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Does extensive motor learning trigger local sleep?

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Do. Or do not. There is no try.

Abstract

After prolonged learning we all have experienced a reduction of alertness, resulting in errors that we would normally not make. Despite this being a common situation in everyday life, the reasons for this phenomenon are unclear. A possible explanation is that the regions of the brain which are involved in the learning, go off-line trying to partially recover. This event is defined as local sleep and it has been detected in animals and sleep-deprived humans performing learning tasks. Local sleep is a sleep-like electrophysiological activity occurring locally, while the rest of the brain is fully awake, and producing performance deterioration. However, since all the studies included both lack of sleep and learning, it is uncertain whether such phenomenon is related to sleep deprivation or if it is the consequence of prolonged learning. Further, local sleep has not been related to electrophysiological changes occurring during the task.

This thesis aimed to assess, for the first time in well rested subjects, whether local sleep and performance decline occur because of prolonged learning. Specifically, the goal was to discriminate between sustained practice and learning, as to determine whether learning is required to cause local sleep. Also, a 90-minute nap was evaluated to establish whether sleep is necessary to counterbalance neuronal fatigue and performance decrease. The starting hypothesis was that local sleep is a plasticity-related phenomenon affecting performance and requiring learning to be triggered. Consequently, sleep would be a prerequisite to counterbalance performance and electrophysiological changes.

High-Density EEG and behavioral data of 78 healthy young subjects were collected during and after two learning tasks performed for three hours: a visual sequence learning task, and a visuo-motor rotation task, randomly selected. Afterward, subjects were divided in two groups: those who slept for one hour and a half and those who remained awake and quietly rested for the same amount of time before being tested for electrophysiological and behavioral changes. Moreover, to discriminate between the effects of prolonged learning and practice, 11 additional subjects performed a control condition consisting in planar upper limb reaching movements instead of the above-mentioned learning tasks. In detail, the power spectrum of the EEG activity during the task and at rest with eyes opened was divided into

five ranges to determine frequency changes of the EEG activity: delta 1 to 4 Hz; theta 4 to 8 Hz; alpha 8 to 13 Hz, beta 13 to 25 Hz, gamma 25 to 55 Hz. Additionally, movement-related beta activity of 35 young subjects was analyzed to find a relationship between task related oscillations and performance indices, as the modulatory activity during practice may reflect plasticity-related phenomena that can describe the occurrence of local sleep. Finally, 13 young subjects were compared to a dataset of 13 older participants who performed planar upper limb reaching movements to determine whether beta oscillations were affected by age. Specifically, beta activity was assessed during reaching movements in different brain regions, in terms of topography, magnitude, and peak frequency.

Results demonstrated that sustained learning produced electrophysiological changes both at rest and during the task. In fact, resting state was characterized by a progressive slowing of the EEG activity over areas overlapping with those engaged during the task. Precisely, we detected task-related activity mainly in the high-frequency ranges (gamma and beta right temporo-parietal activity for the visual sequence learning task; alpha and beta activity over a fontal and left parietal areas for the visuo-motor rotation); the same areas were characterized by a progressive increase of the low frequency EEG activity at rest ranging from alpha, beta after one hour of practice, to theta after three one-hour blocks. The control task did not trigger such EEG slowing, as reaching movements without learning did only left an alpha, beta trace in the resting state over a cluster reflecting the motor area contralateral to the movement. Further, continuous learning triggered performance deteriorations only in tests sharing the same neural substrate of the previously performed task. In other words, the visuo-motor learning task only affected performance in a motor test consisting in random reaching movements; conversely, visual sequence learning altered performance on a visual working memory test, but did not influence reaching movements. Also, the control condition did not affect performance in any of the two exercises. Performance decline, learning ability and local sleep were partially renormalized by a 90-minute nap but not by an equivalent period of wake. As such, the global EEG activity, computed as the mean power of all the electrodes, was not affected by either 90 minutes of sleep or quiet wake. However, the regions characterized by low frequency at rest benefited from the sleep period, as the low frequencies content partially decreased after the nap but not after quiet wake. Task-related beta activity during motor practice presented similar magnitude and timing patterns in different brain areas, with a progressive increase with practice, in both young and older subjects, despite the older subjects performing slower, less accurate movements. Intriguingly, the motor areas showed a post movement beta synchronization having a peak between 15 and 18 Hz, as opposed to a frontal area that has it between 23 and 29 Hz. Finally, results did not reveal any

direct relationship between EEG beta oscillations and performance indices.
Altogether, these results indicate that local sleep and performance decrease can be triggered by prolonged learning in well rested subjects; furthermore, some amount of sleep can partially renormalize learning ability, EEG activity and performance. Also, differences in the brain oscillations during motor activity can express separate processes underlying motor planning, execution and skills acquisition. The present study adds some important knowledge in the field of local sleep; in fact, it suggests that such phenomenon is triggered by sustained learning rather than sleep deprivation, thus being a plasticity-related phenomenon. Finally, the role of sleep on counterbalancing local sleep has been proved, despite additional studies are required to establish whether a full night of sleep rather than a specific amount of time is needed to fully restore learning ability and electrophysiological activity. In conclusion, the present findings are of importance in all the fields where sustained learning is required, such as rehabilitative programs, sport and military trainings, and must be taken into account when plasticity plays a fundamental role in the acquisition of new skills.

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Symbols

ANOVA	Analysis Of Variance
EEG	Electroencephalography
EKG	Electrocardiogram
EMG	Electromyography
EOG	Electrooculography
ERD	Event Related Desynchronization
ERS	Event Related Synchronization
FIR	Finite Impulse Response
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
ICA	Independent Component Analysis
IRB	Institutional Review Board
LTD	Long-Term Depotentiation
LTP	Long-Term Potentiation
mem	memory test
MOT	Motor Reaching Task
mov	motor reaching test
NREM	Non-Rapid Eye Movement

PAS	Paired Associative Stimulation
PCA	Principal Component Analysis
PD	Parkinson's Disease
REM	Rapid Eye Movement
ROI	Region of Interest
ROT	Visuo-motor Rotation
SD	Standard Deviation
sEEG	Spontaneous EEG
SE	Standard Error
SHY	synaptic Homeostasis Hypothesis
SWA	Slow Wave Activity
TMS	Transcranial Magnetic Stimulation
VSEQ	Visual Sequence

Chapter 1

Introduction

1.1 Motivation and Objective

Normally, the brain becomes tired at the end of the day and needs sleep to be restored. There is evidence that sleep need is characterized by the level of EEG slow wave activity (SWA) during non-rapid eye movement sleep (NREM) [Fattinger et al. (2017); Gulati et al. (2017); Gonzalez-Rueda et al. (2018)]. Previous studies revealed that sleep is triggered by the cellular consequence of wake, primarily related to the cost of synaptic plasticity associated with learning [Vyazovskiy et al. (2011b); Hung et al. (2013); Bernardi et al. (2015)]. In fact, cortical areas directly involved in motor learning show a local increase in slow wave activity during the following sleep, which is correlated with performance improvements [Huber et al. (2004)]. Conversely, the local disruption of NREM slow waves limits further motor learning on the following morning [Fattinger et al. (2017)]. Moreover, EEG studies show that complex tasks leave local traces that can be detected afterwards. Specifically, training for less than 1-hour leaves a region-specific trace that is related to the functional changes occurring in the same areas during the task [Moisello et al. (2013)]. In the specific case of motor control and learning, movements are associated with changes of the EEG activity, mainly over the sensorimotor cortices. A possible interpretation of such modulatory activity is that it reflects plasticity-related phenomena; in other words, this pattern likely expresses the recurring activation and inactivation of the sensory and motor areas during motor execution. One of the first studies on local sleep, defined as a sleep-like electrophysiological activity occurring in an awake brain, revealed that when rats stayed awake longer than usual to explore, cortical neurons go off-line, interrupting and resuming their discharge patterns as they normally would do in sleep [Vyazovskiy et al. (2011b)]. These OFF periods occurred intermittently in different cortical areas, were associated with a local slow/theta wave (2-6 Hz), and with

errors on a trained reaching task, all while rats appear fully awake with typical wake activity in the EEG. Studies in humans illustrated the initial evidence that intense use in the context of a sleep deprivation paradigm leads not only to global EEG changes, but also to task-specific increases in parieto-occipital theta power, after 24-h of a driving video game [Hung et al. (2013)]; Bernardi et al. (2015)]. This increase in slow activity had a local component, being more evident over left frontal derivations after listening to audio books, and over posterior parietal regions after a driving simulation videogame. Both conditions resulted in a global increase in spontaneous wake EEG theta power (5-9 Hz) that correlated with an increase in sleep SWA over the same areas. Further, intracranial recordings in humans show that SWA during wake was related to slow and attenuated spiking responses of individual cortical neurons [Nir et al. (2017)] and associated with performances errors. This phenomenon, was recently noted also with intracranial recordings in epileptic patients and it has been related to performance errors [Nir et al. (2017)]. Altogether, these findings represent the first indication in humans that sleep deprivation, together with prolonged use of specific brain regions, can lead to local sleep during wake. However, all the paradigms used to investigate local sleep included both sleep deprivation and intense learning, thus making impossible to discriminate between these two factors.

The main goal of this thesis is to establish whether local sleep is the consequence of prolonged learning, rather than sleep deprivation. In other words, this study aims at demonstrating through EEG recordings, for the first time in healthy subjects having an appropriate sleep schedule, that prolonged motor learning leads to local sleep and a subsequent performance decrease. For this reason, the experimental protocol included three conditions: visuo-motor rotation learning, visual sequence learning and a control condition with repeated reaching movements. This allows to discriminate between sustained learning and practice. Preliminary results revealed a low-frequency trace in the spontaneous EEG following the learning tasks, but not in the reaching condition. Also, extended learning affected performance only in tests relying on the same neural network of the learning. Thus, I focused on movement-related EEG activity to determine whether changes in such activity can explain local sleep occurrence and performance decline. Finally, I investigated the role of 90-minutes of sleep and an equivalent period of quiet wake in restoring electrophysiological activity and performance decreases, as it has been reported that sleep can restore learning ability and EEG activity. In particular, the majority of the studies are focused on a full night of sleep; here, some of the participants were allowed to take a nap in the middle of the day, while the others remained awake and quietly rested. Adding sleep in the experimental protocol was required for two reasons: (i) to strengthen the main hypothesis, suggesting that local sleep is the consequence of plasticity;

thus, restoration of EEG activity and performance require a period of sleep and the associated synaptic renormalization; (ii) to assess whether a short period of time is sufficient to fully renormalize EEG and behavior.

1.2 Organization of the thesis

For this thesis we collected high density EEG and behavioral data from 78 young healthy participant who underwent a full-day experiment, randomly assigned in two conditions: a group performed four hours of a visuo-motor rotation task, while the other completed a visual sequence task for the same amount of time. Additionally, eleven participants performed a planar upper limb reaching task, to discriminate between extensive learning and practice. Subjects were then randomly divided in two groups: those who took a 90-minute nap and those who remained awake and quietly rested for the same amount of time, so as to assess the role of sleep in renormalizing performance and EEG activity changes. For all the groups EEG oscillations, as well as behavioral performance have been analyzed. Results indicated EEG differences between motor learning and its control task, thus task-related activity of reaching movements was analyzed in terms of synchronizations and desynchronizations. Specifically, task-related EEG changes were related to movement features and compared with a dataset of 13 older subjects who performed the same experiment.

The work can be divided into six objectives summarized as follow:

- Determine if intense training in a task involving a specific brain circuits leads to regionally specific slow activity in spontaneous EEG
- Establish if prolonged training leads to progressive, specific impairment in performance and if errors are associated with local EEG slowing
- Assess if a nap, but not an equivalent period of quiet wake, can counteract local EEG slowing and tiredness, as well as performance deterioration
- Characterize the movement-related oscillatory EEG activity in terms of amplitude, latency and peak beta frequency
- Determine whether such activity is directly related to movement features
- Analyze age-related differences in the EEG oscillatory activity during upper limb reaching movements

Specifically, the thesis is divided in two parts: the first part (chapter 3) includes the first three objectives and it is focused on local sleep and learning. The second part (chapter 4 and 5) is about movement-related oscillatory activity. All the data in this manuscript have been collected at the "Neuroplasticity Lab" of the New York City College, CUNY, New York USA, where I spent eighteen months of my PhD. Part 1 and 2 are followed by a general discussion and a conclusion section and preceded by an introduction and a background section with theoretical information about the main topics of the dissertation: motor control and learning, movement-related oscillatory activity, plasticity, sleep and local sleep.

Chapter 2

Background

2.1 Motor control and reaching movements

Movements are associated with a planning and execution phase [Fleischer (1989)]. Planning is the process of selecting the most appropriate motor command to complete a movement [Orban de Xivry et al. (2017)]; as such, it occurs before the onset of the movement [Henry and Rogers (1960); Wong et al. (2015)], and it is associated with movement accuracy [Gottlieb et al. (1989)]. In case of upper limb reaching movements, the planning phase is relatively simple, as opposed to more complex tasks, where there are more muscles and dynamics involved [Gordon et al. (1994b)]. The primary motor and premotor cortices (Fig. 2.1) are the main cortical structures devoted to movement planning, execution and directing sequences of voluntary movements [Purves et al. (2001)]. In general, upper limb reaching movements have specific features that can be summarized as follow [Morasso (1981); Gordon and Ghez (1987)]:

- straight path
- direction defined at the beginning of the movement
- bell-shaped velocity profile with a minimum at the beginning and end of the movement
- peak velocity and acceleration scaled with the target distance

Multiple repetitions of the same movement show an elliptic distribution of the end points, oriented in the direction of the movement [Gordon et al. (1994b)]. Such distribution is visible in both slow and fast movements, likely originating from errors in the planning process. Furthermore, the length of the major and minor axes has been related to variability

of movement extent and directional errors, respectively [Gordon et al. (1994b)]. The former increases with target distance; the latter seems independent from it as, for distant targets, it increased together with peak velocity [Gordon et al. (1994b)]. These results suggest that movement direction and extent are two parameters which are set separately in the brain. Specifically, movement direction may be linked to the selection of a particular spatiotemporal activation of muscles; conversely, movement extent may correspond to a specific degree of activation of the muscles [Gordon et al. (1994b)]. Despite this reasoning, it is hard to believe that joint angles and torques, extent and direction are mechanically independent. In fact, the initial resistance of the limb is the main biomechanical factor that causes variations of velocity and acceleration with different directions [Gordon et al. (1994a)].
Other studies showed that accelerations were greatest in the two directions of least inertial resistance, i.e. perpendicular to the forearm; and lower for movements directed on the axis of the forearm [Gordon et al. (1994b); Gordon et al. (1994a)]. Moreover, directional changes in movement duration compensated for the differences in accelerations. This means that when subjects program the initial force to accelerate the hands, they do not totally take into account direction-dependent differences in inertial resistance. Additionally, seeing the cursor during a movement largely reduces errors and increases movement accuracy [Gordon et al. (1994b); Gordon et al. (1994a)], probably due to a greater ability to compensate for direction-dependent variations for limb inertia.
Altogether these results, suggest a set of considerations: (i) healthy subjects planned reaching movements in a hand-centered coordinate system using the direction and the extent of hand movement; (ii) the nervous system might not fully preplan the actual kinematic changes and the time course of the movement; (iii) an accurate movement planning requires a model of mechanical properties of the arm that is possible thanks to the proprioception contributes; (iv) the internal model of the dynamic properties of the limb used for planning reaching movements require continuous updating.

2.2 Beta oscillatory activity

Changes in brain oscillations are related to the activity level of neuronal populations [Nauhaus et al. (2009)], as well as to the degree of spike synchronization [Denker et al. (2011)]. Moreover, oscillations at different frequencies reflect different neuronal populations and network states, given that the main frequency of brain oscillations is associated with the underlying excitation-inhibition balance, and the extent of neuronal networks [Kopell et al. (2000); Whittington et al. (2000); Brunel and Wang (2003); Jensen et al. (2005); Miller (2007)]. At the

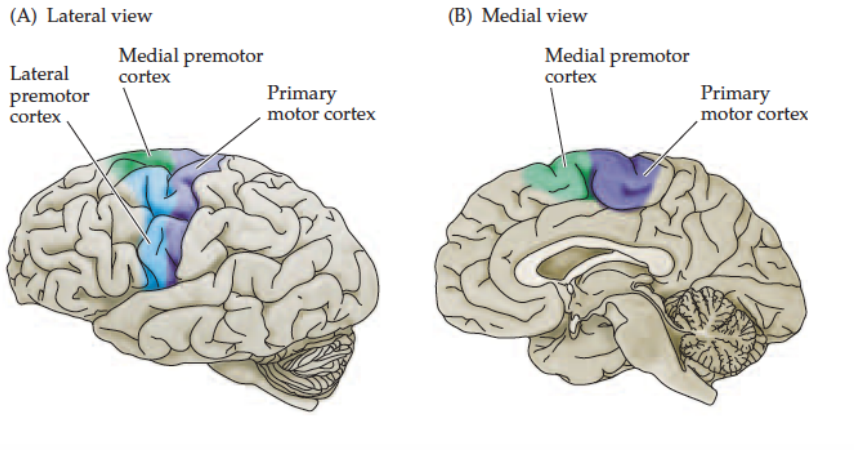

Figure 2.1 Lateral and medial view of the primary motor cortex and the premotor area in the human cerebral cortex [Purves et al. (2001)]

present time, it is not clear whether such oscillations have specific functions or instead if they are a by-product of brain activity. Hypothesis on their role include heightened visuomotor attention [Roelfsema et al. (1997); Classen et al. (1998)]; top-down control [Buschman and Miller (2007); Siegel et al. (2012)]; promotion of the existing cognitive states [Engel and Fries (2010)].
Voluntary movements are associated with EEG oscillatory activity in different frequency bands [Babiloni et al. (2016); Babiloni et al. (2017)]. In particular, the power of beta rhythm (15–30 Hz), recorded over sensorimotor areas, decreases before movement onset, reaches its negative peak during execution (event-related desynchronization, ERD) and sharply rebounds afterwards (event-related synchronization, ERS; [Pfurtscheller and Da Silva (1999); Kilavik et al. (2013)]; Fig. 2.2).

ERD was reported for finger movement, as well as for foot, tongue, wrist and shoulder movements [Crone et al. (1998); Pfurtscheller and Da Silva (1999); Stancak (2000); Alegre et al. (2006); Gaetz et al. (2010)]; moreover, both self-paced and stimulus-triggered movements show ERD [Alegre et al. (2006); Gaetz et al. (2010)]. Such desynchronization lasts for the whole movement, until a muscle contraction is stable [Stancak and Pfurtscheller (1996); Baker et al. (1999); Erbil and Ungan (2007); van Elk et al. (2010)]. Several studies investigated whether ERD amplitude differed with movement types: results showed that it was independent from movement speed [Stancak and Pfurtscheller (1995); Stancak and Pfurtscheller (1996)], number of fingers involved [Salmelin et al. (1995)], type of grip, [Stancak et al. (1997); Pistohl et al. (2012)], type or amount of information about the move-

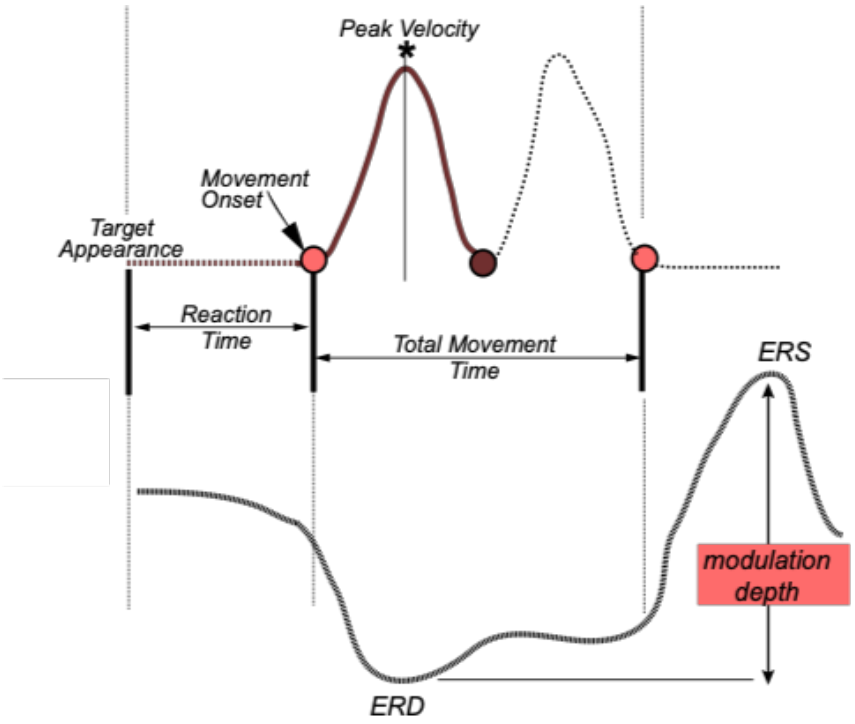

Figure 2.2 Definition of ERD, ERS and modulation depth with respect to movement

ment [Leocani et al. (2001)], subject's focus on speed rather than accuracy and vice versa [Pastotter et al. (2012)]. ERD is noticeable over the two sensorimotor areas, with a contralateral preponderance [Salmelin and Hari (1994); Pfurtscheller et al. (1996); Stancak and Pfurtscheller (1996); Leocani et al. (1997), Leocani et al. (2001); Alegre et al. (2003); Rau et al. (2003); Bai et al. (2005); Doyle et al. (2005); Erbil and Ungan (2007)]. In addition, it can be detected, albeit with reduced amplitude, when a movement is imagined, observed, or passively executed [McFarland et al. (2000); Babiloni et al. (2002); Koelewijn et al. (2008)]. There is increasing evidence that ERD is functionally related to motor control, as motor impairment shows altered oscillatory activity. In fact, many studies support the idea that ERD denotes the activation of the sensorimotor cortex [Pfurtscheller and Da Silva (1999)], associated with an increase in corticospinal excitability [Chen et al. (1998)]. However, such hypothesis presents a few criticisms: first beta power is stronger during single-joint than during multi-joint movements [Stancak (2000)], despite the fact that complex movements require more cortical resources [Ehrsson et al. (2002)]. Second, force does not affect ERD [Stancak et al. (1997); Pistohl et al. (2012)], even though high forces induce stronger cortical activity than low forces [Keisker et al. (2009)]. Altogether, these finding suggest that ERD may reveal the union of sensory and motor factors [Muller et al. (2003)]; even though current

literature has not fully explained its functional role yet.
ERS occurs between 300 to 1000 ms after the end of a movement. A few works related ERS magnitude to movement speed [Parkes et al. (2006)]; however, the majority of the studies could not find such relationship [Stancak and Pfurtscheller (1995) Stancak and Pfurtscheller (1996)]. Another possibility is that ERS magnitude is related to static EMG activity [Demandt et al. (2012)], although the synchronization was detected even after imagined movements [Solis-Escalante et al. (2012)]. In fact, studies with transcranial magnetic stimulation (TMS), showed a reduction of corticospinal excitability between 700 and 1000 ms after the movement [Chen et al. (1998)], suggesting that ERS may reveal an active inhibition of motor networks [Solis-Escalante et al. (2012)]. Alternatively, the sensorimotor cortex may use the post-movement period to prepare itself to a new movement, thus resetting and recalibrating it [Gaetz and Cheyne (2006)]. Finally, part of the beta spectrum can facilitate sensorimotor signal transmission [Cassim et al. (2001)]; in this contex, ERS may represent the coordination of sensory inputs and motor outputs [Gaetz and Cheyne (2006)].
Another important point to consider is that beta oscillatory activity is affected by several aspects of the experiment that is performed. As an example, the sensorimotor beta power changes after the presentation of warning Cues [Rubino et al. (2006)]. Specifically, the power decreases in the contralateral sensorimotor area after the warning cue, returning to pre-cue level before movement-related ERD [Doyle et al. (2005); Alegre et al. (2006); van Wijk et al. (2009); Saleh et al. (2010); Tzagarakis et al. (2010); Pastotter et al. (2012)]. Such pattern has been detected in several paradigms, even though it is still not clear whether it is affected by the information provided by the cue or whether it is linked to the motor act [Fujioka et al. (2012)]. Also, 800 ms after the cue, the beta power starts increasing over sensorimotor and frontal areas [Alegre et al. (2004); Alegre et al. (2006); Fischer et al. (2010)]. Finally, beta power shows a further desynchronization starting 1-2 s before movement onset in upper limb tasks [Doyle et al. (2005); Tombini et al. (2009); van Elk et al. (2010)], specifically when a "GO" signal is predicable [Alegre et al. (2003); Alegre et al. (2006); Spinks et al. (2008)]. This pre-GO decrease, which has a contralateral preponderance, depends on load [Stancak et al. (1997)], uncertainty about the direction of the movement [Tzagarakis et al. (2010)], and subjects focus on speed rather than accuracy [Pastotter et al. (2012)]. Indeed, it has been related to movement preparation [Wheaton et al. (2008)] and response selection [Doyle et al. (2005); van Wijk et al. (2009)] and thus linked to movement related ERD [Kilavik et al. (2013)]. A last consideration concerns the peak frequency of all these phenomena: beta ranges from 13/15 to 25/30 Hz, including different rhythms that may be mixed together hiding different sources and mechanisms [Salmelin et al. (1995); Szurhaj et al. (2003)].

Overall, there is no clear evidence as to whether ERD and ERS characteristics are related to specific movement attributes [Salmelin et al. (1995); Stancak and Pfurtscheller (1995); Kilavik et al. (2013)] or whether they change with aging or neurodegenerative processes [Dushanova et al. (2010); Gaetz et al. (2010); Heinrichs-Graham et al. (2018)]. A recent study, indicated that, during practice in a reaching task, ERS magnitude increases [Moisello et al. (2015b); Nelson et al. (2017)], independently of possible changes in mean power. Such practice-related increases were also evident in the beta modulation depth, computed as the ERS-ERD peak-to-peak difference. Importantly, beta modulation decreased to baseline levels twenty-four hours later and the magnitude of its increase during practice was correlated with retention of motor skill tested the following day [Nelson et al. (2017)]. Also, the changes in movement-related beta modulation did not correlate with the increased speed or improvements in other kinematic measures that occurred during the task. Increases of beta power have been associated with high GABA levels and a reduction of cortical excitability in animal and human studies [Jensen et al. (2005); Roopun et al. (2006); Hall et al. (2010), Hall et al. (2011); Muthukumaraswamy et al. (2013); Rossiter et al. (2014)]. In this context, the recurring activation and inactivation of the sensory and motor areas during our task with repetitive reaching movements may be an appropriate scenario to trigger long-term potentiation (LTP)-related phenomena and may result in an increase of beta modulation depth. In turn, such increase may reflect a progressive saturation of the mechanisms related to LTP-like plasticity. This interpretation is supported by recent observation that the beta modulation amplitude is linked to movement adaptation to new sensorimotor transformations and thus to formation of new internal models [Tan et al. (2016)]. Other support comes from previous finding that movement-related beta modulation does not significantly increase with practice in patients with Parkinson's disease (PD) [Moisello et al. (2015b)], a disease that is accompanied by a decrease of skill retention [Marinelli et al. (2009); Bedard and Sanes (2011); Moisello et al. (2015b)] and by deficits in the induction of use-dependent and LTP-like plasticity [Morgante et al. (2006); Kishore et al. (2012)].

2.3 Plasticity mechanisms

Neural plasticity is the ability of the brain to change in order to make memories and learn skills [Purves et al. (2001)]. Such mechanism is particularly evident in the developmental phase of neural circuits; even though also the adult brain shows a certain degree of plasticity [Purves et al. (2001)]. In fact, synaptic networks can be remodeled throughout life, through mechanisms of synapse formation, stabilization and elimination [Holtmaat and Svoboda

(2009)], other than rearrangements of existing networks [Purves et al. (2001); De Roo et al. (2008); Holtmaat and Svoboda (2009); Caroni et al. (2012)].
One of the main issues of investigating neural plasticity is the enormous number of neurons forming the human brain and the subsequent complexity of synapses [Purves et al. (2001)]. However, synaptic plasticity should be a fundamental property of neurons, that is evident also in simpler nervous systems [Purves et al. (2001)]. For instance, studies on primates revealed that the somatic sensory cortex changes its organization due to an amputation Merzenich et al. (1984)]. Also, studies in animals showed that new learning is correlated with enhanced synaptic dynamic [Caroni et al. (2012)]. Similar plastic changes have been demonstrated in the visual, auditory and motor cortices [Purves et al. (2001)], as a consequence of a peripheral deprivation or injury, but also because of sensorimotor experience [Jenkins et al. (1990)]. More recent studies in humans showed that motor training results in a rapid rewiring through the formation and elimination of synapses in the primary motor cortex, affecting different sets of synapses for different motor skills [Xu et al. (2009); Yang et al. (2009)]. Also, a repetitive motor learning task creates clustered synapses specifically confined to projection neurons driving activity-related muscles [Xu et al. (2009); Yang et al. (2009); Wang et al. (2011); Yu and Zuo (2011); Fu et al. (2012)]. Furthermore, changes in synaptic strength have been associated with recovery after diseases such as stroke [Caroni et al. (2012)].
Neural plasticity can be divided in two phenomena: short-term and long-term plasticity. Short-term plasticity typically ranges between milliseconds to minutes and involves modification of direction and duration of synaptic potentials; long-term plasticity is a longer phenomenon occurring within days, weeks or longer and causing changes in synaptic growth [Purves et al. (2001)]. Short-term plasticity consists in facilitation and depression, i.e. a temporary increase and decrease of synaptic strength, respectively. However, such transitory changes cannot explain memory formation and other long-lasting behaviors [Purves et al. (2001)]. In this context, a variety of studies have been investigating long-term plasticity, defining it the cellular correlates of learning and memory [Purves et al. (2001)]. Long-term plasticity can be divided in: long-term potentiation (LTP) and long-term depression (LTD), according to the direction of change in synaptic efficacy. LTP and LTD have been reported in various regions of the brain, showing input specificity and associativity [Purves et al. (2001)]. Specificity is defined as the selective stimulation of active synapses. In other words, when LTP is induced by the stimulation of one synapse, inactive synapses that contact the same neuron are not affected by it [Malinow et al. (1989)]. Associativity consists in the selective enhancement of simultaneous activations of synapse. In detail, if one synapse is lightly activated at the same time that a neighboring one onto the same cell is strongly activated, both undergo

LTP [Malinow et al. (1989)]. As a result of LTP and LTD the synapses are stabilized, thus producing behavioral learning [Caroni et al. (2012)]. In fact, new experiences, as well as subsequent training, promote synaptic stabilization [Holtmaat and Svoboda (2009); Xu et al. (2009); Yang et al. (2009)] that can be considered as a reversible property of synapses linked to plasticity [Caroni et al. (2012)].
Altogether, these results suggest that long-term neural plasticity is likely involved in memory formation; even though there is still a gap in the relationship between LTP and learning, memory, or other aspects of behavioral plasticity in mammals [Purves et al. (2001)]. As an example, it is not clear how learning becomes long lasting and how the amount of repeated training triggers memory consolidation and reconsolidation processes [Caroni et al. (2012); Lai et al. (2012)]. Answering to these questions is even more complicated considering that several factors influence the numbers, arrangements and dynamics of synaptic connections. For example, environmental enrichment, hormones, stress, seasonal changes [Caroni et al. (2012)]. Likely, learning is the result of a combinations of external and biological factors acting together in a global and local scale.

2.4 Motor learning

Motor learning skills are crucial in everyday life. Tasks as playing sports, instruments and teeth brushing could not be achieved without motor learning, retention and practice. Generally, motor learning can be defined as a progressive improvement in the velocity and accuracy of a movement [Willingham (1998)]. Furthermore, the process of learning a motor skill can be divided into fast learning, slow learning, off-line learning, retention. Especially, a motor skill is usually learned fastly over repeated practice, then it reaches a plateau (slow-learning), with an overall duration of the fast and slow learning which is task-specific [Dayan and Cohen (2011)]. Moreover, performance changes are detectable during training (online) and after it (offline learning or consolidation [Muellbacher et al. (2002); Robertson et al. (2004); Doyon and Benali (2005)]. Finally, retention is the maintenance of motor skills over time [Romano et al. (2010)]. Importantly, learning may be explicit or implicit: the former consists in a learning which is conscious; the latter is an incidental and automatic acquisition of information [Frensch (1998)].
Fast learning has been investigated in animals and humans, showing modulatory activity in various brain regions: prefrontal cortex, primary motor cortex and supplementary motor area (Fig. 2.1, 2.3; [Sakai et al. (1999); Floyer-Lea and Matthews (2005)]). Such complex pattern of activations and deactivations indicates that fast learning relies on different cortical

and subcortical regions. However, the motor cortex remains one of the most relevant brain regions. In fact, it shows interactions with the supplementary motor area at the beginning of an explicit sequence learning [Sun et al. (2007)], suggesting transformations between spatial and motor features of motor sequences [Hikosaka et al. (2002)]. Functional connectivity studies, aimed at evaluating the correlation or covariance between the activation of different regions [Friston (1994)], also revealed an interaction between prefrontal and premotor cortices [Sun et al. (2007)], likely due to the attentional demands of fast learning [Petersen et al. (1998); Hikosaka et al. (2002)].

Slow learning produces smaller behavioral gains, compared to fast learning [Karni et al. (1995); Ungerleider et al. (2002); Doyon and Benali (2005)] and its magnitude and time course are reported to be task-dependent [Dayan and Cohen (2011)]. Under certain conditions, motor performance requires lower attention, thus resulting into an automatic process that does not require executive and attentional networks and is not affected by interference [Schneider and Shiffrin (1977); Doyon and Benali (2005); Ashby et al. (2010)]. Studies on both motor and non-motor learning show that fast learning is characterized by an anterior activation of the brain which shifts toward more posterior regions during slow learning [Floyer-Lea and Matthews (2005)]. As for fast learning, the primary motor cortex is strongly involved in slow learning; functional Magnetic Resonance Imaging (fMRI) studies on finger movements showed a greater activation of this area lasting several weeks after the end of the practice [Karni et al. (1995), Karni et al. (1998); Floyer-Lea and Matthews (2005); Lehericy et al. (2005)]. Furthermore, slow learning is associate with structural plasticity, i.e. ability to change its physical structure, in both gray and white matter [May and Gaser (2006); Draganski and May (2008); Della-Maggiore et al. (2009); Johansen-Berg (2010); Tomassini et al. (2011)]. Specifically, subjects trained for three months to learn a three-ball juggling routine showed a gray matter expansion in the visual cortex, as well as in the intraparietal sulcus, two areas involved in visuomotor processing and movement perception [Draganski et al. (2004)], despite such increase and the task performance rebounded to baseline three months after the last training. The same result was replicated after a juggling test and a whole-body balance experiment [Driemeyer et al. (2008); Scholz et al. (2009); Taubert et al. (2010)]. Similarly, changes in white matter microstructure have been related to learning variations [Della-Maggiore et al. (2009); Johansen-Berg (2010)]; Tomassini et al. (2011)], and thus to changes in the velocity and synchronicity of impulse conduction between distant cortical regions, required to optimize the information flow during skills acquisition [Fields (2008)].

Offline learning consists in the consolidation of recently acquired memories [Dudai (2004)].

Such phenomenon is the combination of two processes, starting during practice and lasting over time after training [Dayan and Cohen (2011)]: performance improvement after a motor practice session [Robertson et al. (2004)]; reduction in fragility of a motor memory trace after encoding [Robertson et al. (2004); Robertson (2009)]. Forms of offline learning are affected by sleep, such as explicit motor sequence learning [Fischer et al. (2002)]; Korman et al. (2003); Diekelmann and Born (2010); while others are not sleep-dependent, i.e. implicit forms of sequence learning [Robertson et al. (2004); Song et al. (2007)]. Additionally, consolidated memories may be changed [Nader et al. (2000); Walker et al. (2003)].
Finally, retention is the phenomena controlling the maintenance of memories for extended periods of time. A small interval of explicit motor learning can generate long-term retention [Savion-Lemieux and Penhune (2005)], suggesting that retention is strongly related to consolidation [Dayan and Cohen (2011)]. Furthermore, other factors can positively affect retention: reward [Abe et al. (2011)]; Wittmann et al. (2011)]; and random or unpredictable order condition of the practice [Shea and Morgan (1979)].

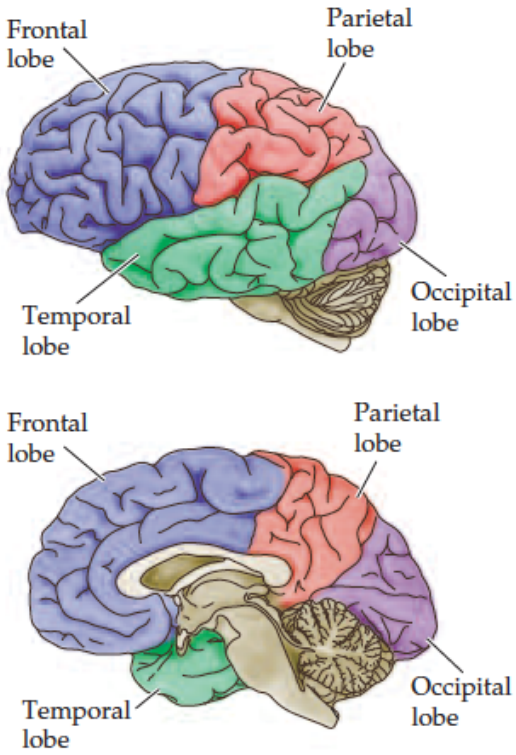

Figure 2.3 Subdivision of the cerebral hemispheres [Purves et al. (2001)]

2.5 The role of sleep

Human sleep is a highly regulated yet mysterious behavior involving multiple neuronal systems which implies that it is a behavior that performs some essential biological functions [Hobson (1989)]. Numerous functions have been proposed and studied, revealing that sleep is necessary for adjusting metabolic need, energy conservation, memory consolidation, brain waste clearance, development, modulation of immune responses, tissue restoration, yet a single core function remains elusive [Cirelli and Tononi (2008); Zielinski et al. (2016)].
The first stage of sleep (stage N1) is characterized by a slowing of the EEG activity, and a subsequent amplitude increase of cortical waves [Purves et al. (2001)]. Stage N1 is followed by stage N2, which consists in a further decrease in the frequency of the EEG waves and an increase in their amplitude, together with intermittent high-frequency spike clusters called sleep spindles [Purves et al. (2001)]. Sleep spindles are bursts of activity at about 10–12 Hz that generally last 1–2 seconds [Purves et al. (2001)]. Finally, in stage N3, the predominant EEG activity consists of very high-amplitude low frequency waves (delta 0.5–2 Hz) [Berry et al. (2017)]. Overall, the entire Non Rapid Eye Movement (NREM) sequence lasts approximately one hour and is followed by rapid eye movement (REM) sleep [Purves et al. (2001)] (Fig. 2.4). During REM sleep which lasts about ten minutes, EEG activity is similar to the awake state [Aserinsky and Kleitman (1955)]. Once a full cycle is completed, the brain cycles back to non-REM sleep for an average of five periods of REM sleep during an 8-hours sleep cycle [Foulkes and Schmidt (1983)]. Initial reports of REM sleep associated dreaming with this paradoxically wake-like state but recent work indicates that the ability to recall a dream is associated with a local decrease in SWA in both REM and NREM [Siclari et al. (2014); Siclari et al. (2018)]. NREM sleep is characterized by slow rolling eye movements. Also, muscle tone, body movements, heart rate, breathing, blood pressure, metabolic rate and temperature decrease [Foulkes and Schmidt (1983)]. Conversely, REM sleep presents blood pressure, heart rate, and metabolism similar to wake [Purves et al. (2001)], other than rapid eye movements, pupillary constriction, paralysis of large muscle groups and twitching of smaller muscles [Purves et al. (2001)]. Overall, sleep stages are defined through traits, i.e. muscle tone, eye movements, cortical EEG [Malhotra and Avidan (2013)]. The union of traits is defined by polysomnography and includes EEG, electrooculography (EOG), electromyography (EMG), electrocardiogram (EKG), snoring, nasal and oral airflow, chest and abdomen movements, pulse oximetry [Malhotra and Avidan (2013)].
The sleep-wake system is regulated by the interplay and interaction of two processes: one that

regulates the rise of sleep propensity during wake and its dissipation during sleep (Process S); a circadian process alternating periods with high and low sleep propensity based on a daily cycle (Process C). Furthermore, an ultradian process alternates NREM and REM sleep episodes [Borbély and Achermann (1999); Achermann and Borbely (2003)]. (Fig. 2.5). Briefly, process S, also defined as homeostatic process, rises during wake and declines during sleep [Borbély and Achermann (1999)]. Process C tends to synchronize the sleep-wake cycle with the environmental light-dark cycle. However, it is a self-sustained biological rhythm, meaning that in absence of any information about the time of the day it still maintains an approximately 24-hour cycle. Finally, there is another ultraradian rhythm, running between 90 and 110 minutes which controls for REM episodes [Achermann and Borbely (2003)] (Fig. 2.5).

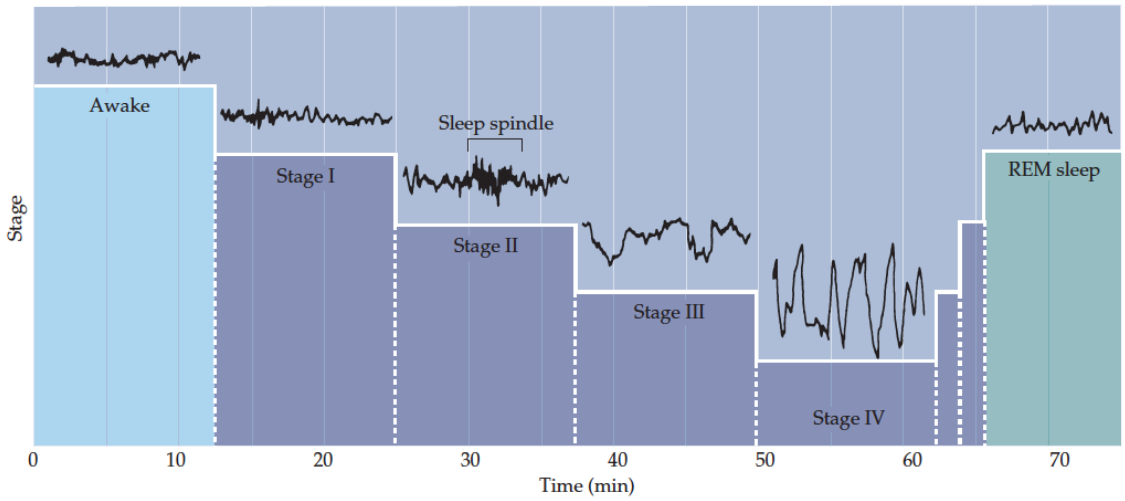

Figure 2.4 EEG recordings during the first hour of sleep [Purves et al. (2001)]

2.6 Sleep and Plasticity

Sleep is necessary for our brain functions; as such, without sleep we become irritable and tired. Conversely, after a night of sleep our brain and body feel restored [Tononi and Cirelli (2014); Tononi and Cirelli (2019)]. For all these reasons, sleep occupies several hours a day in all species [Tononi and Cirelli (2014); Tononi and Cirelli (2019)]. Sleep is characterized by a loss of vigilance, immobility and more generally by a disconnection from the environment [Tononi and Cirelli (2014); Tononi and Cirelli (2019)]. Furthermore, sleep loss alters synaptic strength and structural plasticity thus resulting in changes of the functional output of the

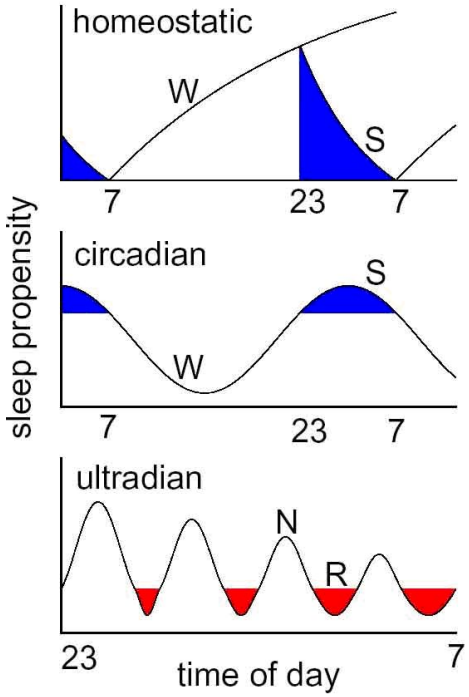

Figure 2.5 Three major processes underlying wake-sleep regulation: homeostatic, circadian and an ultradian process. W, waking; S, sleep; N, NREM sleep; R, REM sleep [Achermann and Borbely (2003)]

brain such as alertness, cognition, and mood [Raven et al. (2018)]. In this context, sleep has the ability to positively affect memory acquisition, consolidation and integration, defined as the integration of new materials with old memories [Bartlett and Bartlett (1995)McClelland et al. (1995); Tononi and Cirelli (2014)]. Moreover, sleep can protect declarative memory from interference Ellenbogen et al. (2006); Korman et al. (2007); Alger et al. (2012); Sheth et al. (2012)], as well as promote forgetting of details which are less integrated with the overall structure of knowledge [Hashmi et al. (2013)]. In this perspective, sleep may solve the plasticity-stability dilemma of learning new materials, without forgetting previously learned ones [Grossberg (1987); Abraham and Robins (2005)].

Despite its importance, it is still not clear which are the mechanisms behind sleep-dependent memory formation [Timofeev and Chauvette (2017)]. Currently, two main hypothesis are proposed: (i) synapses are potentiated during wake, and scaled-back during sleep, so that they become available for the learning tasks in the next day; (ii) sleep slow oscillations potentiate synapses that were depressed due to persistent activities during wake [Abel et al. (2013); Timofeev and Chauvette (2017)].

The Synaptic Homeostasis Hypothesis (SHY) belongs to the first group and suggests that sleep is required to restore synaptic strength and consequently consolidate learning and memories [Tononi and Cirelli (2014);Tononi and Cirelli (2019)]. Synaptic strength results into higher energy consumption, reduction of selectivity of neuronal responses and saturation of learning ability [Tononi and Cirelli (2014);Tononi and Cirelli (2019)]. According to SHY, sleep can reduce the burden of plasticity, while restoring neuronal selectivity and ability to learn. As discussed earlier, neurons are plastic and can enhance the strength of their synapses because of external stimuli. This mainly happens during wake when organisms explore and interact with the environment. In order to remain selective, the synaptic strength of neuron should be restored during sleep, that is a period of time during which the brain is disconnected from the environment. However, the brain cannot renormalize the total synaptic strength; in fact, synapses underused during the day would be weakened, resulting in loss of older memories [Grossberg (1987); Abraham and Robins (2005)]. Currently, it is not clear how the brain preserves old memories, while consolidating new ones. Existing hypothesis include: (i) proportional strength decreases during sleep [Hill et al. (2008)]; (ii) lower depression of stronger synapses compared to weaker ones [Olcese et al. (2010)]; (iii) protection from depression of neurons that fires strongly during sleep [Hashmi et al. (2013); Nere et al. (2013)]. Changes in synaptic strength may be detected by changes in Slow Wake Activity (SWA), as reported by animals studies [Huber et al. (2007); Vyazovskiy et al. (2008)]. Furthermore, slow oscillations producing SWA may directly affect synaptic

renormalization [Tononi and Cirelli (2014);Tononi and Cirelli (2019)]. In detail, synapses are potentiated due to learning in wake, this would produce higher neuronal firing rates and synchrony and finally high SWA during sleep leading to synaptic depression.
Finally, there are studies, not in agreement with the SHY hypothesis, suggesting that sleep may promote synaptic formation. For instance, three hours of recovery sleep after deprivation have been reported to be sufcient to restore synaptic density [Havekes et al. (2016); Raven et al. (2018)]. Additionally, studies on the visual cortex of mice, suggest that synapses are potentiated rather than downscaled during sleep [Aton et al. (2014); Raven et al. (2018)]. The same result was achieved by another research group working on ocular dominance plasticity [Frank et al. (2001); Raven et al. (2018)]. The general idea is that, during wake, the neural network is active and the synaptic efficacy is low [Timofeev and Chauvette (2017)]. Thus, waking is associated with high reliable steady-state synaptic dynamics, resulting in a not much plastic synaptic state [Timofeev and Chauvette (2017)]. As opposite, SWA reduces steady-state synaptic plasticity, that overall increases synaptic responsiveness [Timofeev and Chauvette (2017)].
Altogether, there is an extensive amount of literature supporting the idea of synaptic down-scaling across sleep. However, recent works supports the opposite view that sleep promotes synapse formation and sleep deprivation leads to synaptic loss. In this context, the direction of synaptic changes during sleep remains a controversial topic [Raven et al. (2018)].

2.7 Local sleep

Generally, when the brain is awake its electrophysiological activity is characterized by low-amplitude, high frequency fluctuations. Conversely, sleep EEG activity displays high amplitude slow waves. By staying awake too long both the wake and the subsequent sleep EEG activity show traces of the wake/sleep history with an increase of theta (4 – 8 Hz) and delta (0.5 – 4 Hz) power, respectively [Borbély and Achermann (1999); Finelli et al. (2000); Vyazovskiy and Tobler (2005); Leemburg et al. (2010)]. In addition, extended wake produces attention lapses, poor judgement and increase in the number of mistakes in cognitive tasks, without the feeling of sleepiness [Dijk et al. (1992); Van Dongen et al. (2003)]. Further, there is increasing evidence that sleep occurs not only within an entire organism, but also in localized areas [Huber et al. (2004); Hanlon et al. (2009); Murphy et al. (2011); Vyazovskiy et al. (2011a)]. For example, cortical areas directly engaged in learning a visuo-motor task showed a local increase in SWA during subsequent NREM sleep, which is correlated with performance improvements [Huber et al. (2004)]. Conversely, the local disruption of NREM

slow waves impaired further motor learning the next morning. This phenomenon was also visible during parasomnias, a disorder characterized by abnormal or unusual behavior of the nervous system during sleep [Nir et al. (2011); Howell (2012); Zadra et al. (2013)], as well in case of sleep deprivation [Vyazovskiy et al. (2011b); Hung et al. (2013); Bernardi et al. (2015)].

One of the first studies on local sleep during wake detected localized sleep-like periods following sleep deprivation and prolonged learning [Vyazovskiy et al. (2011b)]. In particular, rats were kept awake with novel objects while electrophysiological activity and performance were recorded. Results indicated both a global increase in the delta and theta power during wake, and an increase of local sleep episodes with time spent awake. Importantly, these local sleep events were not microsleep moments, i.e. small periods during which a person appears suddenly asleep [Tirunahari et al. (2003)], as the rats were fully awake. Performance analyses on a reaching tasks [Krueger et al. (2008)] revealed that OFF periods occurring in a brain area relevant for the behavior were associated with failures in the reaching. Of note, errors increased during the extended wake and the behavior became progressively unstable. With this study, [Vyazovskiy et al. (2011b)] concluded that local sleep is associated with sleep pressure and triggers behavioral deterioration. Indeed, local sleep may represent neuronal tiredness due to use-dependent factors, such as synaptic overload [Tononi and Cirelli (2006)].

A set of recent studies investigated the occurrence of local sleep in sleep deprived human subjects performing extended learning [Hung et al. (2013); Bernardi et al. (2015)]. The hypothesis was that the brain regions challenged by plasticity exhibit low frequency activity during wake followed by a more intense sleep. In order to test their hypothesis, the authors recorded high-density EEG on healthy subjects kept awake for 24-h performing either a language task or a visuomotor task. The former involved left fronto-temporal areas, the latter relied on occipito-parietal networks. Results highlighted: (i) a global increase of theta activity (5-9 Hz) with time spent awake; (ii) a local task-dependent increase in the power and amplitude of theta waves; (iii) a renormalization of both global and local increases after sleep; (iv) a correlation between regional theta power increases and higher reaction time and lapses in a psychomotor vigilance test; (v) a selective decline of performance only in in tests sharing the same neural substrate of task performed during the extensive wake.

Likewise, intracranial recordings in sleep deprived epileptic patients detected local slow/theta activity during wake which is associated with delayed behavioral responses in a face characterization psychomotor vigilance test, and attenuated, delayed and slower spiking responses of individual cortical neurons [Nir et al. (2017)]. Similarly, EEG recordings of astronauts in the International Space Station (ISS) revealed a relationship between local sleep events and

slower reaction times in docking a simulated vehicle [Petit et al. (2019)]. Even in this case, astronauts did not have a proper sleep schedule [Petit et al. (2019)]. No specific localization of local sleep episodes was detected in this study, probably due to the complexity of the tasks performed during the day and the small sample of participants. In addition, an EEG study on children tested in the morning and in the evening on an auditory attention task, associated theta events with slower reaction times, mostly in the premotor, parietal and somatosensory cortex [Fattinger et al. (2017)].

Speculation on these results associated fatigue, sleep pressure, and its consequent EEG theta increase with a localized reduction of neuronal activity, delayed responses and decrease in alertness [Nir et al. (2017); Petit et al. (2019)]. However, several points need to be addressed, as the topic has not been extensively investigated yet. For instance, all the studies were focused either sleep deprived subjects or children that are characterized by higher sleep need compared to adults [Fattinger et al. (2017)], thus making hard to discriminate between sleep pressure and task-related fatigue. Also, it is uncertain whether local sleep causes errors or rather errors produce local sleep. Finally, it is not clear whether local sleep represents micro sleep episodes of selected regions or instead if its activity is similar to those of sleep with a different underlying phenomenon.

Part I

LOCAL SLEEP AND LEARNING

Chapter 3

Neuronal fatigue after intense learning and the restorative action of nap

3.1 Introduction

Do local neural circuits fatigue, and why? Surprisingly, the answer to these questions is not clear. We do know, however, that our brain becomes tired by the end of a waking day, the more so the longer we have been awake, and that it needs sleep to be restored. We also know that the homeostatic regulation of sleep need can have a local component that can affect performance [Vyazovskiy et al. (2011b); Hung et al. (2013); Bernardi et al. (2015)]. In this work, we first sought to establish whether local neural circuits fatigue through intense training in an otherwise well-rested brain. To do so, we studied well-rested subjects who trained extensively in either a visuo-motor learning task or an explicit sequence learning task during the morning hours. We hypothesized that sEEG over cortical areas involved in learning would show a progressive power increase in low frequency activity, a phenomenon akin to local sleep as described after prolonged wake [Vyazovskiy and Tobler (2005); Hung et al. (2013); Bernardi et al. (2015)]. Moreover, we tested whether such local EEG changes would lead to progressive increase in errors in the performance of tests involving the neural circuits

The content of this chapter is part of two manuscripts in preparation as Aaron Nelson, Serena Ricci, Elisa Tatti, Priya Panday, Elisa Girau, Jing Lin, Brittany O. Thomson, Henry Chen, Giulio Tononi, Chiara Cirelli and M. Felice Ghilardi. 2020. "Neural fatigue due to intensive learning is reversed by a nap but not by quiet waking" and Serena Ricci, Elisa Tatti, Aaron Nelson, Priya Panday, Henry Chen, Giulio Tononi, Chiara Cirelli and M. Felice Ghilardi. 2020 "Extended visual sequence learning leaves a local trace in the spontaneous EEG that can be rescued by a nap"

fatigued by learning. If so, it would be important to know whether local neuronal fatigue is caused primarily by a sustained increase in neural activity associated with task performance or by the cumulative cellular costs of synaptic plasticity associated with learning [Tononi and Cirelli (2014)]. We reasoned that, if local sleep during wake were mainly due to excessive neuronal activity, leading to a depletion of energy supply, and not to synaptic plasticity, then a period of rest in quiet wake should restore both EEG activity and test performance. Conversely, if local sleep were due to wake-induced plasticity, restoration of EEG activity and performance should require a period of sleep and the associated synaptic renormalization. Thus, we examined whether sEEG and performance after a morning of extended learning in a motor task would be restored by an intervening period of quiet wake or only by an equivalent period of sleep (nap). To test our hypothesis, we employed three tasks with different learning characteristics and relying on different neural substrates. Specifically, for extended motor learning, we employed a reaching movement task with adaptation to a visually rotated display, ROT, a task that depends on the activity of sensorimotor and frontal areas [Ghilardi et al. (2000); Huber et al. (2004); Perfetti et al. (2011b)]. For the control experiment, we used MOT, a reaching movement task without the learning adaptation component. MOT has the same basic kinematic demands of ROT and activates the sensorimotor network similarly to ROT. However, unlike MOT, the adaptation learning typical of ROT requires further activity of frontal and right posterior parietal regions [Ghilardi et al. (2000); Huber et al. (2004); Perfetti et al. (2011b)]. Also, we performed VSEQ, a visual sequence, declarative learning task with attentional and working memory components involving frontal and occipito-temporal areas [Ghilardi et al. (2003), Ghilardi et al. (2009); Moisello et al. (2013)], to test whether our results were specific of motor learning or if they could be extended to other types of learning. The effects of extended training were assessed using two performance tests: *mov* (reaching for random targets), a test with kinematic features and involvement of sensorimotor areas like ROT and MOT; *mem*, a test that, like VSEQ, involves attention/spatial working memory and and fronto-occipito-temporal areas but not motor activity.

3.2 Materials and Methods

3.2.1 Subjects

For this study we tested a total of 89 right-handed healthy subjects (age range: 19-35 years, mean $\pm$ Standard Deviation - SD 23.7 $\pm$ 3.9 years, 49 female). All subjects did not have any history of sleep, medical disorders or vision impairment and were asked to maintain

consistent bed rise times and a total sleep of 7-8h/night, filling daily a sleep diary for one week before the experimental session. Moreover, they were asked to abstain from alcohol and caffeine-containing beverages starting the night before and throughout the experiment. The study was approved by the local Institutional Review Board (IRB) and all the subjects signed and IRB-approved consent form. Subjects were randomly assigned to three different conditions defined in the text as ROT, MOT and VSEQ (Tab. 3.1)

Table 3.1 Number of subjects collected for each condition and group and number of subjects whose EEG data was excluded from the analysis due to a technical problem during the acquisition. Note: In VSEQ we excluded 9 subjects in the morning (M) and 2 additional subjects in the afternoon (A)

	N	**Age**		**Female**	**Nap (N)**	**Quiet Wake (W)**	**Excluded EEG**	
		Range	**Mean + SD**				**sEEG**	**Task**
ROT	36	20 - 33	23.6 ± 3.5	19	20	16	11	15
MOT	11	20 - 34	24.7 ± 4.7	8				
VSEQ	42	19 - 35	23.6 ± 4.1	41	23	19	9M + 2A	13

3.2.2 Experimental Design

Subjects arrived in the lab by 8 AM and were fitted with hd-EEG cap (256 channels, HydroCel Geodesic Net). Data collection started around 9 AM and lasted until 3 PM (Fig. 3.1). Participants were seated in front of a screen and underwent a baseline recording that included 2-minute sEEG with eyes opened and closed and two tests, *mem* and *mov* (described below). After the baseline, they performed three 45-minute session of ROT, MOT or VSEQ according to their condition, each followed by sEEG and the two tests. After three blocks, subjects belonging to ROT and VSEQ condition had lunch and were randomly assigned to one of two groups: nap or quiet wake (Tab. 3.1). The nap group was asked to sleep for 90 minutes; while quiet wake group rested with eyes closed while listening to a series of guided meditation and audio books for 90 minutes. After 90 minutes all the subjects performed a final block with sEEG, *mem*, *mov* and task (ROT or VSEQ, Fig. 3.1). The final block was performed within fifteen-thirty minutes after the end of either the nap or the quiet wake. High density EEG was recorded throughout the entire session. Experimenters took turns to ensure adherence to the protocol throughout the entire experiment. In particular, during all tasks and EEG recordings, the experimenters alerted the participants when signs of drowsiness were

detected. Due to a technical problem affecting the amplifier of the EEG system, we had to discard EEG data from a few subjects (Tab. 3.1). Behavioral data were not affected by this issue and thus we could include all the subjects in the behavioral analyses.

mov

In this planar upper-limb reaching test, a target appeared on a screen in non-repeating, unpredictable order at 3-s interval together with a central fixed starting point. Targets were at three different distances (4, 7 and 10 cm) and eight directions (45° separation). Subjects were asked to perform 96 out and back overlapping movements, reaching for targets as soon and as fast as possible, but without anticipating or guessing the target position (Fig. 3.1).

mem

This learning test is about encoding visual sequences without any motor activity. After three warning flashes, five or six out of eight targets successively lightened up on a screen for 250 ms at a 1-s time interval (Fig. 3.1). Subjects were asked to memorize the target sequence, to hold it in memory for 10 s, to report verbally the order of the sequence and to be ready for the one. For sequence verbalization, a color-coded target array was presented, and subjects reported the order by mentioning the corresponding color. Sixteen different sequences were presented in each of sessions.

ROT

In this motor adaptation task (Fig. 3.1), a circular array of eight targets (4 cm from a central starting point) was presented on a screen together with a cursor indicating the hand position. Targets lighted up in a random, unpredictable order, one every 1.5 seconds; they were presented in 21 sets of 56 with 30 second inter-set intervals. Subjects were asked to make out-and-back movements with their right hand by moving a cursor on a digitizing tablet and reaching the highlighted target “as soon as possible” and “as fast and as accurately as possible”, thus minimizing reaction and movement time, but avoiding anticipation. Unbeknownst to subjects, the direction of the cursor on the screen was rotated relative to the direction of the hand on the tablet in incremental steps of 10°, 20° or 30° each, either clockwise or counterclockwise, starting from 0° (no rotation of the cursor) up to a maximum of 60°. For each rotation step, subjects performed two sets of movements (112 movements, Tab. 3.2) Importantly, all the ROT blocks started ended with two sets of movements without rotations to avoid interference with performance in the *mov* test.

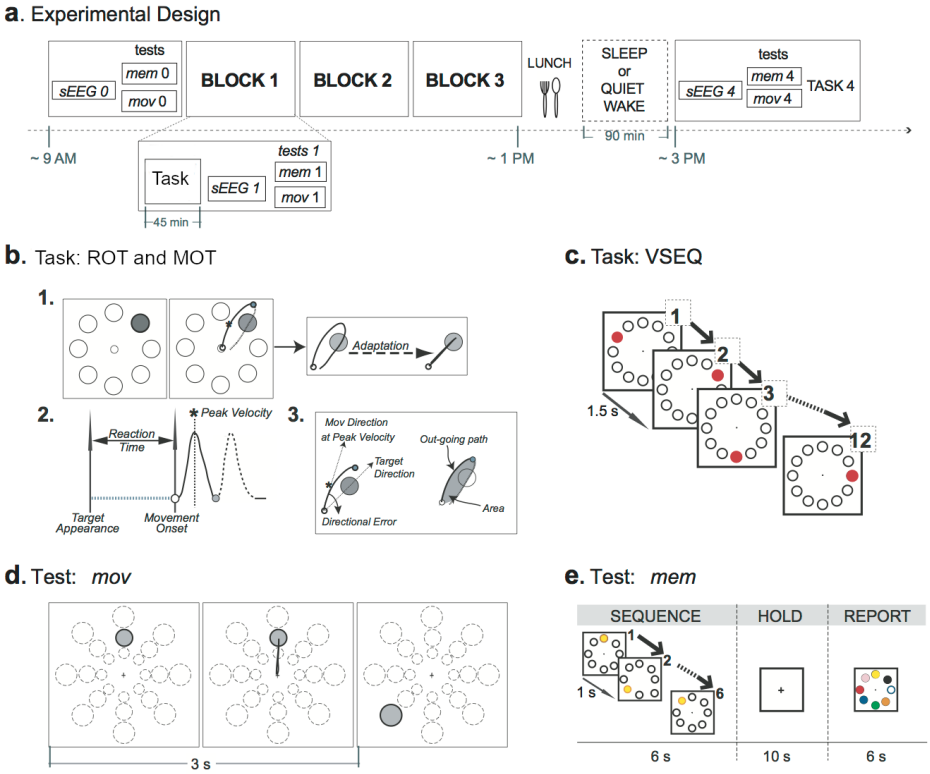

Figure 3.1 a. Experimental design. After a baseline, which included two-minute sEEG (sEEG0) and two tests (*mov0* and *mem0*), subjects completed three blocks, each with a 45-minute task (ROT, MOT or VSEQ, according to the assigned condition), sEEG and the two tests. After lunch, a group took a 90-minute nap, whereas the other remained awake and quietly rested for the same amount of time. sEEG was then recorded followed by the two tests and a task block (block4). b. 1. ROT is a visuomotor adaptation task, where adaptation to a rotated display occurs progressively and implicitly with reduction of directional errors; during MOT instead visuo-motor rotation did not occur and subjects had to reach for targets using a mouse. 2. Velocity profile of a reaching movement; the asterisk represents the point of peak velocity. Reaction time is defined as the difference between target appearance and movement onset. 3. Directional error at peak velocity and normalized hand path area. c. VSEQ is a visual sequence learning task in which participants learned 12-element sequences continuously for 45 minutes. The same sequence was repeated until subjects reached full score. d. *mov* is a test of reaching movements without adaptation with 24 possible targets located at 4, 7 or 10 cm from the center in eight directions. e. *mem* is a visual working memory test without learning component. Instructions were to memorize a sequence, to hold it in memory for 10 s and then to report it, before moving to the next one; the test consisted in 16 sequences.

Table 3.2 Degrees of visuo-motor rotation in the four ROT block. Each level of ration was repeated for 112 movements

Degrees of Rotation in ROT [°]			
Block1	**Block2**	**Block3**	**Block4**
0	0	0	0
10	20	-10	-10
20	30	10	-20
30	10	-20	-30
40	30	0	-40
50	40	-20	-50
60	20	-30	-60
50	10	-10	-50
40	-10	10	-40
30	-30	20	-30
20	-20	0	-20
10	10	-10	-10
0	0	0	0

MOT

In this control motor reaching task, target array and presentations were the same as in ROT. Subjects were asked to make out-and-back movements with the same instructions as for ROT. However, no cursor rotations were imposed. Subjects performed a total of 20 sets of 56 movements in every session (Fig. 3.1).

VSEQ

Subjects were asked to learn 12-element spatial sequences presented on a screen (Fig. 3.1). Twelve equidistant targets were displayed on the screen. Every 1.5 s one target randomly blackened for 300 ms in repeating sequences of twelve, with a target appearing only once in a sequence. A verbal report of the sequence order was collected every three complete presentations (i.e., set) of the sequence, using a color-codes pallet, as for *mem*.

3.2.3 Kinematic analyses

Kinematic data were collected with custom-designed software by E.T.T. s.r.l., MotorTaskManager Genoa, Italy. For each movement, we computed, among other parameters: directional error at peak velocity, hand-path area (area included in the trajectory normalized by path length, a measure of inter-joint coordination and thus of trajectory accuracy), reaction time,

movement time, peak and mean velocity. For each rotation step in ROT, we computed the adaptation reached in the last eight movements in percentage as: % Adaptation=[1-(average DirErr/imposed rotation)] *100. Mean adaptation rate of a block was measured as the average of all rotation steps in that block. This index of adaptation rate is based on the changes of directional errors normalized by each step of rotation and their starting point [Moisello et al. (2015a)]. For *mov*, we also computed the number of correct movements, defined as movements with values of reaction time, normalized movement area or directional errors within 1.5 standard deviation of the mean of the baseline *mov0*. Importantly, also in ROT and MOV, movements whose parameters exceed 1.5 standard deviation of the mean were excluded from the analyses.

3.2.4 EEG analyses

EEG Recording

High density EEG (256 electrodes; Electrical Geodesic Inc., Hydrocel net, Eugene, OR) was recorded with a sampling rate of 250 Hz, using the Net Amp 300 amplifier and Net Station 5.0 software (Electrical Geodesic Inc, Eugene, OR). Impedance was maintained below 50 kΩ throughout the whole session. During the recording, the signal was referenced to the vertex (Cz).

EEG Recording

Data were preprocessed using the public Matlab toolbox EEGLAB version 14.1.1 [Delorme and Makeig (2004)]; the signal was filtered between 1 and 80 Hz using a Finite Impulse Response filter (FIR) between 1 and 80 Hz and a Notch filter centered at 60 Hz. Then, the recording was divided into 4-s epochs and visually examined to remove epochs and channels containing artifacts, defined as evident abnormalities of the signal, such as abnormal tension, bursts and other involuntary movements [Cohen (2014)]. Additionally, we applied Independent Component Analysis (ICA) with Principal Component Analysis (PCA)-based dimension reduction [Jung et al. (2003)] in order to remove stereotypical artifacts such as blinks, eye movements and motion-related signals. Afterwards, channels previously removed were interpolated using spherical spline interpolation and electrodes located on the face and neck were removed from the analyses. This results in 180 channels which were averaged referenced before being analyzed.

sEEG

We first computed power-spectral representations using the fast-Fourier transform function of Fiedltrip toolbox for Matlab [Oostenveld et al. (2011)]. For each subject, the power at each channel was normalized by the baseline, i.e. the first sEEG recorded at the beginning of the day, within five frequencies ranges (SWA also called delta 1 – 4 Hz; theta 4.5 – 8 Hz; alpha 8.5 – 13 Hz; beta 13.5 – 25 Hz; gamma 25.5 – 35 Hz), according to the following equation: $\frac{sEEG-sEEG0}{sEEG0}$ Differences in the spontaneous EEG activity across the morning sessions were assessed using cluster-based nonparametric permutation testing. Specifically, nearest neighbor channels were determined via triangulation with three as the minimum number of significant channels for inclusion in a cluster. The reference distribution was created using the Monte Carlo method with 10,000 random iterations and a critical alpha of 0.05 was used at the cluster level [Maris and Oostenveld (2007)]. This method allowed to determine topographical regions of interest (ROI) in which there was a significant power difference in two recordings.
To assess whether 90-minute nap or quiet wake provoke changes in the sEEG, we compared the power spectra of sEEG4, after the nap, with those of sEEG3, recorded at the end of the morning. Specifically, we evaluated the global power spectra, as well as, a personalized and local ROI, defined as the region showing significant sEEG3 differences from baseline and correlating with the activity during the task. Specifically, for each subject and condition, we defined the ROI, selecting the electrode with the highest theta power in sEEG3 and its six closest neighbors, within the group of electrodes forming an average cluster in sEEG3. For both sEEG3 and sEEG4 the power across the ROI was averaged to detect differences in the nap and quiet wake groups.

ROT, MOT and VSEQ

In ROT and MOT, epochs associated with invalid movements, were rejected from the EEG recording. Then, frequency representations of all the tasks were computed within the five frequency ranges using Complex Morlet Wavelets at linearly spaced frequencies (0.5 Hz bins) and a constant time window (1.5 s). The number of wavelets cycles and length were increased as a function of frequency (cycles 3 to 10; length 2.5 to 0.17 s). Nonparametric cluster-based permutation testing was performed to define significant ROIs, as for the sEEG activity. Particularly, we were interested in evaluating task differences between the first and the last set of VSEQ sequences and ROT/MOV movements in the first session.

Sleep and quiet wake

EEG recorded during the nap and the quiet wake period was scored for sleep stages [Iber et al. (2007)] using an open source, Matlab based toolbox [Mensen et al. (2016)]. Recordings were scored in 30-s epochs as follows: wakefulness (W), NREM sleep stage 1 (N1), NREM sleep stage 2 (N2), NREM sleep stage 3 (N3). REM sleep (R) was not present in either group. Transition from wakefulness (W) to stage N1 were associated with the disappearance of the rhythms such as posterior alpha oscillations (8–10 Hz) and slow rolling eye movements. K complexes and sleep spindles marked the transition to N2. The transition and maintenance of N3 was determined by occurrence of >75 uV slow waves for more than 20 % of the epoch. Sleep scoring was performed on classical derivations from the 10–20 montage (F4, F3, C4, C3, P3, P4, O1, O2), with a mastoid reference.

3.2.5 Statistical Analyses

Differences in behavioral performance across blocks were tested with repeated measure analysis of variance (ANOVA) with sets as within-subject factor. ANOVAs were followed by post-hoc tests (with Bonferroni correction for multiple comparisons when appropriate). Greenhouse-Geisser correction was applied when required. Paired t-tests were implemented: (i) to compare performance at baseline to that at the end of the morning in *mov* (number of correct movements, *mov3* vs *mov0*) and *mem* (number of correct sequences, *mem3* vs *mem4*); (ii) to verify the within-group effects of a nap and quiet wake (block3 vs. block4) on measures of ROT (adaptation, reaction time and hand-path area), MOT (reaction time and hand-path area), VSEQ (number of memorized sequence, number of repetition required to learn a sequence), *mov* (number of correct movements) and *mem* (number of correct sequences). Pearson coefficients were used to explore significant correlations between: performance measures and sEEG changes; sEEG power changes after a nap and sleep parameters; local power changes occurring during both the task and sEEG; performance changes and sleep parameters. For each analyses Bonferroni corrections was used in case of multiple comparisons. Nonparametric cluster-based permutation testing was used to assess EEG difference between sEEG recordings and task repetitions, as described in the previous paragraph.

3.3 Results

3.3.1 Extensive learning produces a local trace in the spontaneous EEG

For all the conditions, we firstly characterized the task and then investigated power differences comparing sEEGs recording after each session with sEEG0 recorded at the beginning of the experiment. Additionally, we correlated sEEG power differences with task-related changes. Overall, we found local and task-specific EEG changes progressively involving lower frequencies.

ROT

During the three sessions of ROT, subjects adapted their movements to the rotated display implicitly and constantly by decreasing their directional error. Repeated measure ANOVA showed that the degree of adaptation to the rotated display did not differ across the three blocks ($F_{(2,\,70)} = 0.28, p = 0.758$, Fig. 3.2). Also, reaction time and hand-path area displayed a small but significant decrease across blocks ($F_{(1.5,\,52)} = 4.43, p = 0.026; F_{\mathrm{F}(1.5,\,52)} = 12.126; p < 0.001$, respectively; Fig. 3.2). In particular, hand-path area decreased across blocks with significant differences between the firsts two blocks and the last one (two-tailed paired t-tests with Bonferroni correction: block1 vs. block2: $t = 2.175, p = 0.11$; block1 vs. block3: $t = 4.099, p = 0.001$; block2 vs. block3: $t = 3.95, p = 0.001$; Fig. 3.2), suggesting the achievement of better inter joint coordination. Similar results were found for reaction time (block1 vs. block2: $t = 0.70, p = 0.9$; block1 vs. block3: $t = 2.56, p = 0.046$; block2 vs. block3: $t = 3.35, p = 0.008$; Fig. 3.2). In summary, we found minor, but significant practice-related improvements across ROT sessions.

In previous studies, sEEG recorded after visuo-motor adaptation tasks showed power increases over the areas mostly engaged during the exercise. This trace was around 10 Hz when a single 40 minute-practice block was used in normal wake conditions [Landsness et al. (2011)], and moved to lower frequencies (5-9 Hz) when several practice blocks were used during extended wakefulness [Hung et al. (2013); Bernardi et al. (2015)]. Such power changes could result from extended practice, prolonged wakefulness, or a combination of the two.

To tease them apart, here we first determined the EEG correlates of adaptation practice during the task by comparing recordings during the last and the first sets of ROT1 movements, using cluster-based analysis. Consistent with previous studies using reaching movements [Perfetti et al. (2011b); Perfetti et al. (2011a); Moisello et al. (2015b); Moisello et al. (2015a);

Nelson et al. (2017)], we found a regional pattern that reflects the activation of frontal and sensorimotor areas during practice. This pattern included significant power increases over frontal areas in the alpha (mean± Standard Error SE: 37±11%, cluster T=49.21; p=0.003), beta (24±7%, cluster T=40.25; p=0.006) and gamma (24±6%, cluster T=86.89; p=0.002) ranges; over the left parietal area in alpha (28±9%, cluster T=21.60; p= 0.007) and beta (21±6%, cluster T=33.17; p=0.006) ranges; over the right parietal area in alpha (29±9%, cluster T=14.84; p=0.007) and beta (20± 6%, cluster T=15.05; p=0.011) ranges; and over a small right occipital cluster in alpha (25±7%, cluster T=13.76; p=0.007; Fig. 3.2, 3.3) range. We then determined whether the EEG correlates of adaptation changed after extended morning practice during ROT3. The pattern was somewhat different (Fig. 3.4), with the presence of a significant cluster in the theta range over the frontal area extending posteriorly to the right parietal area and to the left parietal-occipital region and an enlargement of the frontal cluster in alpha. Interestingly, as opposed to ROT1, there was no significant cluster in the gamma range (Fig. 3.4). We then compared the sEEG power topography after each ROT block (sEEG1, sEEG2, sEEG3) with that of the sEEG recorded before ROT1 (sEEG0; N=25; Fig. 3.2). Significant changes became apparent in sEEG2, with power increases in the alpha range over a left fronto-central area and in the beta range over a left centro-parietal cluster (mean±SE: 19±4%, cluster t=157.65, p<0.005; Fig. 3.2, 3.3). A non-significant increase in the theta range over a centro-frontal area (38±15%) was also present in sEEG2 and became significant by the end of the morning, in sEEG3 (41±11%, cluster t=138.50, p<0.005). Cluster-based analysis in sEEG3 also revealed significant increases in the alpha range in two symmetrical centro-parietal areas (left: 49±14%, cluster t=44.96, p<0.005; right: 45±12%, cluster t=58.42, p<0.005) and in the beta range over a large cluster of electrodes in a centro-parietal area mostly on the left (27±7%, cluster t=217.75, p<0.005). There were no significant changes in the gamma range.

Altogether, these results show that intense training leads to sEEG local power increases that spread from beta and alpha to theta ranges. Importantly, the sEEG increases in theta power were mostly localized to the electrodes that showed the effects of practice during ROT (Fig. 3.2), suggesting a link between EEG changes during the task and those in the sEEG. To formally test this link, we determined whether the theta frontal changes in the sEEG3 correlated with power changes in the same region ROT1. We focused on ROT1 to assess the effects of learning-related activity *per se* during ROT because ROT3 was likely affected by consolidation processes as well as by fatigue that presumably accumulated across the three ROTs. Indeed, in the frontal cluster, alpha and beta power changes during ROT1 positively correlated with theta power increases in sEEG3 ($r = 0.67, p = 0.006; r = 0.70, p = 0.003$,

respectively, p corrected for multiple comparisons, Fig. 3.2), while correlation with gamma changes in ROT1 did not reach significance ($r = 0.25, p = 0.29$). Thus, progressive low frequency increases in sEEGs might be related to local traces of learning-related activity in higher frequency ranges during the task itself. Local sEEG power increase in low frequencies was also linked to learning improvements in ROT3. Specifically, we found significant correlations between the increases in trajectory accuracy and in theta power over the frontal cluster in sEEG3 ($r = 0.55, p = 0.003$). Overall, these results suggest that intense daytime learning, even without sleep deprivation, leads to local power increases in the sEEG that first involve the beta and alpha ranges and later spread to the theta range. A significant local increase in theta power occurs after three learning blocks and is associated with learning-related power increases in the alpha and beta ranges that occur over the same areas in the initial phases of learning (ROT1). Also, this local increase of theta power is positively correlated with improvement in task performance, further suggesting that it could reflect fatigue due to plasticity-related phenomena.

MOT

Following the same pipeline of ROT, we found that there were no significant changes of performance indices across the three blocks, including reaction time (N=11, $F_{(1.1,\ 10.82)} = 0.56, p = 0.58$), hand-path area ($F_{(1.22,\ 12.2)} = 0.020, p = 0.93$), peak velocity ($F_{(1.1,\ 11)} = 1.006, p = 0.384$), suggesting that no significant learning occurred across blocks (Fig. 3.5). We first determined the EEG correlates of practice in MOT by comparing recordings during the last and the first set of MOT1 (Fig. 3.5; 3.6). We found significant increases in the theta range over the left area (35±11%, cluster T=32.82, p=0.025); in the alpha range over a left cluster (20±6%, cluster T=85.14, p=0.013) and in the beta range over two clusters, one over the left region (13±3%, cluster T=129.2, p<0.001) and the other over a frontal area (13±3%, cluster T=146.2, p<0.001). In MOT3, beta activity was reduced and there was only a significant increase in the theta range in a cluster over the left area (30±11%, cluster T=29.2, p=0.046, Fig. 3.4).

We then compared sEEG1, sEEG2 and sEEG3 to sEEG0: we found only a significant increase of sEEG2 beta power (24±5%, cluster T=45.87, p=0.007; Fig. 3.4) in a single cluster of electrodes over a left parietal area. This power increase was still present in sEEG3, although it did not reach significance (33±10%), likely because of inter-subject variability. No significant power increases were present in other frequency ranges. The absence of a significant increase of frontal theta power in sEEG3 after MOT suggests that the EEG effects of neuronal fatigue are more likely to reflect learning and plasticity phenomena, such as

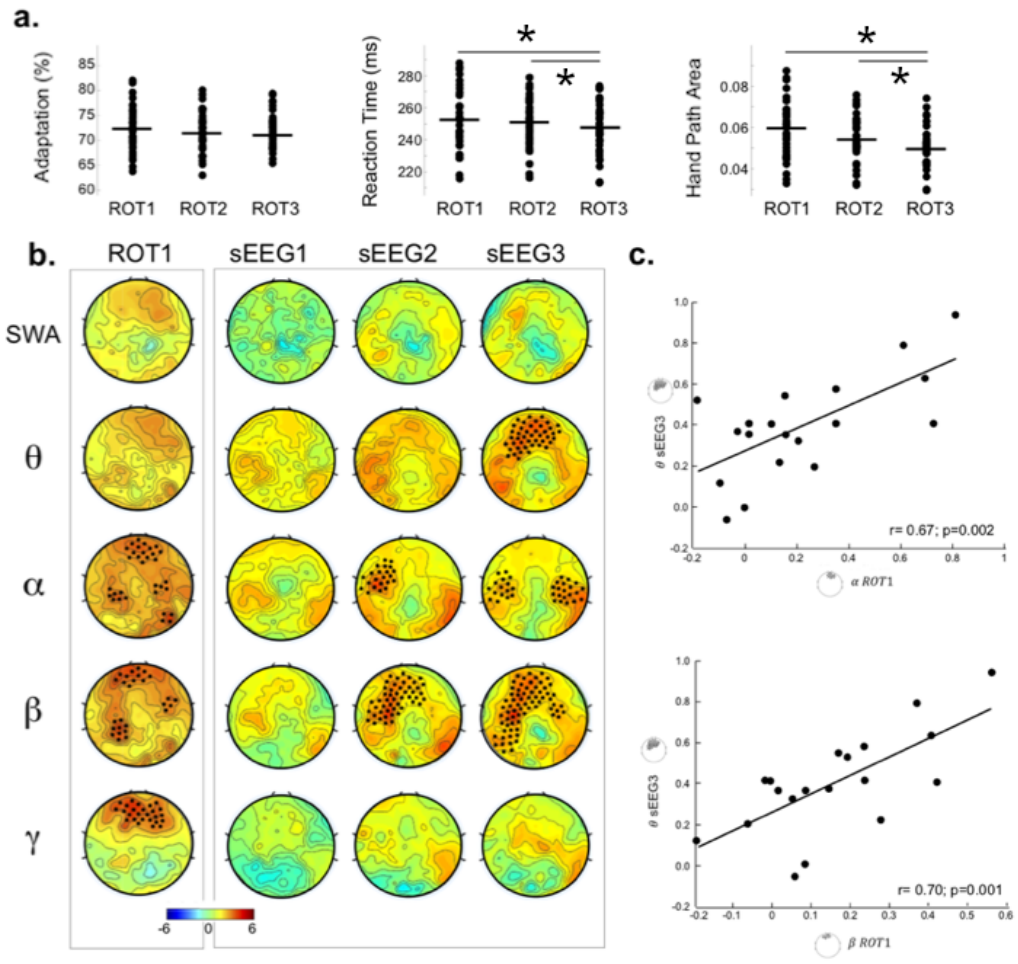

Figure 3.2 Kinematic and EEG results of ROT. a. ROT performance measures in the three blocks showing that learning occurs between blocks. From left to right: adaptation computed as changes of directional errors normalized by the imposed rotation; reaction time and hand path area, i.e. area of the trajectory normalized by squared path length. Each dot represents the measure for one subject while lines indicates the average across subjects. Asterisks show significant differences ($p<0.05$) between blocks. b. T-maps during ROT1 execution and sEEGs in the five frequency ranges. The left box shows the differences between last and the first sets in ROT1. On the right, sEEG activity recorded after each ROT block is compared with the baseline recording in sEEG0. Significant clusters of electrodes are highlighted with black dots ($p<0.05$, non-parametric cluster-based permutation testing). c. Top: correlation between the EEG activity during ROT1 in the alpha range and the EEG activity at the end of the morning (sEEG3) in the theta range over the frontal ROI. Bottom: correlation between ROT1 beta activity and theta sEEG3 in the frontal ROI. The average change of each ROIs in each frequency was used for both correlations. Overall correlations display a link between task-related activity and low-frequency content at rest.

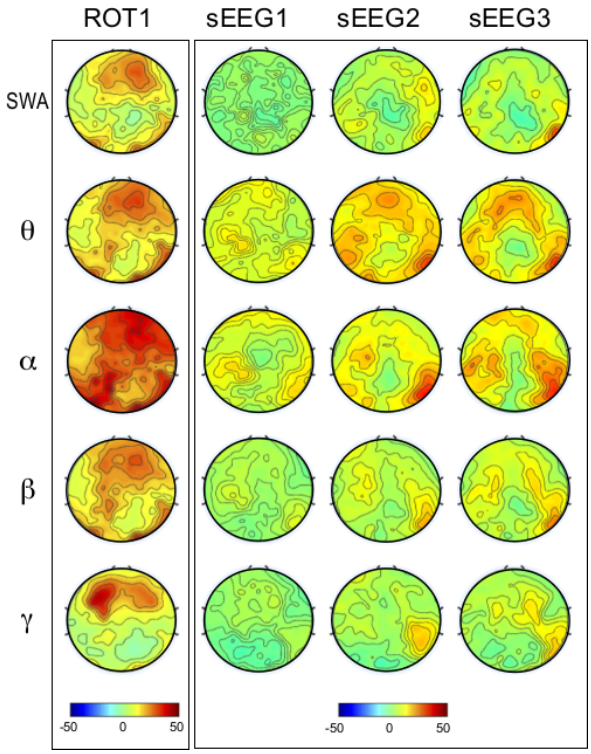

Figure 3.3 Topographical power changes occurring during ROT1, comparing the last rot0 set to the first one, within five frequency ranges. Right, sEEG power differences between sEEG recorded after three ROT blocks and sEEG0.

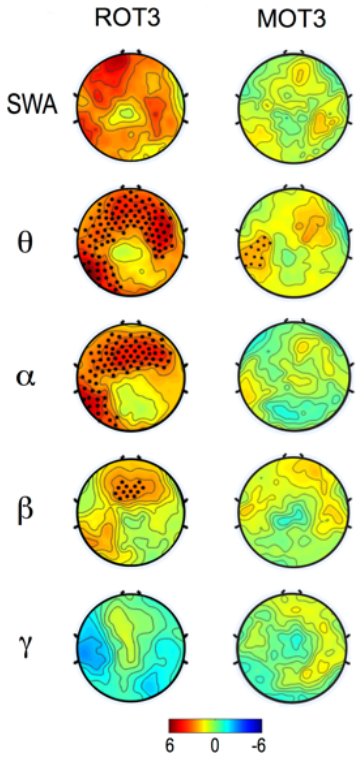

Figure 3.4 From left to right: T-maps during the execution of ROT3, average across ROT blocks, MOT3 and average across MOT blocks in the five frequency ranges. The maps represent the differences between the last and the first sets of the blocks. Significant clusters of electrodes are highlighted with blackened dots ($p<0.05$, non-parametric cluster-based permutation testing).

those that must occur during ROT, rather than mere neuronal activity without substantial new learning, as in MOT.

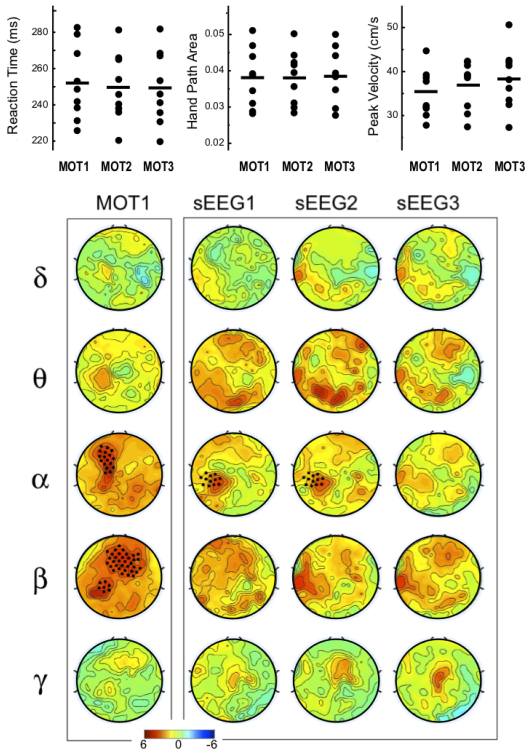

Figure 3.5 Kinematic and EEG results of MOT. Top: MOT performance measures in the three blocks; from left to right: reaction time, hand path area and peak velocity. Each dot represents the measure for one subject, while lines show the average across subjects. Kinematic results results suggest that no learning occurred with this task. Left: T-maps MOT differences between the last and the first sets of movements. Right: comparisons between sEEGs recorded after each MOT block sEEG0 in the five frequency ranges. Significant clusters of electrodes are highlighted with blackened dots (p<0.05, non-parametric cluster-based permutation testing).

VSEQ

During the VSEQ task, subjects learned several 12-elements visual sequences in the three blocks (mean during the three morning sessions ± SD: 27.35 ± 1.24). Signs of learning were evident across the three morning blocks with a significant increase of learned sequences across blocks (repeated measure ANOVA: $F_{(2,\,82)} = 3.31; p = 0.041$) and a good trend towards improving the learning index ($F_{(2,\,82)} = 3.01; p = 0.055$; Fig. 3.7). In general, during the last block, VSEQ3, a greater number of sequences were learned compared to the

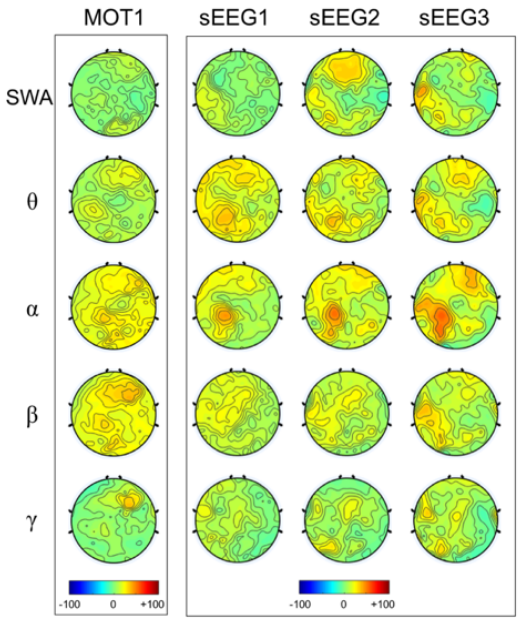

Figure 3.6 Topographical power changes occurring during MOT1, comparing the last and the first mot sets, within five frequency ranges. Right: sEEG power differences between sEEG recorded after three MOT blocks and sEEG0

first block (post hoc T-test: t=2.325, p=0.025) and the numbers of sets required to learn a sequence decreased (t=2.71, p=0.010; Fig. 3.7). Such performance changes suggest that subjects enhanced their ability to learn sequences across the three blocks and, thus, that meta-learning or "learning how to learn" occurred [Marinelli et al. (2017)].

Comparisons between the last (Mean number of sets ± SD: 3.02 ± 1.20) and first (3.24 ± 1.56) learned sequence in VSEQ1 (Fig. 3.8; 3.9), revealed a significant increase in a cluster of electrodes over a right temporo-parietal region in both the beta (cluster t=18.86, p=0.008) and gamma ranges (cluster t=35.39, p=0.009).

These same areas showed power changes during sEEG after the task; in fact, power in sEEG1, sEEG2 and sEEG3 was significantly greater than sEEG0, recorded at baseline, in a cluster of electrodes over a similar right temporo-parietal area in selected frequency bands at different time points (Fig. 3.8). Specifically, alpha power significantly increased over such area in sEEG1 (mean ± SEM 28 $\pm$ 6%, cluster t=122.24, p=0.002) and in sEEG2 (27 $\pm$11% cluster t=43.75, p=0.004) with a further increase and enlargement in sEEG3 (62 $\pm$15%, cluster t=165.73, p=0.002). Over the same area, we found significant and progressive increase of beta power in sEEG2 (20 $\pm$7%, cluster t=28.93, p=0.003) and sEEG3 (37 $\pm$10%, cluster t=73.17, p=0.004). Importantly, in sEEG3, there was a significant increase of theta power

over the same electrodes (44 ±11%, cluster t=39.89, p=0.008), suggesting a local build-up of power in the low frequency ranges. Finally, we also found a significant cluster in the alpha range over a corresponding area on the left in sEEG1 (29 ±6%; cluster t=105.51, p=0.002) and sEEG3 (36 ±9%; cluster t=119.45, p=0.002). Such increase was present in sEEG2 but did not reach significance probably because of greater inter-subject variability (33±11%). Finally, we correlated theta power in sEEG3 with beta and gamma range during VSEQ over the right temporo-parietal region. For this analysis we used the first block, VSEQ1, to capture mostly the learning-related changes and to reduce the fatigue effects that may sum up in the three blocks. Interestingly, we found a positive correlation between the significant changes of beta power during the task VSEQ1 and those of theta power during sEEG3 (r=0.54, p=0.018). However, correlation between the changes of gamma power in VSEQ1 with those of theta in sEEG3 did not reach statistical significance (r=0.41, p=0.077).

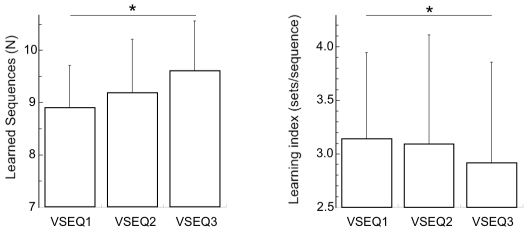

Figure 3.7 VSEQ behavioral results (mean and standard error). Left: Number of sequences learned across the three morning blocks. Right: Learning index defined as the number of sets required to learn a sequence. Asterisks indicate significant differences (p<0.05) between the first and last blocks. Results demonstrate that the number of learned sequences increases form block 1 to 3; further, the number of repetitions necessary to learning a sequence decreases, suggesting that learning occurred during the morning blocks.

3.3.2 Learning results in signs of performance deterioration that are task-specific

Next, we tested whether learning and training affect performance in *mov* and *mem*. In both tests, we measured the number of correct responses. Specifically, in *mov*, we computed the number of correct movements, thus excluding movements with values of reaction time, normalized movement area or directional errors outside 1.5 standard deviation of the mean of the baseline (*mov0*). In *mem*, we computed the number of correctly reported sequences. We then compared the performance at the baseline test (*mem0* and *mov0*) with the performance in the tests after the last block of the morning (*mem3* and *mov3*).

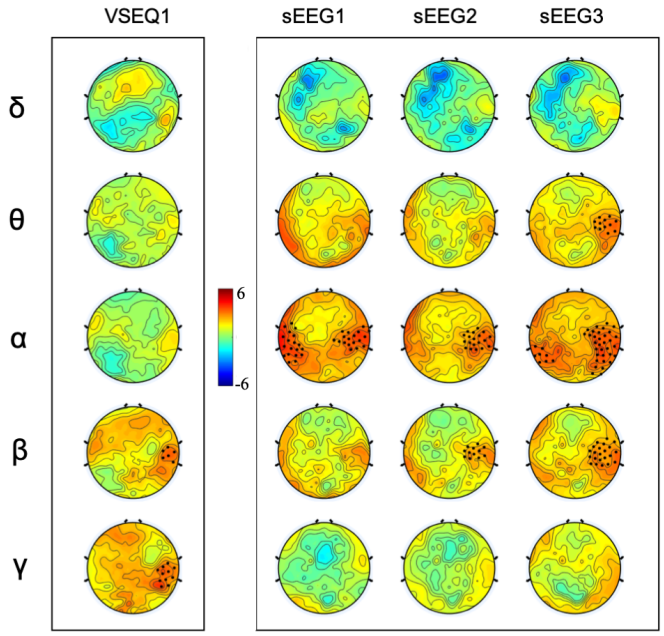

Figure 3.8 Left: t-maps of the comparison between the last and first VSEQ1 sequences learned by the participants. Right: sEEG activity recorded after each VSEQ block is compared with the baseline recording (sEEG0). Black dots highlighted significant clusters of electrodes ($p<0.05$, nonparametric cluster-based permutation testing).

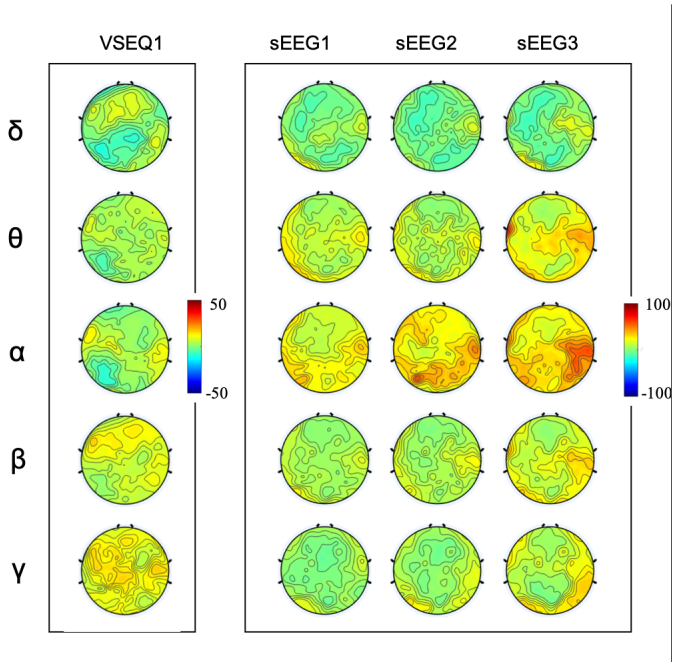

Figure 3.9 Power maps of VSEQ condition. Left: Topography of VSEQ1, comparing all the sets in the last sequence subject with the first ones, within five frequency ranges. Right: sEEG power differences between sEEG recorded after three VSEQ blocks and sEEG0.

We found that, after three blocks of ROT, the number of correct movements in *mov3* significantly decreased (t=4.182, p<0.001; Fig. 3.10), while performance in *mem3* did not show significant decrements (t=1.011, p=0.160; Figure 3.10). Conversely, extended MOT training did not significantly affect performance in *mem* (t=0.28, p=0.787; Figure 3.10) and slightly improved performance in *mov* (t=3.00, p=0.020; Figure 3.10). Finally, during VSEQ, the number of correctly reported sequences in *mem* slightly but significantly decreased after VSEQ3 compared to baseline (t=2.347, p=0.024); while, the percentage of correct movements in *mov* did not change significantly (t=1.290, p=0.204).
Altogether these results indicate that: (i) performance are mainly affected by an extended learning other than exercise; (ii) errors increased only in the test that shared characteristics to the task previously performed; (iii) there might be a relationship between error increase and local sleep.

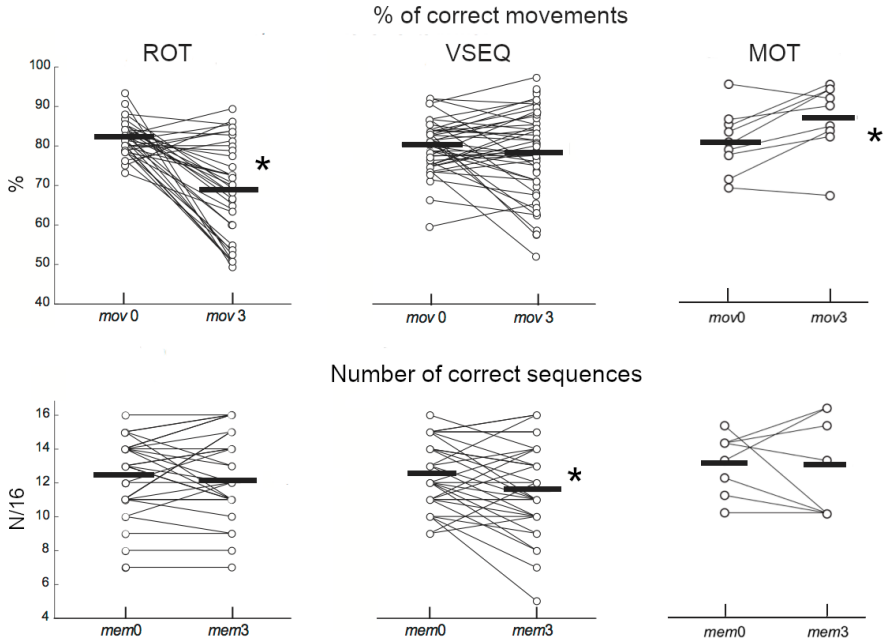

Figure 3.10 Behavioral effects of extended practice in *mov* (top row) and *mem* (bottom row) for the three conditions. Performance at the baseline (*mov/mem0*) is compared to those during (*mov/mem3*), after three blocks of task (ROT, VSEQ, MOT). Dots are single subject's data, while lines represent the mean value. Asterisks highlight significant differences ($p<0.05$) between blocks. Briefly, these data show that extended learning selectively affect performance only in test similar to the tasks. As such, ROT only affects reaching movements (*mov*), and VSEQ causes performance decline in *mem*. The control condition without learning (MOT) instead does not trigger errors increases.

3.3.3 An afternoon nap but not an equivalent period of quiet wake renormalizes spontaneous EEG and improves the ability to learn

For both ROT and VSEQ conditions we analyzed EEG data during and after sleep/quiet wake, as well as behavioral performance.

ROT

In the nap group, the mean sleep time was over 60 min with a total opportunity of 90, with most of sleep spent in NREM stages N2 and N3, indicating that sleep was consolidated and deep. Despite instructions and experimenters' monitoring, a significant amount of light sleep occurred in a few subjects of the quiet wake group. However, unlike in the nap group, sleep mainly consisted of N1 with some N2 (Tab 3.3 and 3.4).
Global power spectra of sEEG4 (after the nap/quiet wake) and sEEG3 (before nap/quiet wake) did not differ either in the nap group or in the quiet wake group (Fig. 3.11). We thus focused on a personalized region of interest (personalized ROI, described in the methods section). Within this personalized ROI, the nap group showed significant decreases in SWA and theta range, on average by 60-70%, in sEEG4 compared to sEEG3 (Fig. 3.11). These local low frequency decreases were correlated with SWA during the nap: the greater the SWA during the nap, the greater the decrease of low frequency power in sEEG4 compared to sEEG3 ($r=0.80$, $p=0.003$). Conversely, the quiet wake group only showed a modest decrease in beta and, to some extent, in theta power (Fig. 3.11). The theta power decrease was likely due to the fact that a few subjects in the quiet wake group actually slept reaching N2 stage, as suggested by significant correlation between N2 duration and low frequency decrement in sEEG4 in the two groups combined ($r=0.70$, $p<0.001$).
Correct movements significantly increased in *mov4* compared to *mov3* after a nap (t-test: $t=2.706$, $p=0.007$; Fig. 3.12), reaching *mov0* performance levels ($t=-1.549$, $p=0.92$). No significant increases were found after quiet wake ($t=-0.003$, $p=0.501$; Fig. 3.12). Conversely, performance in *mem* did not significantly change in either groups (nap: $t=1.021$, $p=0.160$; quiet wake: $t=0.941$, $p=0.182$, Fig. 3.12). The beneficial effect of the nap was not confined to test performance but extended to the learning ability during the task (ROT4) that was performed immediately after the tests. Indeed, compared to ROT3, ROT4 showed significant improvements in adaptation rate, ($t=2.465$, $p=0.012$; Fig. 3.13), trajectory accuracy ($t=2.239$, $p=0.019$; Fig. 3.13) and reaction time ($t=2.982$, $p=0.004$, Fig. 3.13) after a nap, but not after quiet wake (Fig. 3.13). Finally, we determined whether the post-sleep improvements were related to the nap SWA in the personalized ROI. Indeed, we found that SWA during

the nap (N3 stage) correlated with performance improvement in *mov4* compared to *mov3*: the greater the SWA, the higher the post-sleep increase of correct movements (Figure 3.14). SWA during the nap (N2 and N3 combined) also correlated with the improvement in ROT4 learning compared to ROT3: the greater the SWA the larger the decrease in hand-path area (and thus trajectory accuracy, Fig. 3.14).

Table 3.3 Sleep stages duration (percentage of total duration). SEM standard error of the mean; TST total sleep time; N1-3 NREM stages 1,2,3

	ROT		**VSEQ**	
	Nap Mean (S.E.)	**Quiet Wake Mean (S.E.)**	**Nap Mean (S.E.)**	**Quiet Wake Mean (S.E.)**
TST	68.98(3.88) 20/20	19.47 (3.29) 16/16	59.03 (5.90) 16/16	24.18 (4.30) 16/17
N1	16.40 (2.84) 20/20	10.62 (1.57) 11/16	18.78 (3.37) 16/16	17.03 (2.40) 16/17
N2	31.75 (3.05) 20/20	8.85 (2.63) 4/16	28.34 (3.86) 16/16	6.44 (2.20) 10/17
N3	20.78 (3.96) 17/20	0 (0.00) 0/16	11.94 (4.65) 10/16	0.68 (0.46) 2/17

VSEQ

Subjects assigned to the nap group slept for more than 50 minutes out of 90, all of them reached N1 (average time: 18.8%) and N2 (average: 28.3%) stages, while ten subjects reached N3 stage for an average time of 11.9%. Despite the experimenters' monitoring, sixteen subjects in the quiet wake group reached N1(average time: 24.2%), ten of them reached N2 (average time: 6.4%) and two subjects were in N3 for 0.7% of the time (Tab 3.3 and 3.4).

The nap group showed a decrease of sEEG4 SWA global power, compared to sEEG3 (nap: t=-2.449, p=0.029; quiet wake: t=-0.468, p=0.646; Figure 3.15); When we focused on the personalized ROI, we found significant power decreases only in the nap group not just for the SWA range (nap: t=-2.344, p=0.036; quiet wake: t=0.322, p=0.752; Figure 3.15) but also for the theta band (nap: t=-2.414, p=0.031; quiet wake: t=-0.436, p=0.669; Figure 3.15). No significant differences were found for the other frequency bands for either group (Fig. 3.15). Performance results showed significant improvements in the performance of *mem4* compared to *mem3*, only in the nap group (nap: t=2.838, p=0.01; quiet wake: t=-0.373, p=0.714; Fig. 3.12); while performance in the *mov* test did not change after either a nap (t=0.072, p=0.943) or a quiet wake time (t=1.38, p=0.183; Fig. 3.12). Also, the number of repetitions required to learn a sequence in the task significantly decreased after the nap in VSEQ4 compared to

Table 3.4 Sleep characteristics. Mean spectra for the five frequency bands during artifact free EEG normalized by N1 power for the given band. Global power is the average of all the electrodes, while ROI is the personalized region. NREM is the mean power during N2 and N3 sleep. Slow wave energy (SWE) is the mean normalized SWA of N2 and N3 multiplied by their respective duration.

	ROT		**VSEQ**	
	Global Power mean (S.E.)	**ROI mean (S.E.)**	**Global Power mean (S.E.)**	**ROI mean (S.E.)**
		Normalized N2		
Delta	2.78 (0.28)	3.03 (0.54)	2.96 (0.26)	2.78 (0.25)
Theta	1.76 (0.23)	1.69 (0.17)	1.69 (0.12)	1.73 (0.14)
Alpha	1.59 (0.14)	1.82 (0.23)	1.74 (0.11)	1.60 (0.13)
Spindle (12-16 Hz)	2.02 (0.14)	2.20 (0.20)	2.19 (0.19)	2.10 (0.22)
Beta	1.13 (0.06)	1.16 (0.09)	1.21 (0.06)	1.21 (0.08)
		Normalized N3		
Delta	6.90 (0.87)	8.36 (1.86)	7.89 (0.91)	8.60 (1.38)
Theta	2.28 (0.23)	2.55 (0.39)	2.29 (0.15)	2.24 (0.18)
Alpha	1.53 (0.17)	1.97 (0.39)	1.81 (0.13)	1.56 (0.31)
Spindle (12-16 Hz)	1.67 (0.18)	1.80 (0.27)	1.86 (0.14)	1.74 (0.28)
Beta	0.70 (0.04)	0.70 (0.05)	0.79 (0.07)	0.80 (0.11)
		Normalized NREM		
Delta	4.37 (0.66)	5.12 (1.18)	4.13 (0.62)	4.17 (0.72)
Theta	1.96 (0.23)	1.97 (0.18)	1.83 (0.13)	1.85 (0.14)
Alpha	1.55 (0.14)	1.83 (0.23)	1.76 (0.11)	1.60 (0.15)
Spindle (12-16 Hz)	1.87 (0.15)	2.06 (0.22)	2.13 (0.19)	2.02 (0.22)
Beta	0.99 (0.07)	1.03 (0.11)	1.14 (0.08)	1.13 (0.09)
Normalized SWA	2.23 (0.44)	2.66 (0.75)	2.16 (0.67)	2.28 (0.74)

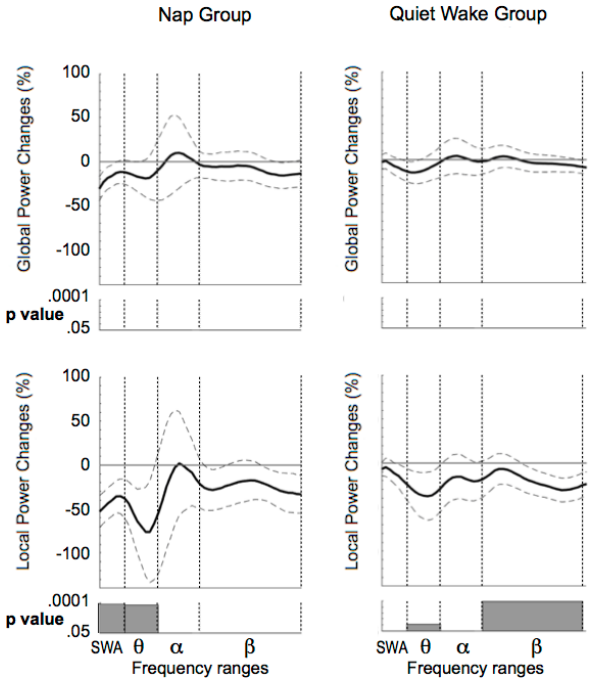

Figure 3.11 Top: Global power differences, computed as the average of all the electrodes, between sEEG4 and sEEG3 in the nap and quiet wake groups of subjects performing ROT. Bottom: Local power changes in the two groups computed in the personalized ROI. Data are displayed as mean difference across subjects $\pm$ standard error (dotted lines). At the global level, neither the nap nor the quiet rest changes the EEG power at rest. However, 90 minutes of sleep reduce the low-frequency power over the areas involved during the task; the quiet wake condition only reduces theta and beta power but not the SWA.

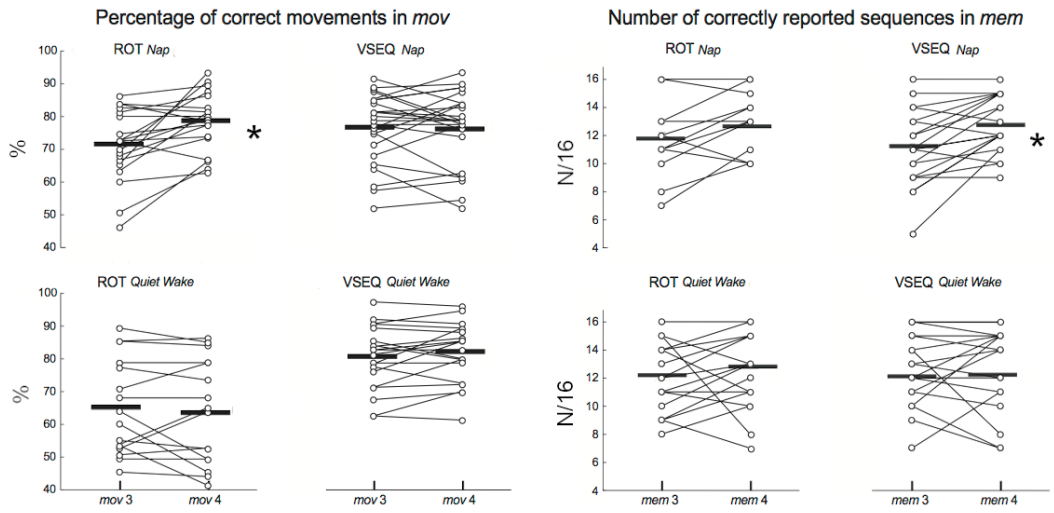

Figure 3.12 Effect of nap (top row) and quiet wake (bottom row) on test performance. Left: Percentage of correct movements during *mov3* and *mov4* in ROT and VSEQ. Right: Number of correct sequences in *mem3* and *mem4* for the two conditions and groups. Dots show single subject data, while lines indicate the mean. Asterisk highlight blocks differences ($p<0.05$), occurring only in the nap condition.

VSEQ3 (nap: t= 2.086, p=0.049; quiet wake: t=0.694, p=0.496; Fig. 3.16). No significant changes were detected in the number of fully learned sequences in either group (t-test: nap t=-1.094, p=0.288; quiet wake: t=-1.202, p=0.245; Fig. 3.16). Finally, SWA predicted improvement in both VSEQ learning and *mem* performance in the nap group: SWA during N3 stage was positively correlated with the increase in number of correct sequences in *mem4* compared to *mem3* (Fig. 3.14). Moreover, the improvement in the learning rate in VSEQ4 (decrease of sets per sequence) was associated with greater SWA in N2 and N3 combined (Figure 3.14).

Altogether, these findings show that intense learning in ROT or VSEQ without sleep deprivation can lead to traces in the sEEG that are local and progressively involve lower frequency ranges. These results also confirm that a nap, but not quiet wake, can partially revert the changes in the sEEG and restore test performance and the ability to learn. Of note, such reversal is only partial, since the power in the theta and 1-8 Hz range was still significantly greater after the nap than before.

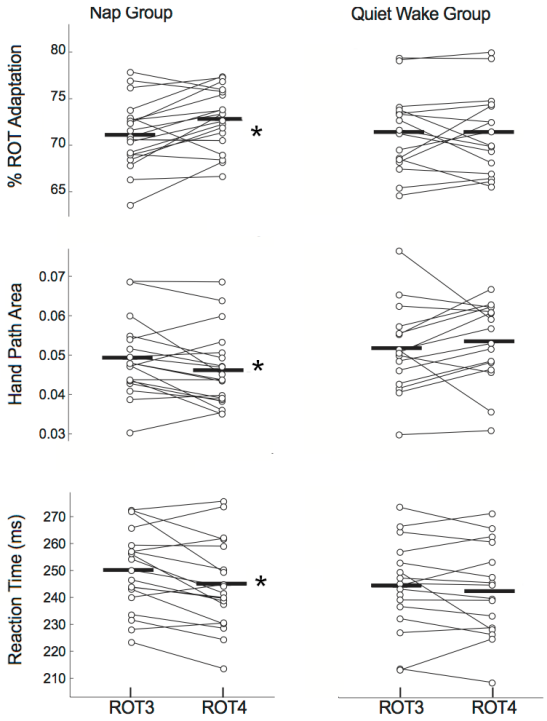

Figure 3.13 Effect of nap and quiet wake on ROT performance. Top: percentage adaptation in ROT3 and ROT4 in nap and quiet wake group. Middle: hand path area, an index of trajectory accuracy. Bottom: reaction Time. Dots: single subjects values; lines average of the subjects; asterisks (significant differences $p<0.05$), indicate that 90-minutes nap can partially restore learning ability of subjects, while the same amount of quiet rest does not affect it.

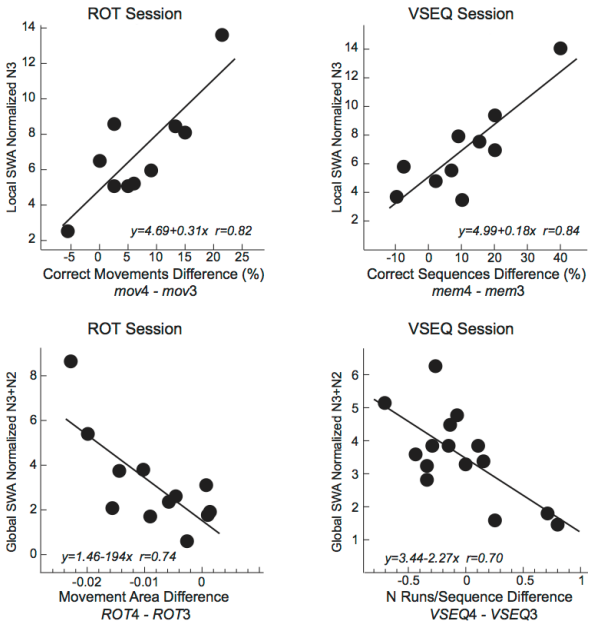

Figure 3.14 Correlations between SWA occurring during different stages of nap and behavioral performance. Top: personalized ROI SWA power in N3 versus difference in correct movements (*mov4-mov3*) and sequences (*mem4-mem3*). Bottom: the sum of the normalized SWA in N2 and N3 across the whole scalp correlated with differences in movement area during ROT 4 and 3 (r=-0.74, p=0.0003) and learning efficiency (VSEQ).

3.3.4 Discussion

This study shows that intense task learning in well-rested subjects – trained in the morning in the absence of sleep deprivation - leads to a local, progressive increase in low-frequency power in the spontaneous EEG over regions engaged during the task. Nevertheless, theta changes in sEEG and during the task are specific of learning, since they were not present in a control task in which the basic motor performance was similar but without the learning.
Altogether, these results suggest that the local theta increase in the spontaneous EEG after intense learning reflects local neuronal fatigue stemming from neuronal plasticity more than mere neuronal activity, because: (i) it occurred in the absence of sleep deprivation, when neurons maintain sustained firing for many hours; (ii) it occurred in response to a learning-heavy task but not after practicing a task, MOT, which is as demanding as ROT but is missing important learning components. Moreover, this learning-related low-frequency EEG trace is suggestive of local neuronal tiredness, because it resembles local low-frequency increases observed after sleep deprivation [Hung et al. (2013); Bernardi et al. (2015)] and it is associated with impaired performance in tests that rely on similar neural substrates as the practiced task. Importantly, both EEG changes and behavioral deterioration are partly

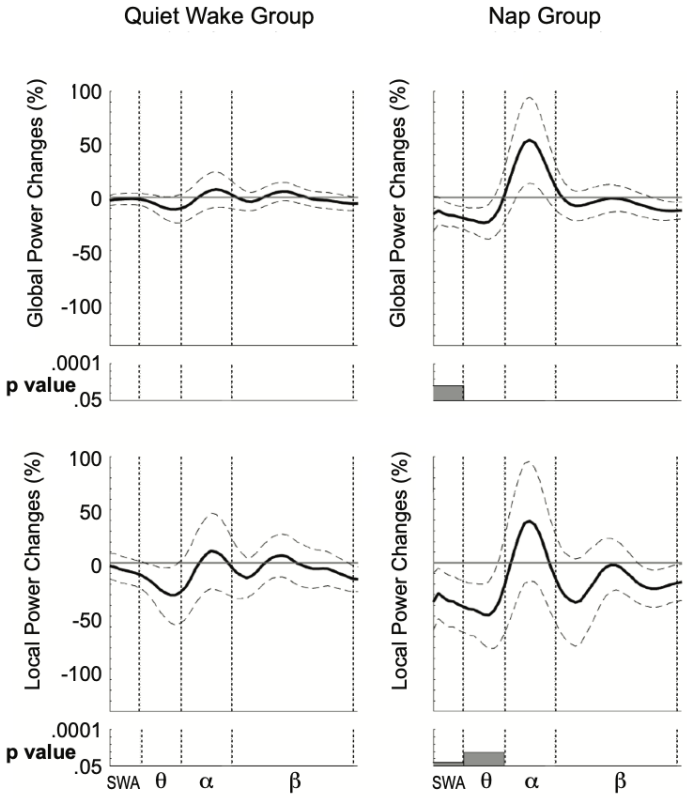

Figure 3.15 Difference between sEEG4 and sEEG3 in the quiet wake and nap condition, considering all the electrodes (top) and the personalized ROI (bottom). Lines indicate mean across all subjects (filled lines) and standard error (dotted lines). The quiet wake condition does not change the spontaneous EEG power spectrum, while a nap reduce the SWA power both globally and locally.

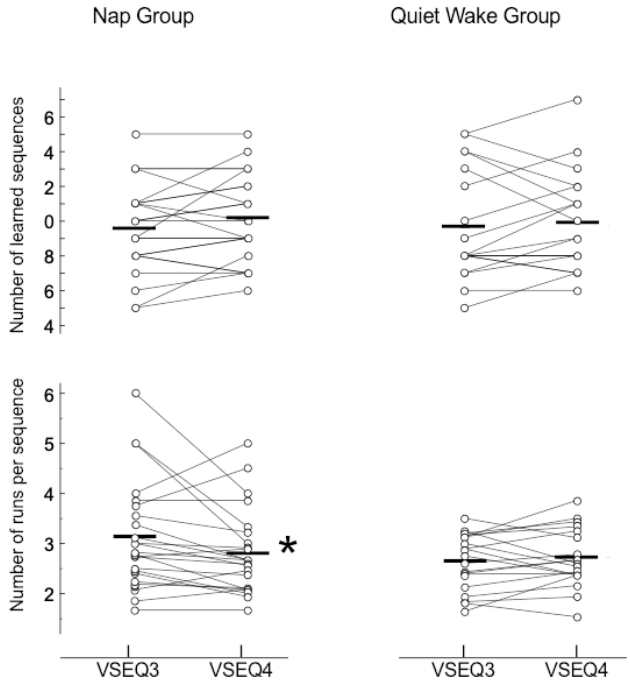

Figure 3.16 Top: number of sequences learned before and after the quiet wake, and nap period. Bottom: VSEQ learning index in the two groups. The plot show both single subjects data (dots) and average (lines). Asterisks $p<0.05$.

renormalized after a nap but not after an equivalent period of quiet wake, suggesting that sleep-dependent processes may be required for recovering from learning-induced fatigue. In our study, 90 minutes of sleep after repetitive practice in two learning task selectively improved the rate of learning, a behavioral change usually associated at the neuronal level with increased synaptic strength [Tononi and Cirelli (2014)]. Furthermore, the extent of learning was correlated with local increases in theta power. Also, local power changes during the task (ranging from gamma to alpha) were positively correlated with the increase in sEEG low frequencies. The local theta increases in sEEG3, which were preceded by increases in beta and alpha ranges [Landsness et al. (2011); Moisello et al. (2013)], might well represent plasticity-related phenomena. A global raise in theta activity is an established marker of sleep need in both humans and animals, since the EEG power in the 5-8 Hz range increases globally with the time spent awake and predicts the level of EEG SWA increase in subsequent sleep [Akerstedt and Gillberg (1990); Cajochen et al. (1995), Cajochen et al. (1999); Vyazovskiy and Tobler (2005)]. Local, as opposed to global, increases of sEEG theta power have been found in animals [Vyazovskiy et al. (2011b)] and more recently in humans, over areas previously involved in learning after 20-24 hours of wake. Those studies have

demonstrated that local, regionally-specific, increases of frequencies lower than 10 Hz of the depth EEG correspond to degraded single unit activity, increased theta activity of the surface EEG and performance errors [Nir et al. (2017)]. The present results demonstrate that extended wakefulness is not a necessary condition for local increases of theta and low frequency power. Instead, "local sleep" signatures can occur after protracted learning without sleep restrictions. Moreover, we found that only a nap enhanced learning-related performance in the tasks, restored test performance to the level of the morning baseline and produced significant power reduction of low frequencies. The need of sleep for renormalization suggests that local sleep and its behavioral consequences are triggered by the cellular costs of increased synaptic strength induced by learning, consistent with previous work [Hung et al. (2013)]; Tononi and Cirelli (2014); Bernardi et al. (2015)]. For instance, animal studies showed that learning and the induction of synaptic plasticity, more than neuronal firing *per se*, drives local SWA increases during subsequent sleep [Cirelli et al. (2005); Huber et al. (2007); Hanlon et al. (2009); Rodriguez et al. (2016)]. As in previous work [Mednick et al. (2003); Cirelli et al. (2005); Kvint et al. (2011); Lo et al. (2014); van Schalkwijk et al. (2017)], we found that a nap improved rate of learning and task consolidation and restored test performance [Huber et al. (2004)], but the extent to which these restorative effects equal those of full night sleep remains unclear. A nap containing both slow wave and REM sleep and lasting 60 minutes or more produced similar behavioral improvement as a full night of sleep on a texture discrimination task [Mednick et al. (2003)]. In another study a daytime nap provided protection against performance degradation in declarative and mirror-tracing tasks, but performance enhancements were seen only after a night of sleep [van Schalkwijk et al. (2017)]. We found that both task learning and test performance improved after a 60-min nap, and the improvement was correlated with the amount of SWA during the nap. However, the nap only partially reversed the local, practice-related increases of low frequency power in the sEEG. Thus, longer naps or a full night of sleep may be needed for full recovery. In conclusion, while practice may "make perfect", it may first "make tired", as intense learning progressively fatigues local neuronal circuits through an accumulation of plastic changes. To make perfect, ultimately, it also takes sleep, which can restore neurons and performance and consolidate the benefits of practice.

Part II

BETA MODULATION AND MOTOR PERFORMANCE

Chapter 4

Beta modulation depth is not linked to movement features

4.1 Introduction

Beta EEG activity reflects inhibition of the motor system, and decreased cortical excitability [Hsu et al. (2011); Noh et al. (2012); McAllister et al. (2013)]. The oscillatory dynamic of beta activity is present during movements with different effectors and characteristics [Pfurtscheller and Da Silva (1999); Tombini et al. (2009); Moisello et al. (2015b); Nelson et al. (2017)]. Also, in the previous study (see chapter 3), beta activity has been linked to theta EEG at rest, after prolongued practice in a visuo-motor rotation learning task. However, important questions still remain unanswered. For instance, do beta ERD and ERS magnitudes reflect specific motor characteristics that can explain the link between local sleep at rest and motor learning? Indeed, many studies failed to find association between beta ERD or ERS magnitude and movement parameters such as speed [Stancak and Pfurtscheller (1995), Stancak and Pfurtscheller (1996)], force [Pistohl et al. (2012); Cremoux et al. (2013)] and muscle pattern [Salmelin et al. (1995)]. Yet, other studies found that beta ERS amplitude increased with increasing movement speed or force [Stancak et al. (1997); Parkes et al. (2006); Fry et al. (2016)]. Nevertheless, it is indisputable that beta modulation is linked to movement planning and execution.

The content of this chapter has been published as Elisa Tatti, Serena Ricci, Ramtin Mehraram, Nancy Lin, Shaina George, Aaron Nelson, and M Felice Ghilardi. 2019. "Beta Modulation Depth Is Not Linked to Movement Features." Frontiers in Behavioral Neuroscience 13: 49.

4.2 Materials and Methods

4.2.1 Subjects

Thirty-five healthy, right-handed subjects (age range: 19-35, mean $\pm$ SD : 24.1 $\pm$ 4.7 years, 19 female) participated in this study that was approved by CUNY IRB. All subjects signed IRB-approved informed consent forms before starting the experiment.

4.2.2 Experimental Design

Subejcts were fitted with a 256-electrode HydroCel Geodesic Sensor Net. They were comfortably seated in a sound-shielded room in front of a display; EEG activity was recorded while they performed a *mov*, a motor task extensively described in the previous chapter. Briefly, participants had to perform out and back reaching movements with their right hand toward targets at three distances (4, 7 and 10 cm, defined throughout the text as short, medium and long trials) and eight directions (45° separation). After a training where they reached 95% hit rate, subjects performed a 96-movement block.

4.2.3 Kinematic and EEG analyses

For each movement we considered: reaction time; movement time (duration of the outgoing movement); movement extent (length of the segment from onset to reversal); amplitude of peak velocity. Movements with parameters outside two Standard Deviations were excluded from analyses.

High-density EEG data were acquired with Net Amp 300 amplifier (250 Hz sampling rate, online reference: Cz) and Net Station 5.0 software. Impedance was maintained below 50 k2 throughout the recording. Data were preprocessed using EEGLAB v13.6.5b toolbox for Matlab [Delorme and Makeig (2004); Makeig et al. (2004)]. EEG preprocessing followed the same steps described in the previous study and resulted, for each subject, in an average $\pm$ SD: 77.85 $\pm$ 9.42 trials (26.26 $\pm$ 3.73 short; 26.5 $\pm$ 3.84 medium; 25.09 $\pm$ 4.90 long). After preprocessing, epochs were time-locked to movement onset, resulting in 3.5 s epochs (-1 to 2.5 s). Time-frequency representations were computed within beta range (15–30 Hz) using Complex Morlet Wavelets at linearly spaced frequencies (0.5 Hz bins, 10 cycles). Data were normalized on the average of beta power over the entire epoch in order to assess the peak ERD, ERS and modulation depth (ERS-ERD) over the two sensorimotor areas (17 electrodes/area, Fig. 4.1). Then, we determined, for each participant, two personalized ROIs

including the electrode with the maximum modulation depth and the six neighbors (Fig. 4.2). Time-frequency representations were re-computed on the left and right ROIs (1:55 Hz, 0.5 Hz bins, 3:10 wavelet cycles). After normalization by total power, beta ERS, ERD, and modulation depth magnitude, as well as peak timing values, were extracted for statistical analysis.

4.2.4 Statistical Analysis

SPSS-based repeated measures one-way analyses of variance (rm-ANOVAs) were run on performance indices, beta ERS, ERD and modulation depth with target distance (short, medium, long) as factor. Violations of sphericity assumption were Greenhouse-Geisser-corrected; significant main effects ($p<0.05$) were followed by Bonferroni-corrected pairwise comparisons. Finally, we characterized specific contributions of peak velocity and movement time on movement extent with single-subject multiple regression analysis. Possible associations between beta modulation and performance indices were assessed with Spearman rank correlation analysis.

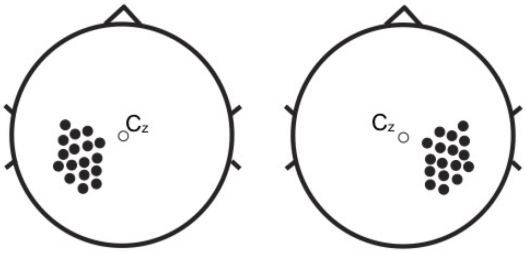

Figure 4.1 Left and right sensorimotor ROI used for the analyses.

4.3 Results

4.3.1 Movement extent results from scaling force to the appropriate target extent

All participants completed the task without difficulty. Movements were overall straight with bell-shaped velocity profiles, with significantly different extents, and reached on average the appropriate target distance ($F_{(1.226,41.697)} = 2954.04, p < 0.001$, Fig. 4.3). Importantly, both average peak velocity and movement time increased significantly with target distance ($F_{(1.067,36.27)} = 375.55, p < 0.001$; $F_{(1.437,48.87)} = 141.5, p < 0.001$, respectively; Fig. 4.3).

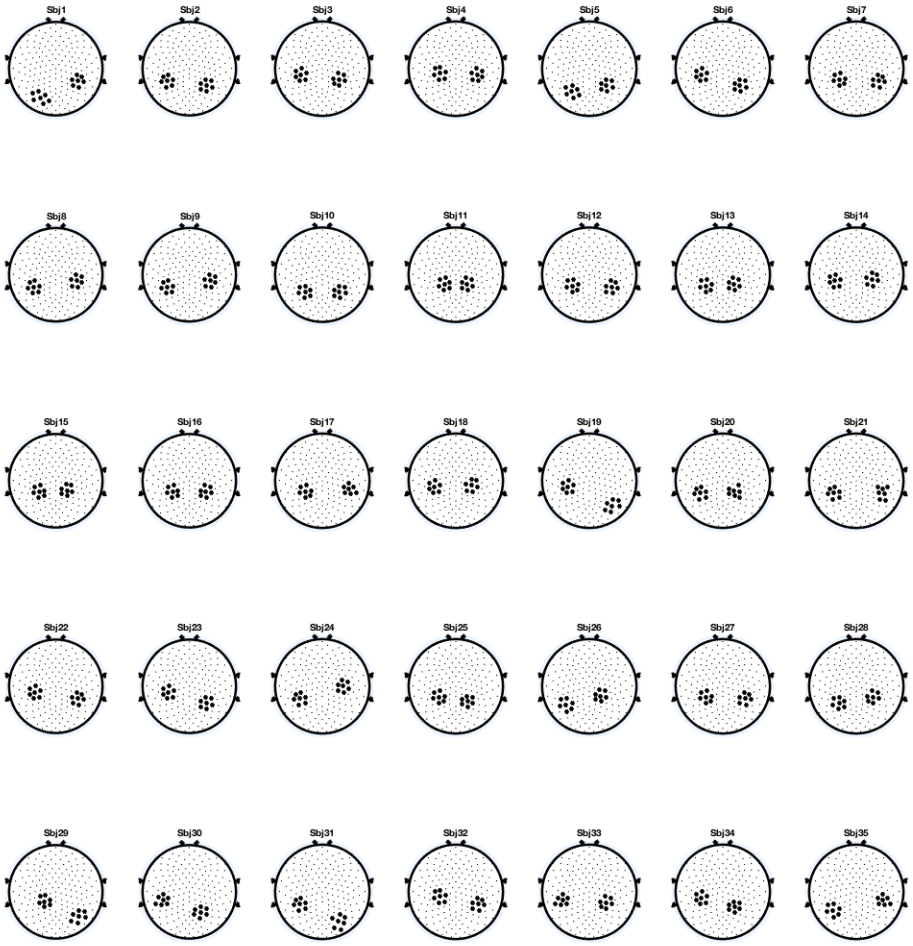

Figure 4.2 Topographies showing selected Left and Right ROIs for each subject.

To ascertain the relative contribution of peak velocity and movement time, we performed a multiple regression on each subject's data. The combination of peak velocity and movement time explained on average more than 90% of movement extent variance (R^2 mean ± SD: 0.93 ± 0.06; range [0.69; –0.99]). In all subjects, the major contributor of the variance in movement extent was variation of peak velocity (standardized coefficient Beta, mean ± SD: 0.86 ± 0.06; range [0.73; 1.02]), while variation of movement time played a lesser role (standardized coefficient Beta, mean ± SD: 0.39 ± 0.09; range [0.12–0.61]). Nevertheless, both contributions were statistically significant in all subjects. Altogether, these findings suggest that movement extent mostly resulted from planning of a force appropriately scaled to the target extent with minimal adjustments of movement duration.

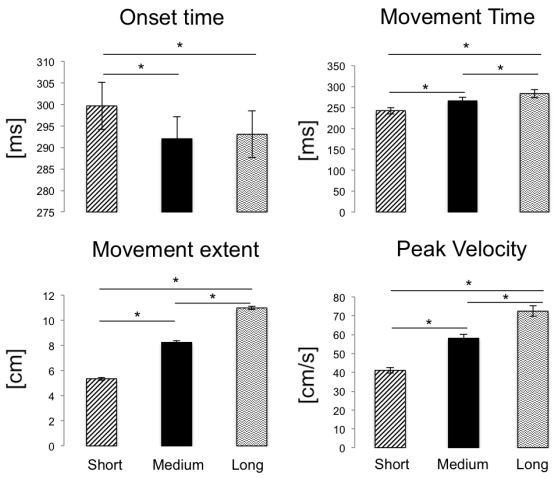

Figure 4.3 Mean and SE of performance measures for the three target distances. Significant Bonferroni-corrected post hoc pairwise comparisons ($p < 0.05$) are marked with *.

4.3.2 Movement extent does not affect beta modulation magnitude

We then determined whether target distance affects the magnitude of movement-related beta ERD, ERS and modulation depth. We first focused on the left ROI, where beta modulation depth was greater (mean ± SD; left ROI: 2.83 ± 0.53; right ROI: 2.34 ± 0.59; two-tailed t-test: $t(33) = 3.67, p = 0.001$). Average modulation depth was higher for the last 16 movements (mean ± SD: 2.914 ± 0.73) than for the first 16 (2.635 ± 0.50, two-tailed t-test: $t(34) = 2.74 p = 0.010$). However, we found no significant effect of target distance on ERD ($F_{(2,68)} = 2.37, p = 0.101$), ERS ($F_{(1.67,56.69)} = 2.46, p = 0.104$) and modulation depth magnitude ($F_{(1.67,57.61)} = 2.34, p = 0.109$ 4.4). Also, peak ERD and ERS timings

were similar for the three target distances (ERD: $F_{(2,68)} = 1.46, p = 0.24$; ERS: $F_{(2,68)} = 1.87, p = 0.162$, Fig. 4.4). Analogous results were found for the right ROI (Fig. 4.5): target distance did not affect the magnitude of ERD ($F_{(2,66)} = 2.1, p = 0.131$), ERS ($F_{(2,66)} = 1.81, p = 0.17$) and modulation depth ($F_{(2,68)} = 1.86, p = 0.16$) as well as peak timings: ERS ($F_{(1.49,49.03)} = 0.18, p = 0.77$) and ERD ($F_{(1.67,54.94)} = 0.18, p = 0.79$).

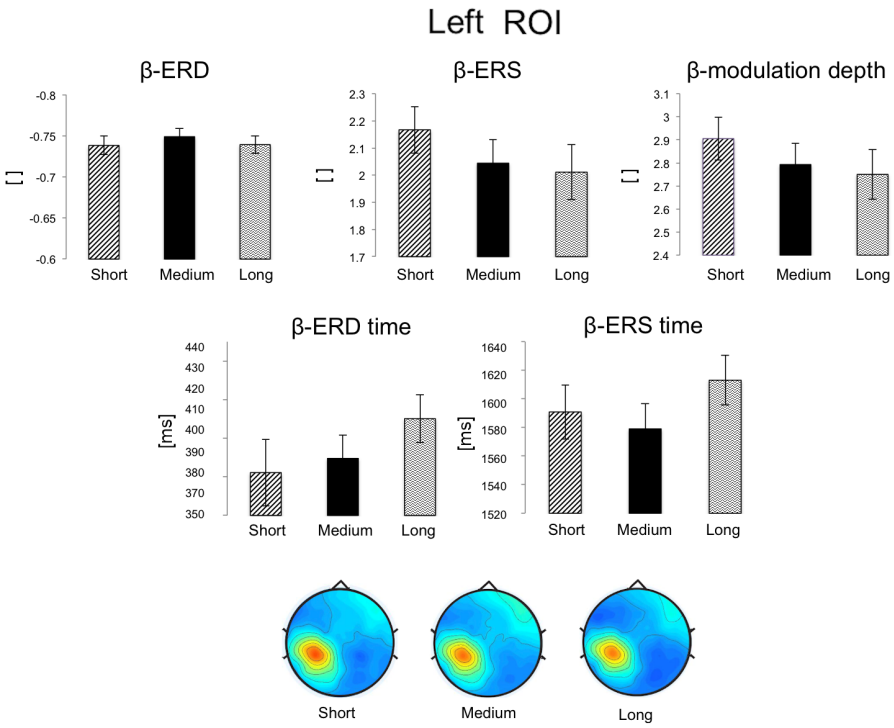

Figure 4.4 Top: Mean and SE of the magnitude of beta event-related desynchronization (ERD), event-related synchronization (ERS) and modulation depth (dimensionless), as well as of ERD and ERS timing for the Left ROI. Bottom: beta modulation depth topographies averaged across subjects.

4.4 Discussion

The main result of this study is that the magnitudes of beta ERD, ERS and modulation depth over the sensorimotor areas do not change with movement length. Also, we found no significant effect of target distance on ERD and ERS timing on both ROIs. Finally, in agreement with previous results, beta modulation depth increased significantly from the beginning to the end of practice [Nelson et al. (2017)]. The movements produced with this

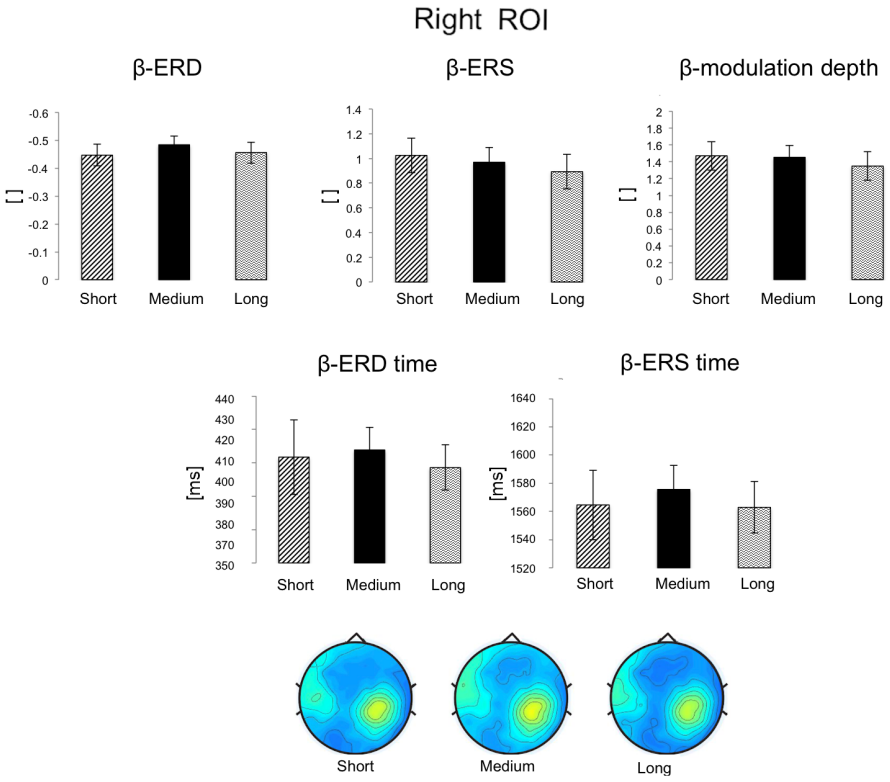

Figure 4.5 Beta modulation results of the right ROI. Top: ERD, ERS and modulation depth amplitude and timings. Bottom: modulation depth topographies for short, medium and long trials.

reaching task had bell-shape velocity profiles that were appropriately scaled to the target distance. Indeed, peak velocity almost doubled for the long target compared to the short, while movement time increased only by 40 ms (less than 20% increase). This suggests that, as previously reported [Gordon et al. (1994a); Gordon et al. (1994b)], movement extent in this task mainly resulted from planning a force that was appropriate to the distance. This may not be the case when using other paradigms with 3-D movements and greater distances [Ferraina et al. (2009); Hadjidimitrakis et al. (2015); Bosco et al. (2016)]. Nevertheless, our results suggest that movement related beta oscillatory activity is not significantly affected by force. This conclusion is in accordance with previous results but contradicts others. In particular, [Stancak et al. (1997)] found that, when external loads opposed finger extension, beta ERS amplitude increased with higher loads. One explanation for this result is that the applied load might have influenced the proprioceptive drive: this, in turn, might have enhanced post-movement reactivation of sensory areas resulting in a greater ERS magnitude. A similar mechanism could also explain the findings of higher rate finger extensions linked to greater beta ERS amplitude [Parkes et al. (2006)]; as movement onsets and offsets were controlled by finger contacts with a button, the blocks with faster (more frequent) movements might have resulted in greater somatosensory input. Finally, a study showed a positive relationship between beta ERS amplitude and force output in isometric wrist flexion movements [Fry et al. (2016)]. While muscle pattern and proprioceptive feedback did not change, force targets were presented in ascending order and a trial-by-trial normalization was applied. Hence, task design and baseline choice do not allow distinguishing the effect of force from that of practice. Indeed, a similar study with isometric elbow flexion, where the required force level was randomized and each trial was normalized by the total power of all the trials, found no relationship between force level and beta ERS magnitude.

Chapter 5

Aging Does Not Affect Beta Modulation during Reaching Movements

5.1 Introduction

There is no clear evidence as to whether Beta ERD and ERS are related to specific movement attributes [Salmelin et al. (1995); Stancak and Pfurtscheller (1995); Kilavik et al. (2013)] or whether they change with aging or neurodegenerative processes [Dushanova et al. (2010); Gaetz et al. (2010); Heinrichs-Graham et al. (2018)]. Recent studies found that during practice in a reaching task, ERS magnitude increases [Moisello et al. (2015b); Nelson et al. (2017); Tatti et al. (2019)], independently of possible changes in mean power. Such practice-related increases are also evident in the beta modulation depth. Importantly, beta modulation decreased to baseline levels twenty-four hours later and its magnitude increase during practice was correlated with retention of motor skill tested the following day. Additionally, a study on extensive motor learning revealed that beta EEG activity increases with practice and such increase correlates with local sleep at rest (see chapter 3). A possible explanation of this link is that beta modulation changes occurring during practice may reflect plasticity-related phenomena, indeed, human and animal studies have shown that beta power increases

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in parallel with a reduction of cortical excitability. Finally, in Parkinson's disease (PD), which is characterized by alterations in the beta frequency range [Cassidy et al. (2002); Levy et al. (2002); Kühn et al. (2005)] and impaired plasticity [Morgante et al. (2006); Ueki et al. (2006); Marinelli et al. (2009); Bedard and Sanes (2011); Kishore et al. (2012); Moisello et al. (2015b)] neither practice-related increases of beta power nor retention of motor improvement were present. As neural plasticity declines with increasing age [Burke and Barnes (2006)], it is possible that practice-related beta modulation would also be affected by aging. However, studies on beta oscillatory activity and plasticity of the sensorimotor cortex report controversial results. For instance, a recent work with a motor sequence task reported increased ERD amplitude over the contralateral sensorimotor area in older (aged from 54 to 75 years) compared to younger adults (aged from 20 to 42 years) [Heinrichs-Graham et al. (2018)]. In contrast, another study with a grip task [Rossiter et al. (2014)] showed a lack of correlation between age and movement-related beta ERD in the contralateral motor area. Similarly, the studies testing LTP-like plasticity of the sensorimotor cortex with paired-associative stimulation (PAS) protocols yielded contrasting results [Müller-Dahlhaus et al. (2008); Tecchio et al. (2008); Polimanti et al. (2016)]. In the present study, we ascertain in a group of younger and older adults whether healthy aging affects practice-related changes both in terms of magnitude and peak latency of ERD and ERS during a reaching task with the right hand. We focused on the left sensorimotor cortex and on a frontal region that, in previous studies, showed robust beta modulation [Moisello et al. (2015a); Nelson et al. (2017)]. Moreover, we investigate whether practice-related beta power changes occur in term of magnitude, timing and peak frequency of the peak ERD, ERS and beta modulation. Specifically, we assessed whether different regions: the left and right sensorimotor areas and a frontal area show movement-related differences in the beta EEG activity.

5.2 Materials and Methods

5.2.1 Subjects

We tested two groups of subjects: a younger group, with thirteen subjects (mean age $\pm$ SD: 24.2 $\pm$ 4.5 years, ten women) and an older group with thirteen subjects (mean age $\pm$ SD: 57.5 $\pm$ 8.2 years, six women). All subjects were right-handed, as determined by the Edinburgh inventory [Oldfield (1971)], and had no history of neurological or psychiatric disorders. Experiments were conducted with the approval of our IRB and written informed consent was obtained from all participants.

5.2.2 Experimental Design

All experiments were run in the morning. Subjects were fitted with high-density 256-electrode EEG cap. The two groups of subjects performed a reaching task (MOT) for 30 minutes, extensively described in the previous section. Briefly, subjects had to perform out-and-back reaching movements toward one of eight targets, being as fast and accurate as possible but avoiding anticipation or guessing (Fig. 5.1) Before the first testing session, all subjects were trained in this task to reach a hit rate of at least 95%. The session encompassed a total of 840 target presentations divided into 15 sets of 56 each. Between two consecutive sets, subjects paused for an average of 30 seconds. For each movement, we computed: reaction time; total movement time; peak velocity; and hand-path area. For each subject, we discarded outlier movements that met one of the following criteria: reaction time exceeding 2 SD from the subject's mean; directional error greater than 22°; movement end less than 100 ms before the presentation of the next target.

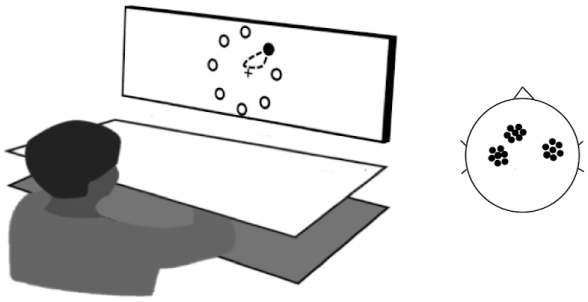

Figure 5.1 Experimental setup and Regions of Interests used for the analysis

5.2.3 Analyses

After EEG data preprocessing, which followed the same pipeline described above, we aligned each valid trial (i.e., trials that were not discarded from either EEG or kinematic preprocessing) to the time of movement onset; then, we computed time-frequency representations in the 15 to 30 Hz range (0.25 Hz steps), using a short-time Fourier transform approach (Hanning taper, time step-size of 20 ms, 5 cycles adaptive window width). Beta power of each trial ROI was normalized using the average beta power value computed over the entire motor session as such: $\sum_i^{1:trials} \frac{BetaEEG_i - TotPower}{TotPower}$, with $TotPower$ defined as the Total beta power across all the trials. First, we ascertained whether the two groups of subjects had a comparable beta power in two ROIs: a left (centered in C3 with the six nearest neighbors) and a frontal one, centered between Fz and F3 (Fig. 5.1), with Nonparametric Permutation Testing with False

Discovery Rate Correction. Then, we determined the amplitudes of ERD and ERS: ERD amplitude was defined as the minimum value of beta power within an interval between 200 ms before movement onset to 700 ms after it; ERS amplitude was the maximum value in the interval from 500 to 1500 ms. Beta modulation depth was computed as the difference between ERS and ERD. We then averaged the data of all the subjects to define an additional 7-electrode ROI symmetrical to the left one (Fig. 5.1). Afterwards, trials were averaged across sets to determine time and groups differences, as well as across all trials to assess time differences in the two groups. All the analyses have been implemented using Fieldtrip toolbox for Matlab [Oostenveld et al. (2011)]. To quantify the changes of EEG (ERD, ERS, beta modulation depth) and kinematic measures (reaction time, peak velocity, hand-path area and total movement time) across sets, we performed repeated-measure Multivariate ANOVAs: with Group (when appropriate, younger and older) as between-subject effect and practice (15 sets), parameters (kinematic indices or EEG metrics) and ROI (left and front, only for the EEG analysis) as within-subject effects. All the results had been Greenhouse-Geisser corrected since the assumption of sphericity was violated (Mauchly's test). Significant main effects were followed by Bonferroni-corrected pairwise comparisons. Also, time-frequency differences between ROIs were assessed through Nonparametric Permutation Testing with False Discovery Rate Correction. Correlation between kinematic and EEG data have been assess through Pearson's coefficients with Bonferroni correction for multiple comparisons, after normality was tested with Lilliefors Test. We used two-tailed paired t-tests to determine significant group difference for both ERD and ERS peak latency. Results were considered significant for p-values <0.05. All statistical analyses were conducted with SPSS v25, Matlab 2017b and Fieldtrip toolbox for Matlab.

5.3 Results

5.3.1 Motor performance differs in young and older subjects and change with practice

All participants completed the session without any difficulty. In general, movements were mostly straight with bell-shaped velocity profiles in all subjects. The performance measures of the two groups across sets are illustrated in Fig. 5.2. The results of the repeated-measure multivariate ANOVA revealed an overall effect of practice ($F_{(56,1297.47)} = 2.86, p < 0.001$) and group ($F_{(4,21)} = 8.80, p < 0.001$) and a trend toward significance in the Practice*Group interaction ($F_{(56,1297.47)} = 1.26, p = 0.096$). Results of the univariate tests are reported in Tab.

5.1. Specifically, peak velocity values were significantly greater in the younger group without significant changes across sets (Tab. 5.1, Fig. 5.2). However, inspection of the data showed an increase across sets, although not significant, only in the older group (Fig. 5.2). In parallel, total movement time was significantly longer in older subjects, with significant decreases across sets in both groups. Hand path area was greater in older participants but decreased in both groups across sets, as shown by a borderline p value (p=0.059). Finally, reaction times were rather stable across sets and were slightly longer in the older group, despite mixed model ANOVA did not reveal any main effect or interaction. The same results were obtained performing a repeated measure ANOVA with the two groups combined. Briefly, reaction time and peak velocity increased across sets but without reaching significance ($F_{(4.86,121.40)} = 1.53, p = 0.188; F_{(1.83,45.73)} = 1.29, p = 0.285$, respectively). Hand path area, showed a borderline significant decrease across sets ($F_{(6.47,161.83)} = 1.96, p = 0.069$). Total movement time showed a significant effect of practice ($F_{(3.24,80.97)} = 8.01, p < 0.001$; Fig. 5.3). In summary, these results suggest that movements in the older group were slower and spatially less accurate than in the younger group, as confirmed by correlations between mean values of kinematic parameters and age (peak velocity: $R^2 = 0.43, p < 0.001$; hand path area: $R^2 = 0.28, p = 0.006$; total movement time: $R^2 = 0.30 p = 0.004$). Additionally, we found a strong correlation between age and the decrease of hand-path area from the first to the last set ($R^2 = 0.29, p = 0.005$, Tab. 5.2).

Table 5.1 Results of the repeated measure ANOVA, univariate tests of Peak Velocity, Hand-path Area and Reaction Time comparing groups across practice

	Group		**Practice**		**Group*Practice**	
	$F_{(1,24)}$	**p**	**$F_{(14,336)}$**	**p**	**$F_{(14,336)}$**	**p**
Peak Velocity	**9.51**	**0.005**	1.32	0.277	1.63	0.209
Hand-Path Area	**8.63**	**0.007**	2.02	0.059	1.80	0.095
Reaction Time	0.47	0.501	1.52	0.189	0.92	0.468
Total Movement Time	**4.82**	**0.038**	**14.94**	**<0.001**	0.78	0.515

5.3.2 Beta modulatory activity does not differ between younger and older subjects

We next analyzed the power changes across sets of beta ERD and ERS in the two groups for the left and frontal ROIs. Results are reported in Tab 5.3, 5.4 and illustrated in Fig. 5.4 Multivariate tests with ERD and ERS magnitude did not reveal significant group differences or interactions (Group: $F_{(2,23)} = 1.121, p = 0.343$; Practice*Group: $F_{(28,672)} = 0.548, p =$

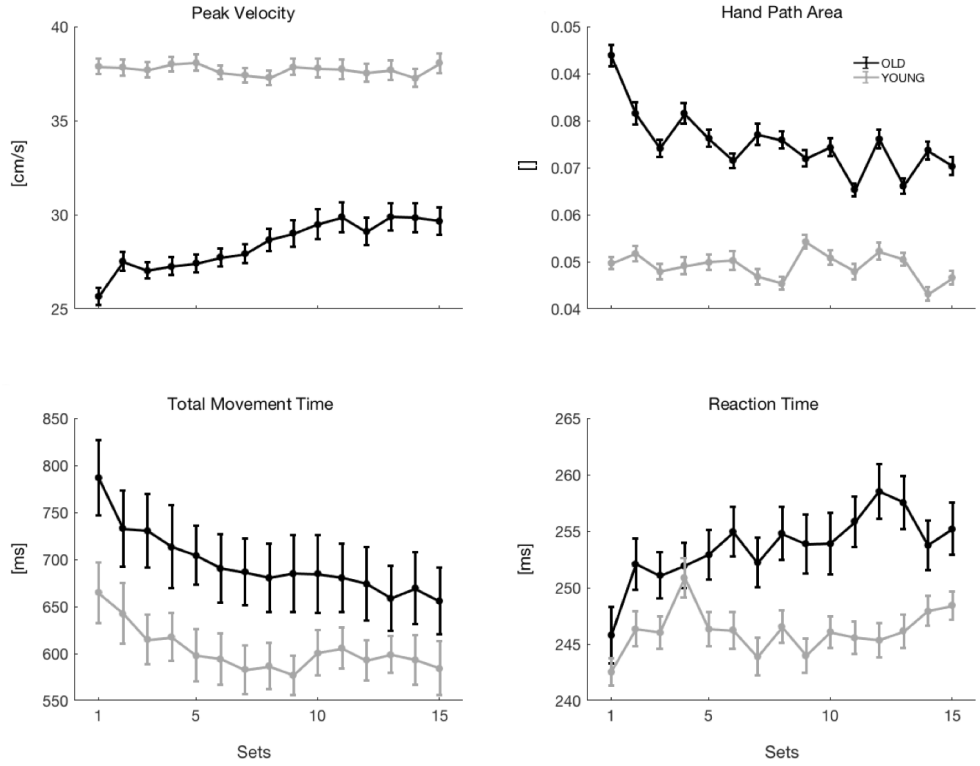

Figure 5.2 Average of kinematic measures of each set (56 movements each) for the younger (grey lines and dots) and older (black lines and dots) groups. The vertical bars represent standard errors of the mean.

Table 5.2 Correlations between Behavioral parameters and age

Δ INDEX VS AGE	R^2	**P**
Reaction Time	0.00	0.853
Peak Velocity	0.02	0.490
Hand-Path Area	**0.29**	**0.005**
Total Movement Time	0.04	0.330
	Left ROI	
ERD magnitude	0.03	0.384
ERS magnitude	0.05	0.286
ERD peak latency	0.01	0.722
ERS peak latency	0.08	0.177
	Frontal ROI	
ERD magnitude	0.12	0.085
ERS magnitude	0.03	0.400
ERD peak latency	0.01	0.612
ERS peak latency	0.09	0.143

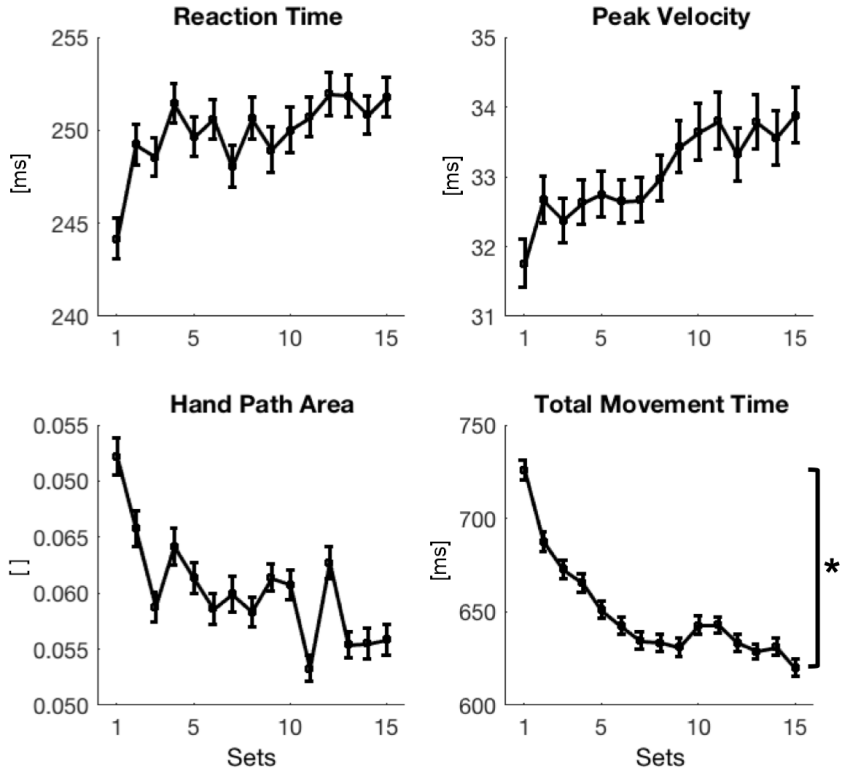

Figure 5.3 Kinematic parameters across 15 sets. Each point indicates mean ± S.E. of 56 movements

0.973; ROI*Group: $F_{(2,23)} = 1.47, p = 0.251$; Practice*ROI: $F_{(28,670)} = 0.899, p = 0.618$; Practice*ROI*Group: $F_{(28,670)} = 1.00, p = 0.465$). Nevertheless, we found main effects of practice and ROI ($F_{(28,672)} = 4.69, p < 0.001; F_{(2,23)} = 3.71, p = 0.040$; respectively). The results of univariate mixed model ANOVAs for ERD and ERS (Tab. 5.3) confirmed a significant effect of practice for both measures. They also revealed a difference between ROIs for ERD magnitude. Over the frontal ROI, the significant across-set increase extended also to beta ERD: inspection of the data in Fig. 5.4 suggests that such an effect was more evident, although not significantly so, in the older group. Univariate mixed model ANOVA for beta modulation depth (Tab. 5.3) revealed only a main effect of practice, without any interaction between variables. Finally, as in previous studies (Moisello, Blanco, Lin, et al. 2015; Nelson et al. 2017) we found no significant correlation between the practice-related changes of ERD, ERS or beta modulation and the performance changes across sets. Altogether, these results suggest that practice-related changes of beta modulation in both ROIs are similar in the two groups. Further analyses on all subjects showed no correlation between the mean values of ERD, ERS and modulation depth and the subjects' age for both left and frontal ROIs (all: $R^2 < 0.01, p > 0.50$). Also, correlations between magnitude difference across sets and age did not reveal any direct link between beta modulation and anagraphical age (Tab 5.2).

Table 5.3 Results of mixed model univariate ANOVAs for the magnitude of ERD and ERS and beta modulation depth

	Group (G)		**Practice (P)**		**ROI (R)**		**P*G**	
	F	**p**	**F**	**p**	**F**	**p**	**F**	**p**
ERD	0.07	0.788	**2.48**	**0.035**	**6.88**	**0.015**	0.51	0.770
ERS	0.68	0.417	**8.97**	**<0.001**	1.09	0.307	0.67	0.654
β Modulation	0.56	0.460	**9.13**	**<0.001**	1.44	0.241	0.67	0.657
	R*G		**P*R**		**P*R*G**			
	F	**p**	**F**	**p**	**F**	**p**		
ERD	3.05	0.094	1.01	0.424	1.39	0.225		
ERS	1.59	0.219	0.69	0.626	0.83	0.526		
β Modulation	1.78	0.195	0.71	0.614	0.78	0.563		

5.3.3 Beta modulation depth in the right sensorimotor area is lower compared to the other ROIs

Since we did not detect any group difference in ERD, ERS and beta modulation amplitude, we combined the two groups to assess differences in three ROIs (Fig. 5.1), as well as their

Table 5.4 Results of the Mixed Model ANOVA for ERD, ERS, and beta modulation comparing groups across practice in the two ROIs

	Group		**Practice**		**Group*Practice**	
	F	**p**	**F**	**p**	**F**	**p**
			Left ROI			
ERD	0.52	0.477	1.36	0.246	0.65	0.664
ERS	1.76	0.197	**7.71**	**<0.001**	0.63	0.666
β Modulation	1.72	0.203	**7.95**	**<0.001**	0.68	0.661
			Frontal ROI			
ERD	1.09	0.308	**3.43**	**<0.001**	0.75	0.591
ERS	0.00	0.959	**6.19**	**<0.001**	0.75	0.571
β Modulation	0.00	0.962	**6.05**	**<0.001**	0.72	0.595

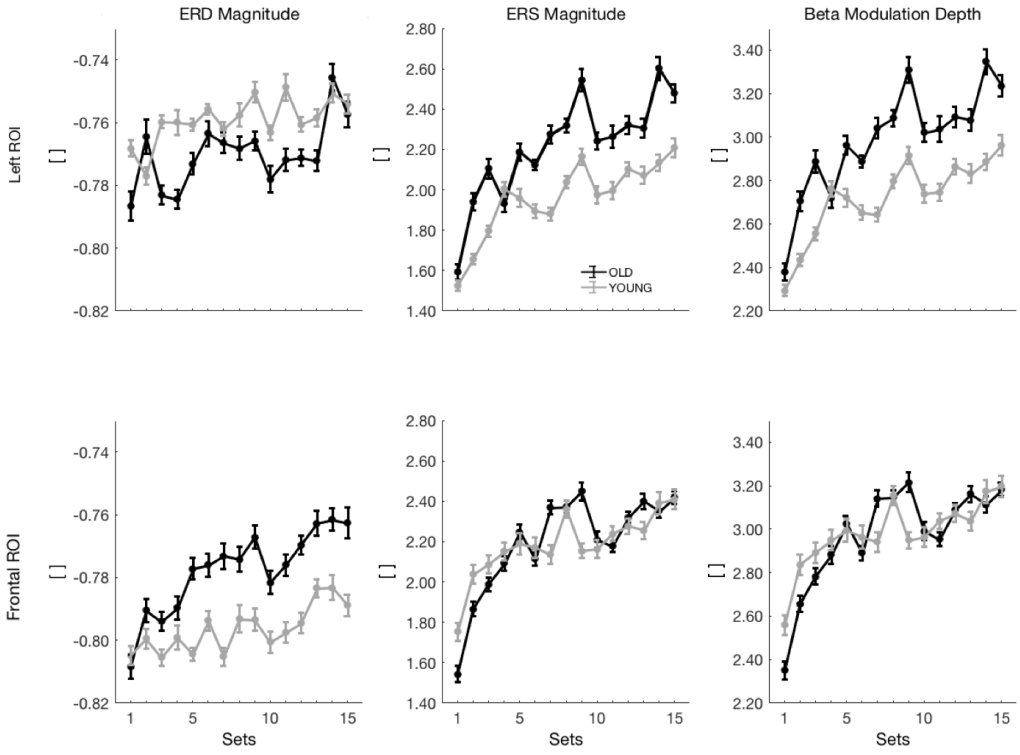

Figure 5.4 Average of ERD, ERS and Beta Modulation magnitudes for the Left (top) and Frontal (bottom) ROIs for each set in the younger (grey lines and dots) and older (black lines and dots) groups. The vertical bars represent standard errors of the mean.

magnitude changes with practice. In agreement with previous results, we found that the right sensorimotor ROI, ipsilaterally to the movement, showed lower ERD, ERS and beta modulation depth than the other two ROIs (Fig. 5.5). Specifically, the right ROI ERD was significantly lower than the left (post hoc test $p = 0.006$) and frontal ($p = 0.002$) ones. Interestingly, the frontal ROI had borderline significant greater ERD than the left ROI. ($p = 0.055$). ERS and beta modulation depth were significantly lower in the right ROI (ERS: right vs. left $p = 0.009$; right vs. frontal $p = 0.004$; left vs frontal $p = 0.936$ Modulation Depth: right vs. left $p = 0.006$; right vs. frontal $p = 0.003$; left vs. frontal $p = 0.743$). Repeated measure ANOVAs also indicated a significant increase across sets for ERD, ERS and modulation depth (Tab. 5.5); no interactions were found between ROIs and sets. We then correlated practice-related kinematic changes with ERD, ERS and beta modulation increases; even in this case, we did not find any direct relationship between performance and beta modulation changes.

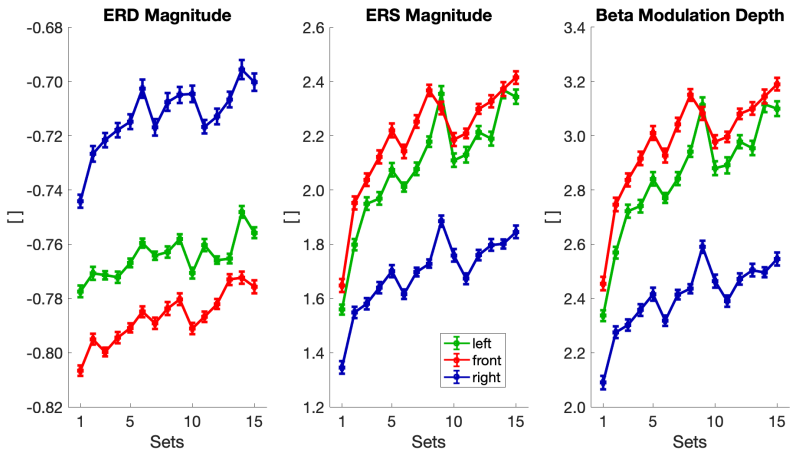

Figure 5.5 ERD, ERS and modulation depth in the ROIs across 15 sets. Error bars indicate standard errors.

Table 5.5 Statistical results of the EEG indices

	ERD		**ERS**		**Modulation Depth**	
	F	**p**	**F**	**p**	**F**	**p**
Sets	**4.77**	**0.001**	**13.89**	**<0.001**	**13.95**	**<0.001**
ROI	**12.73**	**0.337**	**9.55**	**<0.001**	**10.52**	**<0.001**
Sets*ROI	0.60	0.762	0.70	0.679	0.80	0.594

5.3.4 Timing of ERD and ERS is similar in the three ROIs

Subsequently, we investigated whether ERD and ERS timings at their peak occurrence were similar in the three ROIs when the two groups were combined (Fig. 5.6). We found no difference between ROIs (ERD: $F_{(1.17,29.16)} = 0.01, p = 0.956$; ERS: $F_{(1.14,28.60)} = 0.27, p = 0.637$); the results of the ANOVA also revealed that timing of peak ERS decreased in the course of practice ($F_{(6.21,155.15)} = 3.74, p = 0.001$), while the ERD timing did not change ($F_{(14,350)} = 1.22, p = 0.258$) and no interactions were found (ERD: $F_{(11.99,299.78)} = 0.70, p = 0.751$; ERS: $F_{(11.57,289.36)} = 0.74, p = 0.703$). Correlations between timings and kinematic parameters did not revealed any relationship between ERD and ERS time changes and performance.

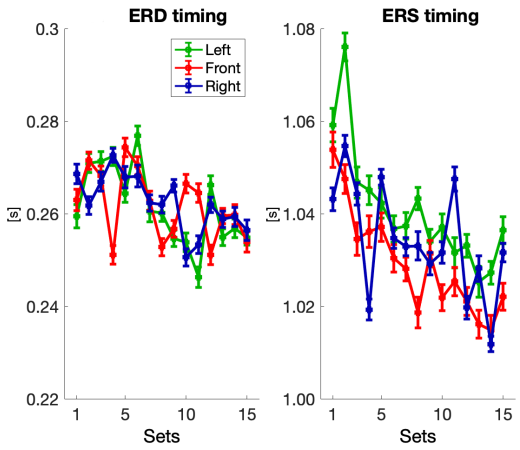

Figure 5.6 ERD and ERS peak timing in the three ROIs across 15 sets of practice. Error bars show standard errors.

5.3.5 ERS timing occurs later in older adults and correlates with total movement time

We then determined whether ERD and ERS peak latency changed across sets and groups. Inspection of the data suggests that ERS peak latency was higher in the older but decreased with practice in both groups (Fig. 5.7). Statistical analyses (Tab. 5.6, 5.7) showed a significant group difference ($F_{(2,23)} = 7.93, p = 0.002$) and a significant effect of practice ($F_{(28,670)} = 1.75, p = 0.010$). However, we found no significant effect of ROI ($F_{(2,23)} = 2.30, p = 0.123$) and interactions (ROI*Group $F_{(2,23)} = 0.634, p = 0.540$; Practice*Group: $F_{(28,670)} = 0.95, p = 0.535$; Practice*ROI $F_{(28,670)} = 0.84, p = 0.705$; Practice*ROI*Group $F_{(28,670)} = 0.80, p = 0.766$). Importantly, the temporal occurrence of ERS peak was linked

to total movement time in both the left and the frontal ROIs ($R^2 = 0.42, p < 0.0001; R^2 = 0.33, p = 0.002$, respectively; Fig. 5.8). However, ERS peak latency did not correlate with other kinematic parameters and with either ERS amplitude or beta modulation depth in both the left and the frontal ROI ($R^2 < 0.08, p > 0.16$). Altogether, these results show no effect of aging on ERS and ERD peak latency, but only a strong dependence of ERS peak latency on movement duration. This is further supported by the lack of significant correlation between changes in peak latency across sets and age (Tab. 5.2).

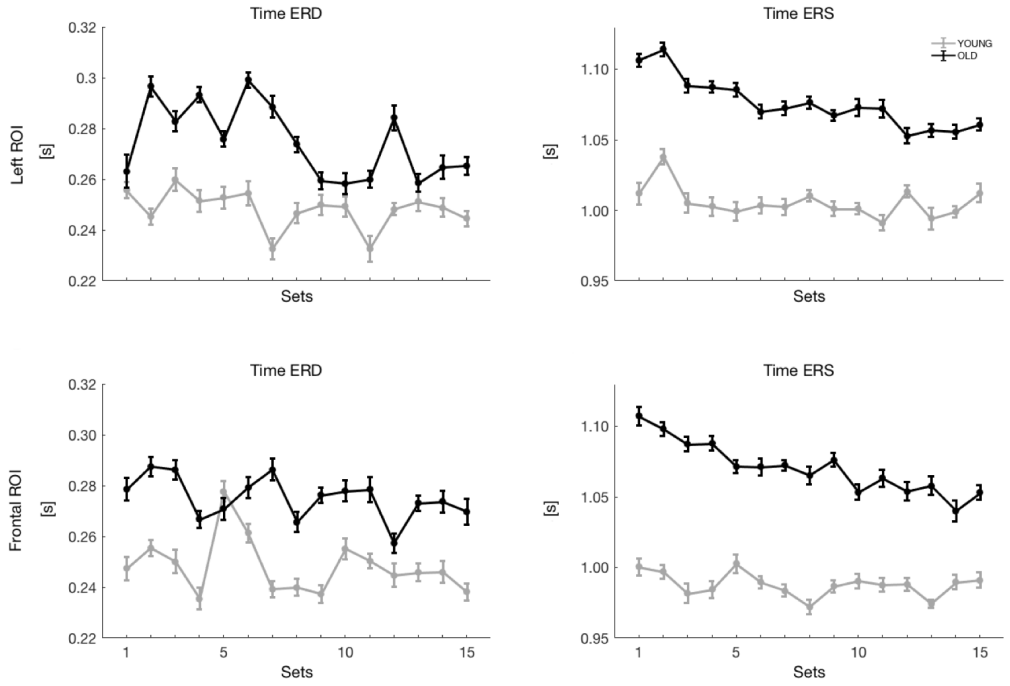

Figure 5.7 Average peak latencies of ERD and ERS for each set in the younger (grey circles and lines) and older (black circles and lines) groups for the Left (upper graphs.) and frontal (lower graphs) ROIs. The vertical bars represent the standard error of the mean.

5.3.6 ERS of the frontal ROI occurs in a different range of the beta band compared to the sensorimotor cortices

We finally verified whether the movement-related beta oscillatory changes occurred in the same frequency range in the three ROIs. Thus, we isolated the frequency of the peak ERD and ERS. As a first step, we checked whether ERD and ERS peak frequency changed across sets and ROIs. ANOVAs results on peak ERD did not reveal any effect of set

Table 5.6 Result of repeated measure ANOVAs for ERD and ERS peak latency.

	Group (G)		**Practice (P)**		**ROI (R)**		**P*G**	
	F	**p**	**F**	**p**	**F**	**p**	**F**	**p**
ERD	**4.35**	**0.048**	1.07	0.386	0.00	0.959	0.78	0.649
ERS	**12.42**	**0.002**	**2.74**	**0.015**	3.96	0.058	1.13	0.350

	R*G		**P*R**		**P*R*G**	
	F	**p**	**F**	**p**	**F**	**p**
ERD	0.00	0.975	1.03	0.419	0.93	0.501
ERS	1.14	0.296	0.65	0.747	0.66	0.730

Table 5.7 Results of the Mixed Model ANOVA for ERD, ERS, and beta modulation peak latency.

	Group		**Practice**		**Group*Practice**	
	F	**p**	**F**	**p**	**F**	**p**
			Left ROI			
ERD	3.99	0.057	1.20	0.296	1.07	0.388
ERS	**9.78**,	**0.005**	**2.46**	**0.023**	0.82	0.562
			Frontal ROI			
ERD	4.20	0.052	0.91	0.516	0.61	0.777
ERS	**13.56**	**0.001**	1.82	0.084	1.16	0.330

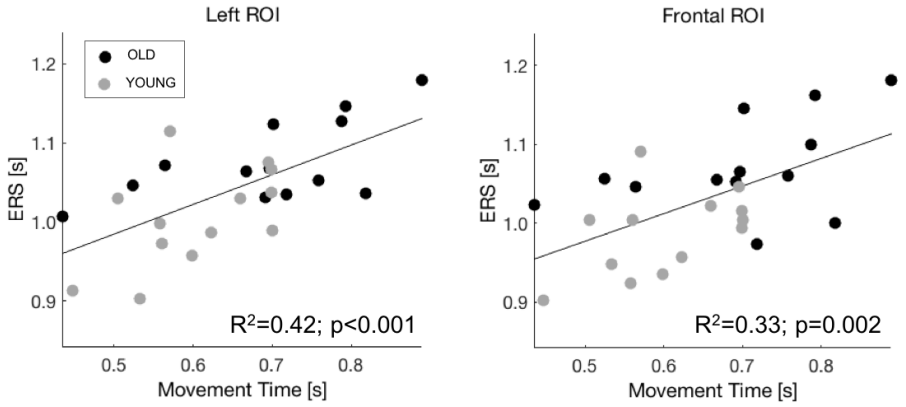

Figure 5.8 Correlations of total movement time with ERS peak latency in the Left (a.) and Frontal (b.) ROIs for younger (gray points) and older (black points) subjects combined.

($F_{(14,350)} = 0.47, p = 0.946$), ROI ($F_{(2,50)} = 0.59, p = 0.561$) and interaction ($F_{(28,700)} = 0.84, p = 0.705$). On the other hand, analysis on ERS peak showed a main effect of ROI (Fig. 5.9; $F_{(2,50)} = 7.93, p = 0.001$). Pairwise comparison revealed that the ERS frequency of the frontal ROI was higher than those of the sensorimotor ones (frontal vs left $p = 0.001$; frontal vs right $p = 0.007$) that did not differ from each other ($p = 1.000$, Fig. 5.4). No effect of sets ($F_{(7.1,177.50)} = 1.28, p = 0219$) nor interaction were found ($F_{(10.59,264.81)} = 1.12, p = 0.348$). This difference of ERS frequency between the frontal and the sensorimotor regions was even more visible when we computed time-frequency representations of the three ROIs (Fig. 5.10) on all the trials. In fact, Nonparametric Permutation Testing with False Discovery Rate correction revealed that ERS occurred in the range between 15 and 18 Hz over the left sensorimotor ROI, while the frontal ROI ERS between 23 and 29 Hz (Fig. 5.11). We did not find any frequency difference between ROIs when we analyzed ERD, which mainly occurred around 19 Hz. Of note, we only compared frequency differences between the left and frontal ROIs, because the significant lower magnitude values of the right ROI could have biased the results. Finally, we did not find any correlation between practice-related peak frequency of both ERD and ERS and kinematic changes.

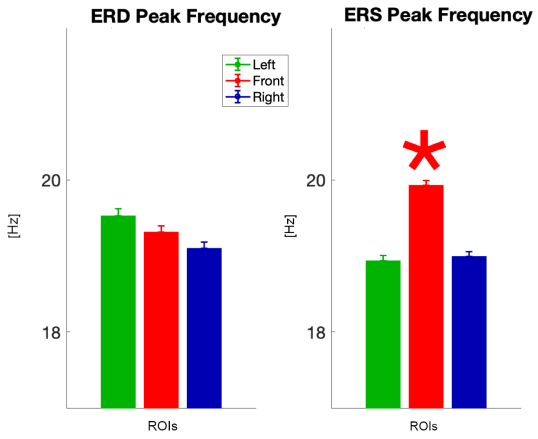

Figure 5.9 ERD and ERS peak frequency in the three ROIs.

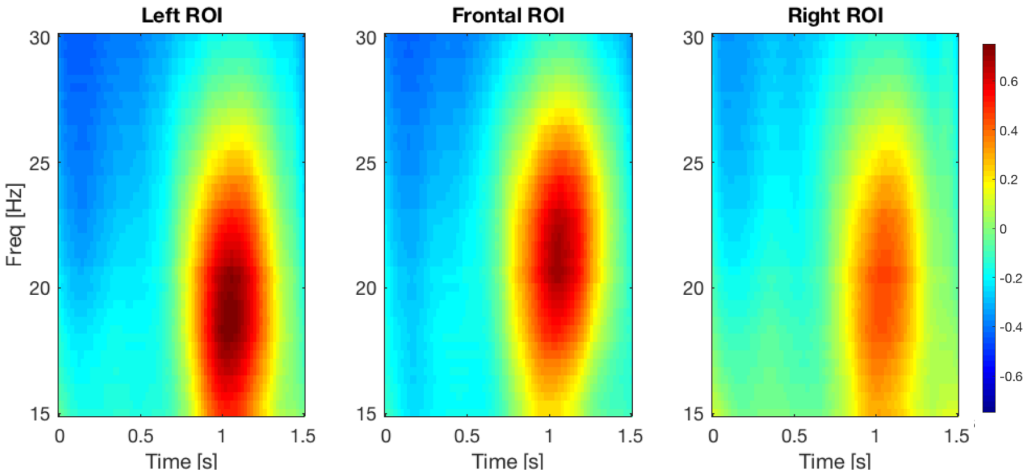

Figure 5.10 Time-frequency plot for the event-related spectral change over the three ROIs, obtained by averaging all trials.

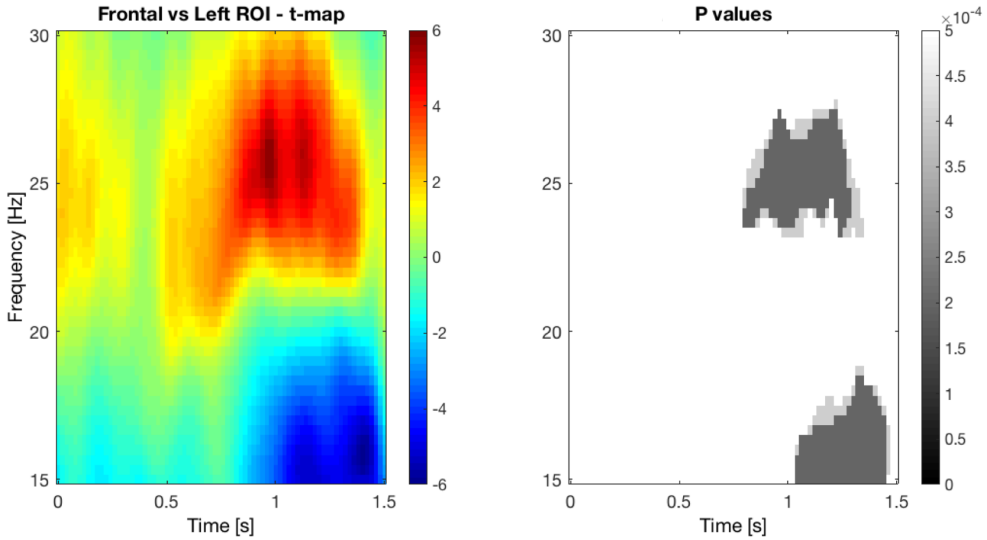

Figure 5.11 Left: t-map resulting from the nonparametric permutation testing of frontal vs left ROIs time-frequency representations. Right: p-values map after false discovery rate corrections of significant results

5.4 Discussion

5.4.1 Performance change with practice with differences between young and older subjects

Deterioration of motor performance in the elderly has been reported in several publications, involving spatial and temporal characteristics of motor performance. The causes of this decline are multiple and may involve, singly or in combination, muscular, skeletal as well as the central and peripheral nervous systems. During aging, progressive muscle deterioration [Hunter et al. (2016)], increased muscle fatigability, and sarcopenia [Metter et al. (1999); McNeil and Rice (2007); Ray and Maunsell (2010); Kent-Braun et al. (2014)] may occur with loss of motor units, remodeling of neuromuscular junctions, and eventually with alteration of peripheral and neuromuscular transmissions [Campbell et al. (1973); Seidler et al. (2010); Hepple and Rice (2016)]. Beside decreasing muscle strength [Perry et al. (2007)], aging may impair also proprioceptive processing [Skinner et al. (1984)], as well as the function of cortical motor regions [Seidler et al. (2010)] and the basal ganglia [Raz et al. (2003)]. This can result in mobility problems and an increased risk of falling [Verghese et al. (2006)].
Our results showed that, besides being slower, the movements of the older group had greater hand path area values, suggesting a worse interjoint coordination [Sainburg et al. (1995); Huber et al. (2006); Moisello et al. (2008)]. This occurred despite the older groups' movements were slower and thus, the interaction torques developing during movement should have been easier to counteract, and movements should have had overlapping trajectories. Intact proprioception is necessary for overcoming these forces by providing feedback during the movement but also by updating the sensorimotor memories used to program movements through feedforward mechanisms [Sainburg et al. (1995); Huber et al. (2006); Moisello et al. (2008)]. Therefore, even small problems in proprioception information processing, as the ones reported in aging, may produce deficits of intersegmental dynamics, despite low movement velocities, thus resulting in increases of both inter-joint timing and hand path area. Importantly, the older group also showed a decrease of hand path area across sets with values approaching the range of the younger group in the last sets. This decrease occurred together with an increase of peak velocity, suggesting that learning occurred in the older group. These practice-related improvements also indicate a shift toward the use of feedforward mechanisms, and possibly suggest memory formation in this particular aspect of performance [Nelson et al. (2017)]. To be noticed, performance of the younger group reached a plateau already in the first set, thus minimizing the significance of the improvements during

the last set. This conclusion is supported also by the fact that the values of hand-path area in the older group hardly reached those of the younger subjects.

5.4.2 Beta modulatory activity increases with practice without differences between groups

During a 30-minute reaching task we found a progressive increase of ERD, ERS and beta modulation depth over all the ROIs. A possible explanation of such ERD, ERS increase might be fatigue: with time subjects may get tired and thus require a higher involvement of the sensorimotor cortex represented by a lower ERD and a higher ERS. However, behavioral data do not reveal any fatigue. Indeed, neither reaction time nor peak velocity decrease with practice. We thus speculated that the lack of correlation between practice-related magnitude changes and kinematic data can depend on the fact that beta modulation does not directly reflect movement characteristics, but instead it can be related to movement planning and execution of a movement through sensorimotor integration processes [Shimazu et al. (1999); Cassim et al. (2000); Tatti et al. (2019)]. Also, practice-related beta modulation may represent plasticity and thus LTP-like phenomena in the sensorimotor cortex [Hall et al. (2010); Moisello et al. (2015a); Nelson et al. (2017)]. Previous works have shown that older participants need to recruit additional resources in sensorimotor and premotor areas to achieve normal movement execution [Sailer et al. (2000); Heuninckx et al. (2005), Heuninckx et al. (2008); Swinnen et al. (2010); Vallesi et al. (2011)]. Thus, the progressive increase of ERD magnitude in older subjects over the frontal ROI may reflect an increased recruitment to improve performance across sets. These results are in agreement with a study showing no age effect on the mean value of ERD recorded over the left sensorimotor area with a grip task [Rossiter et al. (2014)], but at odds with a work demonstrating that mean ERD amplitude was greater in older subjects during a motor sequence task [Heinrichs-Graham et al. (2018)]. It is conceivable that such discrepant results may originate from differences in task characteristics and sample size. Also, anagraphical age may not be the only and best predictor of changes in cortical function and performance, as it is increasingly more evident that exercise and other factors play important roles in decreasing or accelerating aging processes.

As mentioned earlier, the most novel result is that the increases of beta modulation across sets are similar in the younger and older groups and, notably, this occurs despite important group differences in performance indices. This result prompts two sets of considerations. First, the magnitude of movement-related beta oscillations does not directly reflect movement characteristics, in line with other studies reporting a lack of correlation between ERD ERS

and speed [Stancak and Pfurtscheller (1995), Stancak and Pfurtscheller (1996)], force [Wu et al. (2006); Cremoux et al. (2013); Fry et al. (2016)], movement type [Kilavik et al. (2013)] or muscle pattern [Salmelin et al. (1995)]. Specifically, previous studies found beta oscillatory differences in slow versus fast movements [Stancak and Pfurtscheller (1995)]; however, a correlation between EMG burst and ERS latency was detected only for slow movements. Similarly, no direct relationship between movement parameters and ERS, despite an ERS difference between extension-flexion and flexion-extension movements had been found [Stancak (2000)]. Also, a recent work from our research group, indicated that no link between movement extent and beta modulation magnitude is detected in upper limb reaching movements [Tatti et al. (2019)]. Indeed, movement-related beta oscillations may be related to sensorimotor integration processes associated with movement planning and execution rather than explicitly reflecting the coding of distinct movement features [Shimazu et al. (1999); Cassim et al. (2000)]. The second set of considerations is based on the fact that the continuous performance in our motor tasks should induce constant and regular interplay of sensory and motor regions' activities [Shimazu et al. (1999); Cassim et al. (2000)], thus providing the bases for use-dependent LTP induction. Improvements of velocity and inter-joint coordination indices during the task in the older group indicate a major shift of the performance toward a reinforcement of the feedforward mechanisms, and thus of memory formation. Practice-related beta modulation increase may reflect this phenomenon [Nelson et al. (2017)]. If indeed, as also suggested by other evidence [Hall et al. (2010); McAllister et al. (2013)], beta modulation depth increases reflect LTP-like phenomena in the sensorimotor cortex; then one may speculate that plasticity-related mechanisms in the sensorimotor cortex should not be particularly affected by age. Studies testing the effect of age on the plasticity of the sensorimotor cortex with TMS have not shown clear differences between younger and older subjects and the picture may be further complicated by the influence of hormonal levels on PAS results [Fernández et al. (2003); Tecchio et al. (2008) and neural plasticity in general [Adams and Morrison (2003); Hofmann (2006)]. Indeed, our results needs to be replicated in a larger population, also taking into account factors other than age that could affect cortical plasticity mechanisms, such as motor and cognitive reserves.

5.4.3 ERD and ERS occurred at the same time in the three ROIs but with different amplitudes in the right sensorimotor area

In agreement with previous results [Moisello et al. (2015a); Nelson et al. (2017)], we observed greater ERD, ERS and beta modulation over the sensorimotor cortex contralaterally to the moving arm compared to the ipsilateral ROI. In fact, this area has been reported to be active during voluntary movements [Salmelin et al. (1995); Ghilardi et al. (2000)]. However, beta modulatory activity over the ipsilateral motor cortex showed, albeit to a lesser extent, a similar increase across sets and a similar peak occurence, suggesting a direct involvement of such area in movement production. Previous works have speculated on the role of the ipsilateral sensorimotor cortex on movement planning and execution; its activation may be related to movement organization and mirror movement suppression [Kristeva et al. (1991); Leocani et al. (2000); Taniguchi et al. (2000); Cheyne et al. (2006); Schaefer et al. (2009)]. Moreover, animal studies revealed that projections between proximal sensorimotor areas exist and thus the activation of the contralaterally motor areas could spread to the ipsilateral through callosal connections [Pandya et al. (1969); Jacobson and Trojanowski (1974); Pappas and Strick (1981)]. Also, ERS has been related to increased cortical inhibition in the contralateral but not in the ipsilateral motor cortex [Chen et al. (1998); Leocani et al. (2001); Rau et al. (2003)]. The different role of the motor cortices during voluntary movement may explain the magnitude differences of ERD, ERS and beta modulation. Finally, the involvement of the frontal cortex, which shows beta modulatory activity of similar magnitude and latency to that of the contralateral motor cortex, could be explained by the different functions related to motor control that occur in the frontal area, such as attentional processes related to motor planning and performance as well as to the updating of the internal models that are necessary for efficient planning and execution [Jurkiewicz et al. (2006)].

5.4.4 ERS peak latency correlates with total movement time, thus occurring later in the older group

Only a few studies have focused on the ERS peak latency or its duration. It is generally accepted that ERS occurs 300-1000 ms after movement ends and lasts several seconds [Pfurtscheller (1992); Salmelin and Hari (1994); Stancak and Pfurtscheller (1995); Pfurtscheller et al. (1996); Jurkiewicz et al. (2006); Fry et al. (2016))] Indeed, the present study with fast reaching movements at a pace of 1.5 s in a choice reaction time task showed that, on average, the peak latency of peak ERS is highly correlated with the total movement time and that it occurs from 300 to 400 ms from the end of the out and back movement. This

observation is in agreement with the idea that ERS peak coincides with a deactivated state of the motor cortex, and thus to a reduced excitability of the neuronal populations [Chen et al. (1998)]. The peak latency characteristics of ERS are linked to the type of task and the movement duration. In tasks with isometric wrist contractions, ERS occurrence is related to the rate of force development but not the force output [Cremoux et al. (2013); Fry et al. (2016)]. During a task with repetitive movements, ERS occurs earlier than in a task with discrete finger movements [Wu et al. (2006)]. Another work demonstrated that ERS lasts longer after withholding of real foot movements compared to imagined foot movements [Solis-Escalante et al. (2012)], with the faster movements showing earlier ERS peak occurrence.

5.4.5 ERS of the frontal ROI occurs in the higher end of the beta range

One of the most innovative findings is that, compared to the sensorimotor areas, the frontal ERS is overall shifted toward the high beta range. Specifically, time-frequency representations revealed that the ERS in the left sensorimotor cortex occurs between 15 and 18 Hz, the frontal ROI shows an ERS in the higher beta range, between 23 and 29 Hz. The frontal cortex has several functions that require the integration of information from multiple regions of the brain. In fact, it is responsible for learning, memory, attention, and motivation, in order to plan the most appropriate behavior in response to internal and external stimuli. During a movement, the frontal cortex combines information from sensory and motor cortices; in particular, studies on reaching and catching movements underlined the importance of the frontal region during monitoring and correction of an ongoing performance and, most importantly, during updating of internal models [Contreras-Vidal and Kerick (2004); Tombini et al. (2009); Perfetti et al. (2011b)]. Other studies hypothesized that beta activity originates from multiple sources and thus reflects different functional processes [Pistohl et al. (2012); Cremoux et al. (2013); Kilavik et al. (2013)]. Our result perfectly fits this idea that beta can have many roles that can be distinguished by differences in the predominant frequency. Also, our finding is further supported by previous studies showing that the ERS frequency following finger dorsal flexions is lower in the hand motor area, compared to the supplementary motor cortex [Shimazu et al. (1999); Cassim et al. (2000)]. A possible explanation of this phenomenon may be that, after the movement ends, the sensory motor region and the frontal area show different oscillations that may be related to different processes.

Chapter 6

General Discussion

The main goal of this study was to determine whether local sleep, defined as a progressive slowing of the EEG activity during wake, was associated with extended learning in well rested subjects. In particular, we collected and analyzed electrophysiological and behavioral data of healthy subjects performing motor and visual sequence learning tasks during a full-day experiment. Additionally, we collected a sample of subjects performing a planar reaching task without any visuo-motor rotation, in order to discriminate between learning and fatigue. As expected, EEG results showed a task-related activity which was different in the three tasks. The motor tasks were characterized by an activation corresponding to the motor areas, together with a frontal activation, mainly in the alpha and beta ranges. By contrast, the visual sequence learning task presented a beta and gamma posterior activation, specifically on the right side. Similarly, the same regions showed a progressive slowing in the EEG activity at rest, only after sustained learning. Further, learning provoked a selective decline of the performance, only for tests that were similar to the tasks.

As a second step, we were interested in determining whether sleep was necessary for EEG activity and performance renormalization. In other words, the goal was to discriminate between neuronal fatigue caused by extended activity, balanceable by a period of restful quiet wake, and extended plasticity, requiring synaptic renormalization associated with sleep. Our finding further supports the idea that local sleep is triggered by learning; in fact, only 90 minutes of sleep partially renormalized EEG slowing, performance and learning ability.

Starting from the main results, movement-related EEG activity was analyzed, since this activity was prominent in both the reaching task and the visuo-motor learning tasks. Several studies tried to related such pattern with performance changes, linking it to learning and plasticty. Hence, I focused on the event-related desynchronization and synchronization associated with movement execution in the beta range (15-30 Hz), because this pattern

has been extensively characterized over the years in several types of movements. The hypothesis was that changes in such activity could better explain local sleep occurrence, as beta activity changed with practice over the brain regions affected by local sleep. Specifically, I focused on the magnitude, timing and predominant frequency, of both the synchronization and desynchronization, analyzed over three brain regions, namely the two sensorimotor areas and a frontal region, showing a strong oscillatory activity. Further, I compared two populations: young and old healthy participants, as aging may cause changes in both motor performance and learning. Finally, I tried to relate changes in the modulation with specific movement features such as movement extent and time, reaction time and peak velocity. Analysis did not reveal any EEG difference between young and older subjects, despite young participants being faster and more accurate and both groups improving with practice. Of note, this analysis confirmed previous findings on beta modulatory activity. In fact, we found a progressive ERD and ERS increase with practice which may correlate with resting state EEG slowing. Finally, we did not find any direct relationship between beta oscillatory activity and movement features, but we found a frequency difference between the motor areas and the frontal region: the former had a predominant synchronization in the lower edge of the beta range (15-18 Hz), while the latter presented a shift toward the higher edge (23-29 Hz). This result is particularly intriguing considering that the frontal region was the area showing local sleep at rest only after the visuo-motor rotation but not after planar reaching movements, suggesting separate processes underlying motor planning, execution and learning.

Altogether, these results should be taken into account in all the contexts where learning and plasticity play an important role in the acquisition of new motor skills. In particular, it would be important to determine a proper trade-off in the number of repetitions of the same tasks during a session. This is a critical point to address because repetitive practice has been related to motor improvement in both healthy and subjects with pathologies [Lee et al. (1991)]; on the other hand, extended practice may cause neuronal fatigue leading to performance and learning ability deterioration. If we consider populations with a pathology the situation is even more complex: several rehabilitative programs are based on multiple repetitions of the same movement, in order to learn compensative strategies and improve neural plasticity. As an example, studies on stroke patients revealed that increased amounts of task repetition cause cortical changes and functional improvement [Nudo et al. (1996)]. More generally, hundreds of repetitions are required for neural plasticity [Kimberley et al. (2010)]; for this reason, intensive rehabilitation is currently moving toward intensive treatments, i.e. multiple sessions with little or no rest between sessions [Vearrier et al. (2005); Carlson et al. (2006)]. In this context, it is important to determine the correct amount of practice required to maximize the

learning and simultaneously minimize the risk of neuronal fatigue. Of note, other factors play a fundamental role in motor learning, especially for complex movements and pathologies. Among them, physical fatigue, involvement and reward [Carron and Ferchuk (1971); Abe et al. (2011); Wittmann et al. (2011)].

Finally, the present study further supports the idea that sleep is beneficial for restoring learning ability. Indeed, rehabilitative treatments should also consider a proper amount of sleep between sessions. This may include checking for a correct sleep schedule and eventually, adding some periods of sleep, especially in case of demanding and prolonged tasks.

Chapter 7

Conclusion

This study demonstrated that performing a learning tasks for three hours affects selectively EEG activity and performance of well-rested subjects. To the best of my knowledge, this is the first time that local sleep has been detected in well-rested subjects. In particular, the brain regions involved in the learning tasks present a progressively slower activity at rest; further, only performance on tasks sharing the same neural substrate as the learning activity are affected by such phenomenon. Importantly, only learning tasks produce local sleep, as the EEG activity and behavioral data recorded in the control condition do not reveal such pattern. EEG changes, performance decline and learning ability are partially renormalized by a 90-minute nap, but not by an equivalent period of quiet wake, suggesting that local sleep is triggered by the cellular consequence of synaptic plasticity associated with learning. Previous studies in animal human subjects detected local sleep, as a consequence of extensive wake and learning; this project adds some knowledge on the field, discriminating between extensive practice and learning and investigating the role of a brief period of sleep.
Since this is the first study in the field, several future developments can be defined: firstly, different approaches, such as functional connectivity and source analyses could add some knowledge explaining the relationship between task-related and resting state EEG changes. Second, extensive learning should be related to physical fatigue, through biological measures such as electromyography or electrooculography; also, sleep studies should determine the proper amount of sleep required to completely renormalize performance and EEG activity. In addition, brain activity during the learning task should be investigated using time-frequency approaches, especially focused at trials with errors. This would allow characterization of the brain activity underlying mistakes. We started to investigate this point, inspecting movement-related EEG activity and relating it to behavioral measures. Specifically, we did not find any direct relationship between movement-features and beta oscillatory activity, suggesting that

movement-related activity may reflect plasticity-related mechanism, rather than movement execution.

Obviously, studies on more complex learning tasks are required to replicate our findings. However, giving the intricate scenario of neural plasticity and learning, the number of factors possibly affecting motor learning and the diversity of pathologies, designs as the one proposed in this study, mainly involving planar reaching movements in healthy subjects are necessary to understand the basis of neural plasticity after extended learning and thus investigate more complex situations. This is an essential step toward novel discoveries on how the brain learns motor tasks, which factors influence the process and how pathologies can affect it.

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