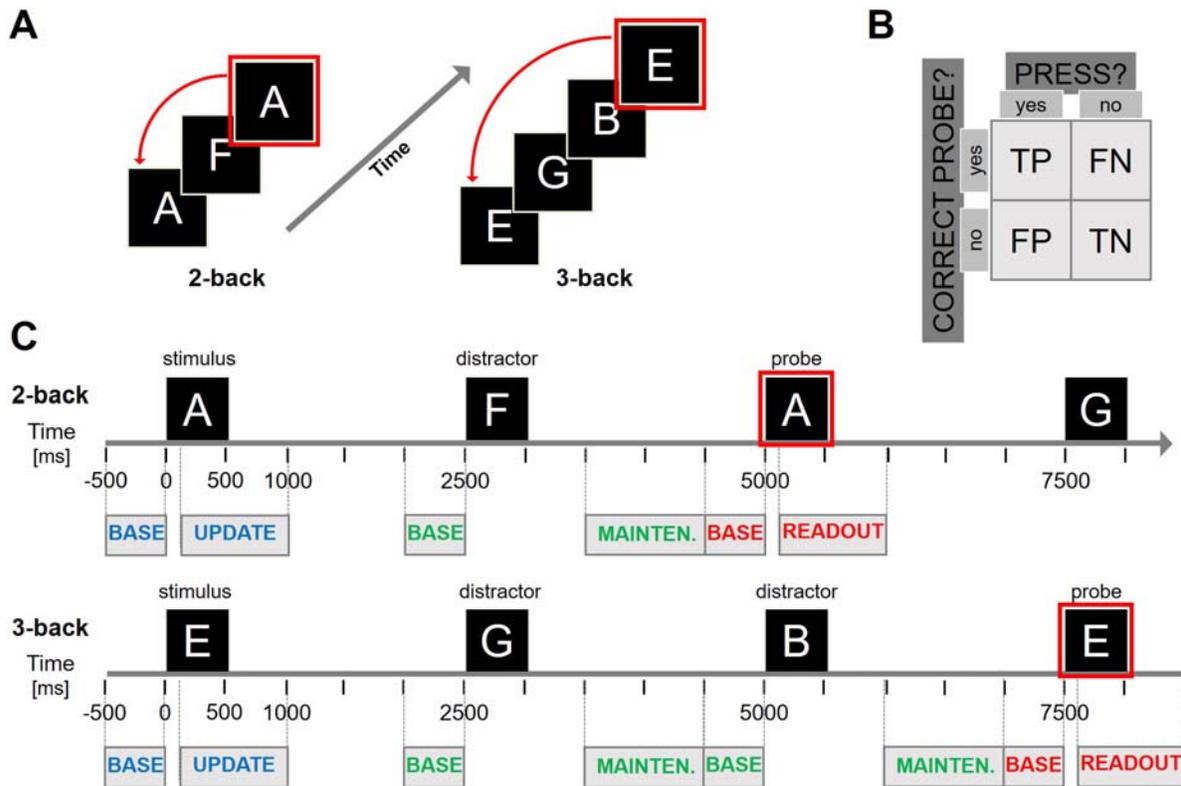


Figure 1. Outline of working memory task. **A)** Graphical representation of n-back tasks: the current letter (framed in red) must be compared with the one presented n times before, n being either 2 or 3 depending on the task. **B)** Contingency matrix of possible behavioral outcomes: true positive (TP) if a correct-probe letter was presented and the user correctly pressed the button; true negative (TN) if an incorrect-probe letter was presented and the users correctly did not press the button; false positive (FP) if an incorrect-probe letter was presented but the user pressed the button; false negative (FN) if a correct-probe letter was presented but the users did not press the button. **C)** Timeline representing 2-back (top) and 3-back (bottom) task timings and intervals chosen for hdEEG analysis. Letters appear on screen every 2500 ms and remain displayed for 500 ms. Analysis of memory *update* was performed by comparing baseline (500 ms preceding letter presentation, indicated as “BASE” in the figure) with a portion of signal ranging from 100 to 1000 ms post stimulus-letter onset (900 ms in total). Analysis of memory *update* was performed by comparing baseline (500 ms preceding distractor-letter presentation) with a portion of signal ranging from 1000 to 2000 ms post distractor-letter onset (1000 ms in total). Analysis of *readout* was performed by comparing baseline (500 ms preceding probe-letter presentation) with a portion of signal ranging from 100 to 600 ms post probe-

- 1 The behavioral task was handled by a custom graphical user interface (GUI) developed
- 2 in Matlab (The Mathworks). The GUI ran on a dedicated computer and was also
- 3 responsible for sending task-related triggers to the EEG recording system. These
- 4 triggers were sent through a NI USB board (National Instruments), which was also

1 responsible of informing both the EEG recording system and the pc used for the
2 cognitive task of a button press event.

3 **Cognitive processes underpinning working memory**

4 With respect to the cognitive processes involved during the task, we distinguished
5 between three WM phases: *update*, *maintenance* and *readout*. According to this
6 distinction, the presented letters assume different roles. As an example, in Figure 1 A,
7 for the 2-back case, the framed “A” represents the *probe* letter, the other “A” is the
8 *stimulus* letter, and the “F” is the *distractor*; For the 3-back case, the framed “E”
9 represents the *probe* letter, the other “E” is the *stimulus* letter, and “G” and “B” are
10 *distractors*.

11 *Memory update* refers to the process of storing the presented letter (stimulus) for future
12 comparison with the next probe letter (probe being either 2 or 3 trials later, depending
13 on *n* value).

14 *Memory maintenance* refers to the process of keeping the previously presented letter in
15 memory, when other letters (distractors) are presented before the probe letter (there is
16 one distractor letter in the 2-back case, and two distractor letters in the 3-back case).

17 *Readout* corresponds to the processing of a behavioral response after the probe letter
18 has been presented.

19 As depicted in Figure 1 B, by observing the behavioral responses we distinguished trials
20 as belonging to one of the following categories:

- 21 • True positive (TP): probe letter correctly recognized as matching the stimulus letter
22 (button press);

- 1 • True negative (TN): probe letter correctly recognized as non-matching the stimulus
2 letter (no button press);
- 3 • False positive (FP): probe letter incorrectly recognized as matching the stimulus
4 letter (button press);
- 5 • False negative (FN): probe letter incorrectly recognized as non-matching the
6 stimulus letter (no button press).

7 In this work, we only observed brain responses during the well-performed trials, i.e. TP
8 and TN, because the number of the badly performed trials (FP and FN) was too small.

9 We observed task performance by computing reaction time, defined as the delay
10 between probe letter onset and button press for TP trials only, and accuracy, defined as
11 the ratio of TP trials over the total number of response (TP + TN + FP + FN).

12 **hdEEG pre-processing and source localization**

13 For analysis of hdEEG data, we made use of a tailored analysis pipeline that was
14 recently developed to reconstruct source of neural oscillations (Liu *et al.*, 2017).

15 We first attenuated the power noise in the EEG channels by using a notch filter
16 centered at 50 Hz. Then, we detected channels with low signal to noise ratio and we
17 labeled them as “bad channels”. We defined a channel as “bad” if it resulted as an
18 outlier with respect to: i) the Pearson correlation of the signal in the frequency band 1-
19 80 Hz against all the signals from all the other channels; and/or ii) the noise variance
20 estimated in the frequency band 200-250 Hz, where the EEG contribution can be
21 considered as negligible. The threshold to define an outlier was set to mean \pm 3
22 standard deviation of the values. The bad channels were interpolated by using

1 information coming from the neighboring channels, as implemented in the FieldTrip
2 toolbox (<http://www.fieldtriptoolbox.org/>). EEG signals were then band-pass filtered (1-
3 80 Hz) with a FIR zero-phase distortion filter and downsampled at 250 Hz.

4 Biological artefacts were rejected using Independent Component Analysis (ICA).
5 Independent Components (ICs) were estimated with a fast fixed-point ICA (FastICA)
6 algorithm (Hyvarinen & Oja, 2000), as described in (Mantini *et al.*, 2008). ICs were
7 marked as bad if correlation with the power of the EOG signals was higher than 0.2.
8 The time courses of the ICs classified as bad were reconstructed at the channel level
9 and subtracted from the data. EEG signals were then re-referenced with a customized
10 version of the Reference Electrode Standardization Technique (REST) (Yao, 2001; Yao
11 *et al.*, 2005; Mantini *et al.*, 2008; Liu *et al.*, 2015).

12 As in (Liu *et al.*, 2017), we generated a volume conductor head model with 128
13 electrodes positioned over a T1-weighted MR anatomical template, as in (Liu *et al.*,
14 2017). Then, we segmented 12 tissue classes: skin, eyes, muscle, fat, spongy bone,
15 compact bone, gray matter, cerebellar gray matter, white matter, cerebellar white
16 matter, cerebrospinal fluid and brainstem and we assigned them with characteristics
17 conductivity values, as in (Haueisen *et al.*, 1997). To create a numerical approximation
18 of the volume conduction model and to calculate the leadfield matrix, we used the
19 Simbio finite element method (FEM) implemented in FieldTrip. The leadfield matrix
20 estimated the relationship between the measured scalp potentials and the dipoles
21 corresponding to brain sources, which were constrained by a regular 6 mm grid
22 spanning the cortical, subcortical and cerebellar gray matter.

1 Sources reconstruction was performed with the exact low-resolution brain
2 electromagnetic tomography eLORETA (Pascual-Marqui *et al.*, 2011) algorithm, using
3 both the artifacts-free hdEEG signals and the head model conductor.

4 **ERS-ERD analysis**

5 We chose to analyze a specific set of regions of interest (ROIs) in the brain, whose
6 activation was previously found related to the n-back task (Mencarelli *et al.*, 2019).
7 Table 1 summarizes the observed ROIs.

8 We computed event related synchronization and desynchronization (ERS/ERD) of
9 source reconstructed data filtered in different frequency bands and during different WM
10 processing phases. Specifically, for each WM phase (update, maintenance and
11 readout) we generated a spectrogram using Short-Time Fourier Transform for the
12 frequency range 1–80 Hz, at steps of 1 Hz, and with temporal resolution equal to 100
13 ms. The spectrogram was epoched, according to each specific condition (see below)
14 and then averaged. Finally, we calculated ERD/ERS intensity as the power change of
15 the signal in a specific time range with respect to a reference period (baseline)
16 (Pfurtscheller, 2001). We chose as baseline the 500 ms preceding letter presentation in
17 all cases, as in (Hoy *et al.*, 2016).

18 The observed frequency bands were θ (4-8 Hz), α (8-13 Hz), β (13-30 Hz), γ_{LOW} (30-50
19 Hz), and γ_{HIGH} (50-80 Hz). The δ band (1-4 Hz) was excluded from analysis, because it
20 is often contaminated by motion artefacts.

21

1 **Table 1.** List of observed ROIs, areas they belong, and corresponding MNI coordinates.

Cluster	Areas	Side	X	Y	Z	Acronym
Medial frontal cortex	Medial frontal gyrus	R	2.19	19.92	44.69	MeFC
	Medial frontal gyrus	L				
Pefrontal Cortex	Dorsolateral prefrontal cortex	R	45.14	38.44	24.49	PFC-R
	Anterior prefrontal cortex					
Premotor cortex	Premotor area	R	31.93	9.21	55.85	PMC-R
Insula	Insular cortex	R	34.68	23.81	-3.85	InsCI-R
	Clastrum					
Posterior Parietal cortex	Superior parietal lobule	R	40.12	-50.39	45.26	PPC-R
	Inferior parietal lobule					
	Precuneus					
Cerebellum	Cerebellar Tonsil	R	32.83	-63.53	-33.84	CerT-R
Dorsolateral prefrontal cortex	Dorsolateral prefrontal cortex	L	-39.41	52.62	9.74	DLPFC-L
Frontal cortex	Premotor area	L	-45.07	8.71	30.67	FC-L
	Dorsolateral prefrontal cortex					
Premotor cortex	Premotor area	L	-27.12	4.54	52.5	PMC-L
Insula	Insular cortex	L	-32.58	22.31	-5.41	InsCI-L
	Clastrum					
Posterior Parietal cortex	Superior parietal lobule	L	-36.4	-49.09	45.35	PPC-L
	Inferior parietal lobule					
	Precuneus					
Fusiform cortex	Fusiform gyrus	L	-46.06	-63.51	-15.36	Fus-L
Cerebellum	Cerebellar Tonsil	L	-31.93	-64.21	-33.44	CerT-L
Cerebellum	Cerebellar Pyramis	L	-8.72	-78.15	-32.26	CerP-L

2

1 Time range for *update* was set between 100 and 1000 ms post stimulus onset, similarly
2 to (Hoy *et al.*, 2016). The lower limit was set to 100 ms instead of 0 ms, because the
3 visual system takes up to 150 ms to process visual stimuli (Thorpe *et al.*, 1996).

4 Time range for *maintenance* was set between 1000 and 2000 ms post distractor onset.
5 We chose this interval in order to discount the contribution provided by the update (100
6 – 1000 ms post letter presentation) of the distractors, which are, at the same time,
7 probe letters for the following trials.

8 Time range for *readout* was set between 100 and 600 ms post stimulus onset. The
9 lower limit was chosen as for the other trials in order to take into account the processing
10 delays of the visual system (Thorpe *et al.*, 1996), while for the upper limit the choice
11 was data-driven and calculated according to the press distribution of all subjects during
12 TP trials. Briefly, we grouped the press times of all subjects during all TP trials during 2-
13 back (507 trials in total) and during 3-back (357 trials in total) and calculated the first
14 percentile of each distribution (686 and 639 ms, respectively). We thus chose 600 ms
15 as upper limit for both cases (2- and 3-back) and rejected trials where the press was
16 made within 600 ms following letter presentation (in total we rejected 1 trial for 2-back
17 and 7 trials for 3-back). The chosen temporal parameters are summarized in Table 2.

18 For statistical analysis of the data, we first assessed data normality with the one-sample
19 Kolmogorov-Smirnov test. Then, a three-way repeated-measure analysis of variance
20 (ANOVA) was run to test the influence on the mean ERD/ERS intensity on TASK (2-
21 back and 3-back), PHASE (update, maintenance and readout) and TRIAL (TP, TN) as
22 main factors within subjects, as well as of their interaction. This analysis was run
23 separately for each ROI and for each frequency band. Post-hoc analysis was performed

- 1 with Fisher Least Significant Difference method. The significance level was set to 0.05
- 2 for all analyses.

3 **Table 2.** Temporal parameters used for ERS/ERD analysis of WM processing.

Condition	Reference [0 ms]	Baseline	Time range [ms]
Update	Target onset	[-500 0]	[100 1000]
Maintenance, 2-back	Distractor onset	[-500 0]	[1000 2000]
Maintenance, 3-back	Distractor 1 onset	[-500 0]	[1000 2000]
	Distractor 2 onset	[-500 0]	[1000 2000]
Readout	Probe onset	[-500 0]	[100 600]

4

5

1 Results

2 Working Memory performance

3 Due to a lower WM load, best performance was obtained for the 2-back than the 3-back
4 task. Figure 2 reports single subjects' scores (panels A and D) as well as average
5 scores (panels B and E) for the two tasks. We found a significant difference between
6 accuracies obtained in the 2- and 3-back tasks (paired t-test, $p = 0.0042$) but not
7 between reaction times (paired t-test, $p = 0.21$). In Figure 2 C we report the normalized
8 distributions of reaction times for the 2-back (top) and 3-back (bottom) task. In Figure 2
9 F we plotted single subjects' accuracy against mean reaction time for the two tasks. We

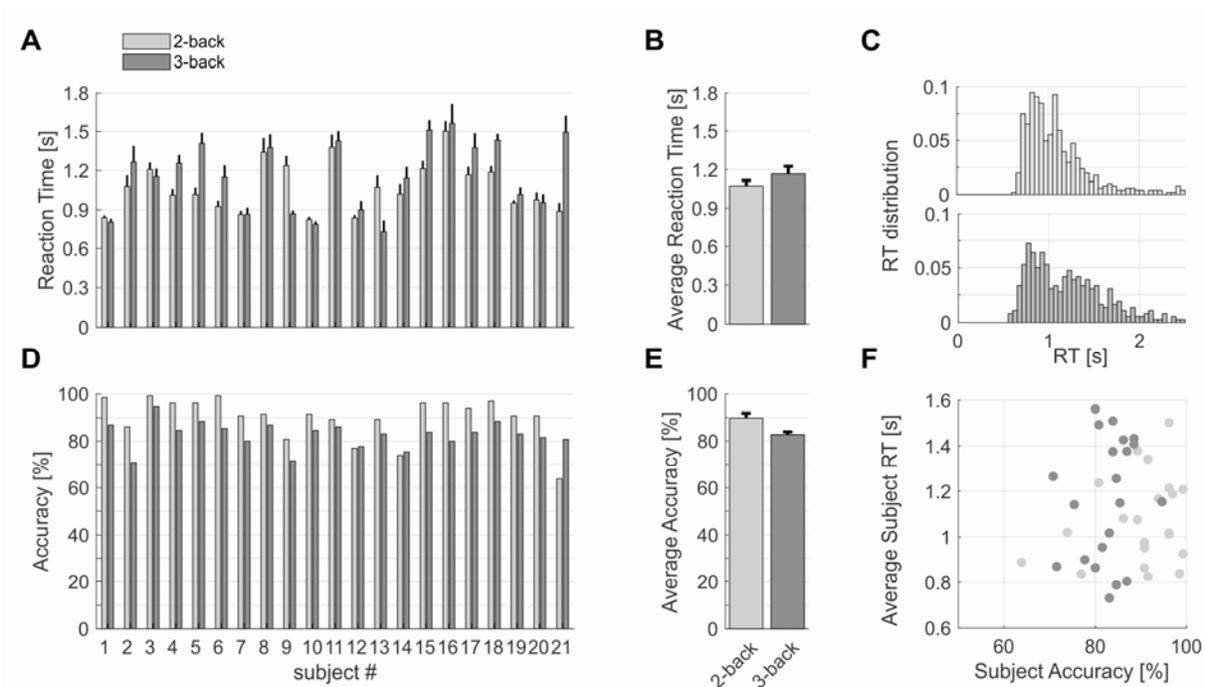


Figure 2. Cognitive performance of n-back task. **A)** Reaction times obtained by single subjects during the 2-back (light gray) and 3-back (dark gray) task (mean \pm standard error of TP trials). **B)** Average reaction time obtained in the two tasks (mean \pm standard error of single subjects' scores). **C)** Normalized reaction times distribution of reaction times during the 2-back (top) and 3-back (bottom) tasks; data obtained from all the TP trials of all subjects. **D)** Accuracy obtained by single subjects during the 2-back (light gray) and 3-back (dark gray) task. **E)** Average reaction time obtained in the two tasks (mean \pm standard error of single subjects' scores). **F)** Accuracy vs mean reaction times of single subjects in the 2-back (light gray dots) and 3-back (dark gray dots) task.

1 found no correlation between these two measures.

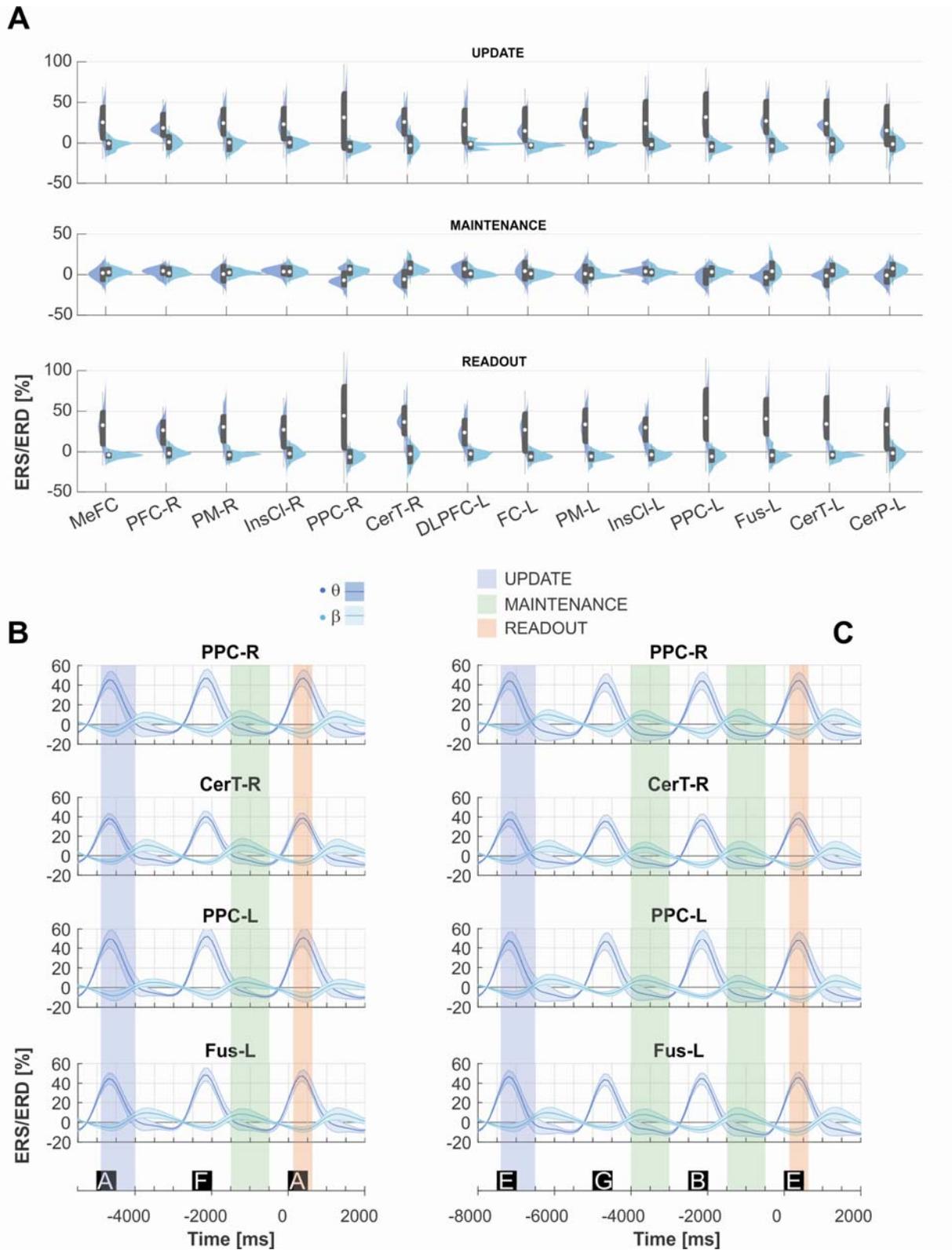
2 **ERS/ERD analysis**

3 For a specific set of ROIs (Table 1), we computed ERS/ERD for different tasks (i.e. 2-
4 and 3-back), different trial types (i.e. TP and TN) and during the different phases of the
5 working memory task (i.e. update, maintenance and readout).

6 We did not observe an effect of TASK on ERS/ERD modulation. Effect of TRIAL was
7 observed in β , γ_{LOW} and γ_{HIGH} bands for few ROIs, with TP showing ERS and TN
8 showing ERD (see Supplementary Materials). For most of the ROIs of interest, we
9 observed a statistically significant effect of PHASE in all bands, with the exception of α .
10 Significant interactions of main effects were never found between TASK and TRIAL,
11 while in the other conditions (TASK*PHASE, TRIAL*PHASE and TASK*TRIAL*PHASE)
12 were found for few ROIs in the γ_{LOW} band.

13 **Effect of PHASE**

14 In the WM network, during update and readout, we found larger θ oscillations and
15 smaller β oscillations respect to maintenance. In the maintenance phase we observed
16 decreased θ oscillations with θ ERD in most of the selected posterior areas, and
17 increased β oscillations (ERS).



1

2 **Figure 3.** Effect of PHASE in the θ and β band. A) Violin plots of ERS/ERD variation in the θ (blue) and β
3 (light blue) bands during update (top), maintenance (middle) and readout (bottom). Superimposed in grey

1 are boxplots describing the median value (white dot), 25th and 75th percentiles (extremes of the thick grey
2 line), and full data range (extremes of the thin grey line) of the distributions. B) Temporal evolution of
3 band power in the θ (blue) and β (light blue) during the 2-back task for PPC-R, CerT-R, PPC-L, and Fus-
4 L.). C) Temporal evolution of band power in the θ (blue) and β (light blue) during the 3-back task for
5 PPC-R, CerT-R, PPC-L, and Fus-L.

6

7 Figure 3 reports ERS/ERD modulation in θ/β bands for all the ROIs of interest. A
8 significant effect of PHASE was observed for the θ band in all the ROIs analyzed (Table
9 3 $p \leq 10^{-5}$ in all cases; Figure 3 panel A). Post-hoc analysis revealed an increase in θ
10 oscillations in the update and readout with respect to maintenance, in all the analyzed
11 ROIs ($p \leq 10^{-3}$ in all cases, except DLPFC-L, FC-L, and CerP-L with $\leq 10^{-2}$; Figure 3).
12 For the β band, a significant effect of PHASE was also observed in all the ROIs (Table 3
13 $p \leq 0.001$ in all cases, except PFC-R with $p = 0.012$, Figure 3 panel A). Post-hoc
14 analysis revealed an increase in β oscillation in the maintenance and a decrease in β
15 oscillation in the update and readout (maintenance vs update and readout, $p \leq 10^{-2}$ in all
16 cases).

17 For γ_{LOW} and γ_{HIGH} bands, ERS/ERD modulation was focally modified in the left
18 hemisphere, in the insular, frontal cortex and in the cerebellar ROIs. Analogously to β
19 activity, we observed in the insular and frontal cortex, smaller oscillations in the update
20 and the readout with respect to maintenance. ERS/ERD modulation in $\gamma_{\text{LOW}}/\gamma_{\text{HIGH}}$ bands
21 is reported in Figure 4 for the ROIs in which the effect of PHASE was found significant,
22 and in Figure S1 for the other ROIs. Indeed, a significant effect of PHASE was observed
23 mostly in the left hemisphere (Figure 4 panel A): γ_{LOW} oscillations were found significant
24 (Table 3, $p \leq 0.05$) in DLPFC-L, FC-L, IncCI-L, Fus-L, and CerT-L, while γ_{HIGH}
25 oscillations in CerT-R, DLPFC-L, IncCI-L, and CerTL. Post-hoc analysis revealed a

- 1 stronger increase in γ oscillation (ERS) in the maintenance phase than in update and
- 2 readout (maintenance vs update and readout, $p \leq 0.04$, Figure 4).

Table 3. Results of ANOVA related to the main effect of PHASE. Asterisks report the level of significance (** $p < 0.01$; * $p < 0.05$).

ROI	θ	β	γ_{LOW}	γ_{HIGH}
MeFC	$F_{2,40} = 21.40^{**}$ $p = 10^{-7}$	$F_{2,40} = 14.61^{**}$ $p = 10^{-5}$	$F_{2,40} = 0.07$ $p = 0.47$	$F_{2,40} = 0.37$ $p = 0.69$
DLPFC-R	$F_{2,40} = 16.08^{**}$ $p = 10^{-6}$	$F_{2,40} = 4.91^{**}$ $p = 0.012$	$F_{2,40} = 0.37$ $p = 0.68$	$F_{2,40} = 0.47$ $p = 0.62$
PMC-R	$F_{2,40} = 21.56^{**}$ $p = 10^{-7}$	$F_{2,40} = 18.74^{**}$ $p = 10^{-6}$	$F_{2,40} = 1.19$ $p = 0.31$	$F_{2,40} = 0.33$ $p = 0.72$
InsCI-R	$F_{2,40} = 18.57^{**}$ $p = 10^{-6}$	$F_{2,40} = 7.67^{**}$ $p = 0.001$	$F_{2,40} = 1.30$ $p = 0.28$	$F_{2,40} = 1.81$ $p = 0.17$
PPC-R	$F_{2,40} = 31.89^{**}$ $p = 10^{-9}$	$F_{2,40} = 37.27^{**}$ $p = 10^{-10}$	$F_{2,40} = 0.71$ $p = 0.49$	$F_{2,40} = 1.57$ $p = 0.21$
CerT-R	$F_{2,40} = 29.61^{**}$ $p = 10^{-8}$	$F_{2,40} = 22.68^{**}$ $p = 10^{-7}$	$F_{2,40} = 2.82$ $p = 0.07$	$F_{2,40} = 4.42^*$ $p = 0.01$
DLPFC-L	$F_{2,40} = 11.71^{**}$ $p = 10^{-5}$	$F_{2,40} = 8.82^{**}$ $p = 0.0006$	$F_{2,40} = 3.11^*$ $p = 0.048$	$F_{2,40} = 3.16^*$ $p = 0.048$
FC-L	$F_{2,40} = 13.55^{**}$ $p = 10^{-5}$	$F_{2,40} = 10.11^{**}$ $p = 0.0002$	$F_{2,40} = 4.43^{**}$ $p = 0.018$	$F_{2,40} = 2.43$ $p = 0.10$
PMC-L	$F_{2,40} = 2065^{**}$ $p = 10^{-7}$	$F_{2,40} = 12.35^{**}$ $p = 10^{-5}$	$F_{2,40} = 1.81$ $p = 0.17$	$F_{2,40} = 0.95$ $p = 0.39$
InsCI-L	$F_{2,40} = 16.68^{**}$ $p = 10^{-6}$	$F_{2,40} = 10.63^{**}$ $p = 0.0001$	$F_{2,40} = 5.44^{**}$ $p = 0.008$	$F_{2,40} = 3.35^*$ $p = 0.045$
PPC-L	$F_{2,40} = 28.54^{**}$ $p = 10^{-8}$	$F_{2,40} = 23.11^{**}$ $p = 10^{-7}$	$F_{2,40} = 0.98$ $p = 0.38$	$F_{2,40} = 1.17$ $p = 0.32$
Fus-L	$F_{2,40} = 27.72^{**}$ $p = 10^{-8}$	$F_{2,40} = 13.34^{**}$ $p = 10^{-5}$	$F_{2,40} = 5.78^{**}$ $p = 0.006$	$F_{2,40} = 2.17$ $p = 0.12$
CerT-L	$F_{2,40} = 24.78^{**}$ $p = 10^{-8}$	$F_{2,40} = 15.58^{**}$ $p = 10^{-6}$	$F_{2,40} = 4.68^*$ $p = 0.014$	$F_{2,40} = 3.23^*$ $p = 0.049$
CerP-L	$F_{2,40} = 13.33^{**}$ $p = 10^{-5}$	$F_{2,40} = 15.03^{**}$ $p = 10^{-5}$	$F_{2,40} = 2.24$ $p = 0.11$	$F_{2,40} = 2.79$ $p = 0.07$

1

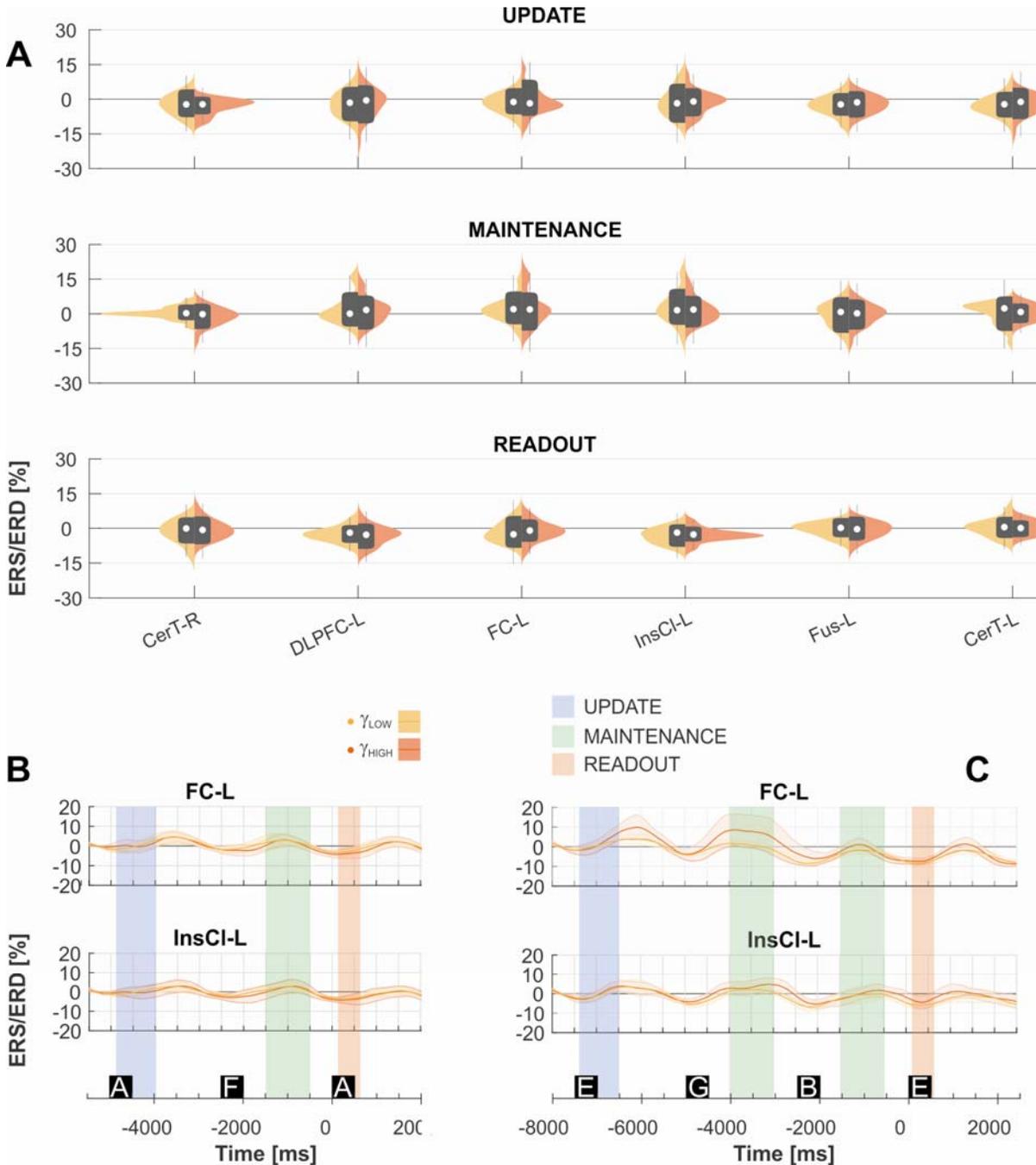


Figure 2. Effect of PHASE in the γ_{LOW} and γ_{HIGH} band. A) Violin plots of ERS/ERD variation in the γ_{LOW} (yellow) and γ_{HIGH} (orange) bands during update (top), maintenance (middle) and readout (bottom). Superimposed in grey are boxplots describing the median value (white dot), 25th and 75th percentiles (extremes of the thick grey line), and full data range (extremes of the thin grey line) of the distributions. B) Temporal evolution of band power in the γ_{LOW} (yellow) and γ_{HIGH} (orange) during the 2-back task for FC-L and InsCl-L. C) Temporal evolution of band power in the γ_{LOW} (yellow) and γ_{HIGH} (orange) during the 3-back task for FC-L and InsCl-L.

1 **Interactions of main effects**

2 Interactions of main effects were found only in the γ_{LOW} band. TASK*PHASE interaction
3 was observed in cerebellum, in both hemispheres (Table 4; CerT-R $p = 0.002$, CerP-L p
4 $= 0.036$), with update during 3-back showing a significant stronger ERD than during 2-
5 back in the CerT-R (post-hoc analysis, $p = 0.010$) and a trend in the the CerP-L (post-
6 hoc analysis, $p = 0.09$).

7 In the left fusiform cortex and left cerebellum it was also observed a significant
8 interaction TRIAL*PHASE (Table 5; CerT-L $p = 0.013$, Fus-L $p = 0.002$). Here we only
9 expect interactions with the response phase, as trial type should not influence update
10 and maintenance phases. Indeed, post-hoc analysis was found significant for CerT-L (p
11 < 0.0005) and Fus-L ($p = 0.0012$), with γ oscillations increasing during readout of TP
12 trials and decreasing during readout of TN trials. Finally, a significant
13 TASK*TRIAL*PHASE interaction was also observed in the left fusiform cortex and right
14 cerebellum (Table 6; CerT-R $p = 0.017$, Fus-L $p = 0.03$). Post-hoc analysis showed, for
15 TP trials in both areas, stronger ERD for the 3-back task with respect to the 2-back task
16 in the update phase ($p = 0.006$ for CerT-R and $p = 0.014$ for Fus-L). In CerT-R we also
17 found a stronger ERS in the 3-back task with respect to the 2-back in the readout phase
18 of TP trials ($p = 0.048$).

19

1 **Table 4.** Results of ANOVA related to the interaction of TASK*PHASE in the γ_{LOW} band.
 2 Asterisks report the level of significance (** p<0.01; * p<0.05; \$ trend). U, update; M,
 3 maintainance; R, readout. In the descriptive statistics, mean \pm standard deviation is
 4 reported.

ROI	Within test	Descriptive statistics	Post-hoc
CerT_R	$F_{2,40} = 7.13^{**}$	U: 2-back (-0.97 \pm 1.13) 3-back (-3.88 \pm 0.95)	p = 0.01*
	p = 0.002	M.: 2-back (-0.84 \pm 1.16) 3-back (-0.86 \pm 1.12)	p = 0.25
		R: 2-back (-2.35 \pm 0.95) 3-back (-0.39 \pm 1.39)	p = 0.16
CerP_L	$F_{2,40} = 3.58^*$	U: 2-back (-0.32 \pm 1.20) 3-back (-2.84 \pm 0.82)	p = 0.09 ^{\$}
	p = 0.036	M.: 2-back (0.79 \pm 1.75) 3-back (0.05 \pm 1.20)	p = 0.09 ^{\$}
		R: 2-back (-0.80 \pm 0.91) 3-back (1.12 \pm 1.28)	p = 0.7

5

6 **Table 5.** Results of ANOVA related to the interaction of interaction of TRIAL*PHASE in
 7 the γ_{LOW} band. Asterisks report the level of significance (** p<0.01; * p<0.05; \$ trend). U,
 8 update; M, maintainance; R, readout. TP, true positive trials; TN, true negative trials. In
 9 the descriptive statistics, mean \pm standard deviation is reported.

ROI	Within test	Descriptive statistics	Post-hoc
CerT_L	$F_{2,40} = 4.76^*$	U: TP (-3.42 \pm 1.26) TN (-1.88 \pm 0.88)	p = 0.2
	p = 0.013	M: TP (0.84 \pm 1.86) TN (-0.87 \pm 0.55)	p = 0.3
		R: TP (2.91 \pm 1.24) TN (-2.44 \pm 0.82)	p = 0.0005**
Fus_L	$F_{2,40} = 6.96^{**}$	U: TP (-4.40 \pm 1.42) TN (-1.15 \pm 0.80)	p = 0.03*
	p = 0.002	M: TP (0.41 \pm 1.83) TN (-0.53 \pm 0.64)	p = 0.9
		R: TP (3.13 \pm 1.42) TN (-1.98 \pm 0.75)	p = 0.0012**

10

11

1 **Table 6.** Results of ANOVA related to interaction of TRIAL*PHASE*TASK in the γ_{LOW}
 2 band. Asterisks report the level of significance (** $p < 0.01$; * $p < 0.05$; \$ trend). U, update;
 3 M, maintainance; R, readout. TP, true positive trials; TN, true negative trials. In the
 4 descriptive statistics, mean \pm standard deviation is reported.

ROI	Within test	Descriptive statistics	Post-hoc
CerT-R	$F_{2,40} = 4.47^*$ $p = 0.017$	TP: U: 2-back(0.71 ± 2.07) 3-back (-5.36 ± 1.91) M: 2 back (0.98 ± 2.27) 3-back (-0.27 ± 1.73) R.: 2-back(-1.74 ± 1.54) 3-back (2.09 ± 2.01)	$p = 0.006^{**}$ $p = 0.64$ $p = 0.048^*$
		TN: U: 2-back(-2.65 ± 0.8) 3-back (-2.39 ± 1.02) M.: 2 back (0.69 ± 0.94) 3-back (-1.4 ± 1.03) R: 2-back (-2.94 ± 0.78) 3-back (-2.87 ± 1.03)	$p = 0.80$ $p = 0.11$ $p = 0.95$
Fus-L	$F_{2,40} = 3.70^*$ $p = 0.03$	TP: U: 2-back (-0.29 ± 1.81) 3-back (-8.5 ± 2.32) M: 2-back (-0.96 ± 2.61) 3-back (0.14 ± 2.05) R: 2-back (3.28 ± 1.62) 3-back (2.98 ± 1.93)	$p = 0.014^*$ $p = 0.71$ $p = 0.89$
		TN: U: 2-back (-0.84 ± 1.08) 3-back (1.44 ± 1.00) M: 2-back (0.26 ± 0.85) 3-back (1.32 ± 0.78) R: 2-back (-1.29 ± 0.92) 3-back (-2.66 ± 0.95)	$p = 0.66$ $p = 0.13$ $p = 0.24$

5

6

1 Discussion

2 The main goal of this study was to obtain information on spatial location and temporal
3 dynamics of neural oscillations associated with the different phases of working memory
4 (update, maintenance, readout) in the n-back task.

5 Indeed, working memory is a high cognitive function that refers to the ability to encode,
6 manipulate and retrieve information online and over a limited period of time (Baddeley,
7 1996). To this aim, taking advantage of recent developments on the accurate
8 reconstruction of neural activity in the brain from hdEEG (Liu *et al.*, 2017; Zhao *et al.*,
9 2019), we analyzed spectral signatures associated with updating of memory
10 information, its maintenance and its readout when used to inform and guide behavior.
11 We a priori selected a large fronto-parietal network (Mencarelli *et al.*, 2019), including
12 also the insula, involved in memory storage, and the cerebellum as subcortical area that
13 has demonstrated to be involved in cognitive functions (Strick *et al.*, 2009).

14 The main results of the present study were the following: (i) in the update and readout,
15 larger θ oscillations accompanied by smaller β oscillations in most of the selected areas
16 and decreased γ_{LOW} and γ_{HIGH} bands in the frontal and insular cortices of the left
17 hemisphere; (ii) in the maintenance, focally decreased θ oscillations and increased β
18 oscillation in posterior areas and increased oscillation in γ_{LOW} and γ_{HIGH} bands in the
19 frontal and insular cortices of the left hemisphere; (iii) in the readout, focal modulation of
20 γ_{LOW} band in the left cortex (fusiform) and left cerebellum depending on the response
21 (ERS in the TP trials and ERD in the TN trials). Noteworthy, only for γ_{LOW} band we
22 observed that some of the modulations in the update and readout of TP trials were

1 stronger for the 3-back than the 2-back task, suggesting that the cognitive load is
2 playing a role in its modulation.

3 **EEG oscillations in relation to working memory: the update phase**

4 Several recent studies highlighted the role played by θ oscillations in working memory.
5 Particularly, activity in this band has been related to increases in the amount of
6 information to be retained, with θ modulations localized to frontal (Gevins *et al.*, 1997;
7 Jensen & Tesche, 2002), hippocampal (Tesche & Karhu, 2000), and parietal (Sarnthein
8 *et al.*, 1998) regions. One of the core functions attributed to θ band oscillations in the
9 hippocampal system is the temporal integration of cell assemblies (Buzsaki & Moser,
10 2013). Although first demonstrated for the tracking of spatial positions, the same
11 mechanism may also support the representation and consolidation of sequentially
12 organized memory traces (Lisman & Jensen, 2013).

13 Our findings revealed synchronization in the θ band in all the areas belonging to WM
14 network following stimulus presentation, consistent with long-range coordination of
15 neuronal activity within WM network. Indeed, neural oscillations are thought to play a
16 central role in coordinating neural activity both in local networks (Gray *et al.*, 1989;
17 Womelsdorf *et al.*, 2007) and over longer distances (von Stein & Sarnthein, 2000).
18 Particularly, δ and θ oscillatory regimens are characterized by long-range interactions
19 (von Stein & Sarnthein, 2000) requiring communication among several different areas.
20 Simultaneously with an increase of θ oscillations, we also found a decrease of β
21 oscillations at stimulus presentation in parietal and frontal areas of both hemispheres. In
22 a recent study adopting magnetoencephalography (MEG) θ and β/γ activity were
23 assessed during the n-back and the Sternberg tasks (Brookes *et al.*, 2011). Similarly to

1 our results, the authors found increased frontline θ power together with decreased
2 power in the β/γ on task initiation. These oscillatory power decreases were most
3 prominent in the 20–40 Hz frequency band, even if modulation could be observed up to
4 80 Hz, implying a broad-band response (Brookes *et al.*, 2011).

5 Our findings are also consistent with the literature suggesting that θ and β/γ oscillations
6 are linked. Whilst amplitude modulation θ and β bands oscillations were seen in almost
7 all areas of WM network, modulation in γ band oscillations were detectable specifically
8 in the clusters containing frontal cortex and insula/clastrum of the left hemisphere.

9 **EEG oscillations in relation to working memory: the maintenance phase**

10 Our results were consistent also in the subsequent phase of WM process; i.e. the
11 maintenance, with increased γ activity in the same areas in which γ activity was
12 modulated in the update. In addition to γ_{LOW} synchronization in the frontal cortex and
13 insula/clastrum of the left hemisphere, in the maintenance phase we observed
14 increased β oscillation (ERS) for most of the selected areas and, accordingly to what
15 observed in the update phase, decreased θ activity, specifically in the posterior areas.

16 In human MEG and EEG recordings, the maintenance of visual information in WM is
17 associated with increased β and γ frequency band amplitudes (Tallon-Baudry *et al.*,
18 1998; Osipova *et al.*, 2006; Jokisch & Jensen, 2007; Haenschel *et al.*, 2009; Palva *et*
19 *al.*, 2011). Related to β oscillations, although β has been widely studied for movement, it
20 has also been suggested a role in cognitive functions such as WM (Lundqvist *et al.*,
21 2011; Lundqvist *et al.*, 2016; Lundqvist *et al.*, 2018). Recent studies recorded prefrontal
22 activity in monkeys performing a delayed match-to-sample task, in which several
23 objects had to be encoded, maintained, and tested sequentially over several seconds

1 (Lundqvist *et al.*, 2016). During encoding, brief γ bursts were associated with spiking
2 activity while β bursts were reduced. Then, in the following delay period, moderate
3 increase of β was observed except at the very end, when information was needed
4 again. At that point, β was reduced and γ increased. The authors speculated that the
5 intermediate elevation of β during the delay period relative to the low levels seen at
6 encoding and readout might serve to protect the current working memory contents from
7 interference. Indeed, human studies have shown increases of prefrontal β when
8 subjects must filter out distractors (Zavala *et al.*, 2015; Zavala *et al.*, 2017) or prevent
9 encoding (Hanslmayr *et al.*, 2014).

10 γ band oscillations have been suggested to represent a generic mechanism for the
11 representation of individual WM items, irrespective of WM content and format (Roux &
12 Uhlhaas, 2014). This is because the synchronization of neuronal discharges at γ
13 frequencies supports the integration of neurons into cell assemblies in different cortical
14 and subcortical structures (Singer, 2009) and thus could represent an effective
15 representational format for WM information (Roux & Uhlhaas, 2014). γ modulations
16 were observed focally in the prefrontal cortex and insula/clastrum of the left
17 hemisphere. Insula is particularly involved in n-back tasks based on the visual
18 presentation of numbers (Mencarelli *et al.*, 2019), possibly linked to its phonological
19 function (Chee *et al.*, 2004). Visual WM operations may rely on activation of letter
20 representations in insular cortex, via top-down feedback from neocortical areas
21 including the prefrontal cortex (Moore *et al.*, 2006). Thus, top-down input from the
22 prefrontal cortex can additionally promote maintenance of visual images in the face of

1 distraction (Sakai *et al.*, 2002; Miller *et al.*, 2018). Following this model, ERS in γ band
2 in these areas may suggest critical role of this network in visual WM maintenance.

3 **EEG oscillations in relation to working memory: the readout phase**

4 The temporal window for the readout started together with the update, 100 ms after
5 letter presentation. Thus the overlap of θ/β oscillations in the readout (i.e.: increased θ
6 oscillations and reduced β oscillations) with respect to update may be suggestive of the
7 overlap of cognitive processes. Indeed in n-back task, it is difficult to disentangle
8 between update and readout, since every new stimulus has to be encoded and
9 simultaneously compared to the 2 or 3 stimuli preceding it, in order to be recognized
10 and to trigger the correct response.

11 However, in addition to θ/β modulation, in the readout we also observed modulation in
12 the γ_{LOW} band activity depending on readout process. Indeed, modulation of γ_{LOW}
13 activity differed when decision was to press the button (TP) or not (TN). γ oscillations
14 increased in the left fusiform cortex and left cerebellum when subjects had to decide
15 that the probe letter was equal to the stimulus (TP trials) whereas γ oscillations
16 decreased in the same areas when subjects had to decide that the probe letter differed
17 from the stimulus (TN trials). In TP trials, increased γ oscillations in the readout phase
18 are consistent with recent evidence coming from animal studies with local field potential
19 recordings (Lundqvist *et al.*, 2011; Lundqvist *et al.*, 2016; Lundqvist *et al.*, 2018),
20 suggesting a role for γ oscillations when working memory needs to be read out. We also
21 generalize this phenomenon to a process of readout instrumental to inform motor
22 behavior (like a button press). The left fusiform gyrus has been connected with visual
23 word processing (Cohen *et al.*, 2002; Dehaene & Cohen, 2011; Price & Devlin, 2011;

1 Wandell, 2011) and represents both phonological information in addition to orthographic
2 information (Zhao *et al.*, 2017). Cerebellar engagement in working memory tasks is
3 reliably reported across multiple studies (Schmahmann & Pandya, 1997; Strick *et al.*,
4 2009). Particularly, connections with association cortices (including the prefrontal
5 cortex) are mainly located within posterior cerebellar lobules (including cerebellum tonsil
6 and pyramis), which provide the anatomic substrate for cerebellar involvement in
7 cognition. Taken together, we can suppose a network based on letter recognition,
8 attention based motion processing and selection of WM information for action
9 preparation, specifically active when the response to be selected is a motor output (and
10 not to suppress the motor output, as it happens in the TN trials).

11 **Conclusions**

12 Overall, our study demonstrated specific spectral signatures based on hdEEG
13 associated with updating of memory information, working memory maintenance and
14 readout, with relatively high spatial resolution. Considering that n-back task is largely
15 used in clinical settings for both diagnosis and rehabilitation, our findings may support
16 the targeted use of non-invasive neuromodulation techniques to boost the WM process
17 in diseases.

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