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Sorbonne Université

École Doctorale Cerveau, Cognition, Comportement (ED3C)

Institut du Cerveau (ICM)

Physiological Investigations of Clinically Normal and Impaired Cognition (PICNIC)

Au-delà du comportement: marqueurs électrophysiologiques du traitement conscient

Emilia Fló Rama

Thèse de doctorat en Sciences Cognitives

Sous la direction de Jacobo Sitt

Présentée et soutenue publiquement le 20 Septembre 2024

Devant un jury composé de:

Tal SEIDEL MALKINSON	Université de Lorraine	Présidente du jury
Raul C. MURESAN	Institut transylvanien de neurosciences	Rapporteur
Damian CRUSE	Université de Birmingham	Examineur
Lucía MELLONI	Max Planck Institute	Examinatrice
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Sorbonne University

The Brain, Cognition and Behavior Doctoral School (ED3C)

Paris Brain Institute (ICM)

Physiological Investigations of Clinically Normal and Impaired Cognition (PICNIC)

Beyond behavior: electrophysiological markers of conscious processing

Emilia Fló Rama

Dissertation for the degree of Doctor in Philosophy

Under the supervision of Jacobo Sitt

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Résumé

L'étude de la conscience pose un paradoxe. La « chose » que nous essayons d'évaluer est omniprésente et inévitable lorsque nous considérons notre propre conscience, mais inaccessible pour celle des autres. Normalement, nous déduisons qu'un individu est conscient de ses réponses et de son comportement adéquats. Cependant, chez les patients avec des troubles de la conscience (DoC), établir le niveau de conscience par le comportement est un défi clinique majeur. Un diagnostic précis est essentiel pour guider les décisions sur les soins et les thérapies de maintien de la vie. L'objectif principal de cette thèse était de développer de nouveaux paradigmes expérimentaux et des analyses pour évaluer l'état de conscience chez les patients cérébrolésés, en utilisant des outils disponibles en milieu clinique, en se concentrant sur deux domaines prometteurs : les interactions cerveau-corps et le traitement du langage.

Dans la première étude, nous avons exploré le potentiel d'une approche réseau des enregistrements électromyographiques (EMG) et électroencéphalographiques (EEG), en combinaison avec la puissance corticale et l'activité cardiaque pour détecter l'imagerie motrice chez des participants sains. Nous avons constaté que bien que les réseaux cerveau-muscle n'étaient pas modulés par l'imagerie motrice, l'activité cardiaque et la puissance corticale étaient cruciales pour détecter quand un participant répétait mentalement un mouvement. Ce travail souligne l'importance de combiner l'EEG et les mesures périphériques pour détecter le suivi des commandes, ce qui pourrait améliorer la détection des réponses intentionnelles cachées chez les patients non réactifs.

Dans la deuxième étude, nous avons développé une mesure de suivi des commandes cachées basée sur l'attention intéroceptive et extéroceptive. Nous montrons que diriger l'attention vers les rythmes corporels ou les stimuli externes induit des réponses EEG spécifiques, permettant de suivre au niveau individuel l'attention cachée chez les participants sains. Dans un groupe de patients cérébrolésés, un patient en état végétatif et un

patient en syndrome d'enfermement ont montré des changements induits par l'attention dans le potentiel évoqué par le battement de cœur (HEP), et leur état attentionnel a été classifié en utilisant des caractéristiques dynamiques et le HEP. Nos résultats soulignent l'importance des mécanismes attentionnels dans le traitement sensoriel intéroceptif et extéroceptif et étendent le cadre des interactions cœur-cerveau pour le diagnostic chez les patients avec troubles de la conscience.

La troisième étude s'est concentrée sur le développement de marqueurs EEG du traitement conscient du langage en explorant les propriétés de la parole produisant des réponses neuronales communes chez les individus sains exposés à des histoires auditifs. En combinant des modèles d'encodage et une analyse de composantes corrélées, nous montrons que pendant l'écoute passive, attentive et non attentive, les caractéristiques acoustiques et linguistiques contribuent à la corrélation intersubjective évoquée par les histoires. Les modèles incluant l'imprévisibilité des mots étaient particulièrement sensibles à l'attention avec un profil topographique cohérente avec le traitement du langage. En suivant cette approche, nous avons analysé les données EEG de patients DoC alors qu'ils écoutaient une histoire dans le sens avant et arrière. Néanmoins, la brièveté des stimuli a entravé des résultats significatifs. Sur cette base, nous offrons quelques recommandations sur l'utilisation de ces outils pour évaluer la profondeur du traitement du langage au niveau individuel chez les patients DoC.

Dans l'ensemble, cette thèse propose de nouvelles méthodes non invasives pouvant être utilisées au chevet du patient pour sonder les capacités cognitives et la conscience chez les patients DoC. Les paradigmes développés ont des degrés de complexité variés et nécessitent différents niveaux d'engagement, allant des tâches passives aux tâches de suivi des commandes, permettant l'exploration de multiples niveaux de traitement de l'information chez les patients avec troubles de la conscience.

Abstract

The study of consciousness posits a paradox. The object of study, the ‘thing’ we try to assess is pervasive and inescapable when we consider our own consciousness, whereas it is inaccessible when we consider everyone else’s. Under normal circumstances, we infer that an individual is conscious from their adequate responses and behavior. In contrast, in patients with disorders of consciousness (DoC) stating the level of awareness through behavior poses a major clinical challenge as volitional responses can fluctuate, be hard to distinguish from reflexes, or even be totally absent. In these clinical situations, an accurate diagnosis is paramount to guide decisions regarding care and life-sustaining therapies. The main objective of this thesis was to develop novel experimental paradigms and analysis to assess and probe the state of consciousness in brain-injured patients based on tools available in common clinical settings by focusing on two promising fields: brain-body interactions and language processing.

In the first study, we explored the potential of a network approach to electromyography (EMG) and electroencephalography (EEG) recordings in combination with cortical power and heart activity to detect motor imagery in a group of healthy participants. We found that while brain-muscle networks were not modulated by motor imagery, heart activity and cortical power were crucial to detect when a participant was mentally rehearsing a movement. This work highlights the importance of combining EEG and peripheral measurements to detect command-following, which could be important in improving the detection of covert intentional responses in unresponsive patients.

In a second study, we developed a measure of covert command-following based on interoceptive and exteroceptive attention. We show that directing attention to bodily rhythms or external stimuli induces specific EEG responses, allowing for the individual-level tracking of covert attention in healthy participants. In a group of brain-injured patients, a patient identified with Unresponsive Wakefulness Syndrome and a locked-in

syndrome patient showed attention-driven changes in the heartbeat-evoked potential (HEP), and their attentional state was classified using dynamical together with HEP features. Our findings underscore the importance of attentional mechanisms in shaping interoceptive and exteroceptive sensory processing and expand the framework of heart-brain interactions employed for diagnostic purposes in patients with disorders of consciousness.

The third study focused on developing EEG markers of conscious language processing by exploring the properties of speech that produce common neural responses in healthy individuals exposed to auditory narratives. By combining encoding models and correlated component analysis, we show that during passive, attended, and unattended listening, acoustic and linguistic features contribute to the intersubject correlation evoked by the stories. Notably, models including word unpredictability were particularly sensitive to attention with timing and scalp distribution consistent with language processing. Following this approach, we analyzed EEG data from DoC patients as they listened to a story in the forward and backward direction. Nevertheless, the brevity of the stimuli hindered meaningful results. Based on this, we offer some recommendations on how to use these tools to assess the depth of language processing at the individual level in patients with DoC.

Overall, this thesis offers novel non-invasive methods that can be used at the bedside to probe cognitive capabilities and awareness in patients with DoC. Importantly, the developed paradigms have varying degrees of complexity and require different levels of engagement, from passive to command-following tasks, allowing the exploration of multiple layers of information processing in patients with disorders of consciousness.

Acknowledgments

I have realized that a PhD is a very 'unconscious' decision. It is jumping on a boat with no clear idea where you are going, and not knowing whether you are prepared for the ride. You get on the boat, quickly look back and you don't see land behind anymore, nor ahead, you can feel a bit adrift. Occasionally you believe you have just seen the horizon or maybe land, then it quickly gets foggy, and you are again a bit lost. As time passes your boat starts to feel more equipped, you can go faster and an implicit sense of direction sets in. You breathe, look around, and realize you are arriving somewhere and you are not alone. I would like to thank everyone who shared this scientific and personal ride with me.

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List of publications

- **Fló, Emilia**; Fraiman, Daniel & Sitt, Jacobo. *Brain-muscle networks: a novel protocol to study covert command-following*. DOI: <https://osf.io/g37be> (In principle acceptance *BMC Medicine – registered reports*).
- **Fló, Emilia**; Belloli, Laouen; Cabana, Álvaro; Ruyan-Belabbas, Alessia; Jodaitis, Lise; Valente, Melanie; Rohaut, Benjamin; Naccache, Lionel; Rosanova, Mario; Comanducci, Angela; Andrillon, Thomas & Sitt, Jacobo. *Predicting Attentional Focus: Heartbeat-Evoked Responses and Brain Dynamics During Interoceptive and Exteroceptive Processing*. DOI: 10.1101/2023.11.03.565584 (second round of revision PNAS Nexus).
- **Fló, Emilia**; Cabana, Álvaro; Valle-Lisboa, Juan; Cruse, Damian; Madsen, Jens; Parra, Lucas & Sitt, Jacobo. *What drives intersubject correlation of EEG during narrative stimuli?* (In preparation).

Related publications

- Alkhachroum, Ayham; **Fló, Emilia**; Manolovitz, Brian; Cohan, Holly; Shammassian, Berje; Bass, Danielle; Aklepi, Gabriela; Monexe, Esther; Ghamasae, Pardis; Sobczak, Evie; Samano, Daniel; Bolaños Saavedra, Ana; Massad, Nina; Kotapally Mohan; Merenda, Amedeo; Graciolli Cordeiro, Joacir; Jagid, Jonathan; Kanner, Andres M; Rundek, Tatjana; O’Phelan, Kristine; Claassen, Jan Sitt, Jacobo D. *Resting-State EEG Measures Improve Prediction of Early Consciousness Recovery in Comatose Traumatic Brain Injury Patients*. *Neurocritical care*, 2024. DOI: 10.1007/s12028-024-02005-2.
- Willacker, L.; Raiser, T.M.; Bassi, M., Bender, A.; Comanducci, A.; Rosanova,

M.; Sobel, N.;Arzi, A.; Belloli, L.; Casarotto, S.; Colombo, M.; Derchi, C.; **Fló Rama, E.**; Grill, E.; Hohl, M.; Kuehlmeier, K.; Manasova, D.; Rosenfelder, M. J.; Valota, C. Sitt, J. D. *PerBrain: a multimodal approach to personalized tracking of evolving state-of-consciousness in brain-injured patients: protocol of an international, multicentric, observational study*. BMC Neurol 22, 468, 2022. DOI: 10.1186/s12883-022-02958-x

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List of abbreviations

- ACC** anterior cingulate cortex. 11, 22, 34
- AmN** amplitude modulated noise. xiv, xvii, 78, 79, 81, 85–88, 96, 97, 102–104, 106, 110, 162
- ANS** autonomic nervous system. xii, 28, 46
- APB** Abductor policis brevis. 49, 53, 60
- AUC** area under the receiver operating characteristic curve. 55–59, 63–65, 70
- BB** biceps brachii. 49
- BCI** brain-computer interface. 56, 64, 157, 158
- BMN** brain-muscle networks. 55, 64, 65
- CA** covert awareness. 15, 16
- CAN** central autonomic network. 30
- CCP** covert cortical processing. 15, 16, 38
- CMD** cognitive motor dissociation. 15, 16, 21, 24
- CRS-R** coma recovery scale revised. 9, 10, 20, 21
- CSP** common spatial pattern. 56–59, 64
- DMN** default mode network. 10–12, 33, 34, 160

DoC disorders of consciousness. xii, 7–12, 14, 15, 17–24, 26, 34–38, 42–44, 67, 116, 117, 138, 155–158, 161–166

E envelope. 124, 125, 127, 128, 134, 141, 148

ECG electrocardiogram. 32, 36, 37, 75, 79, 81–83, 85, 86, 89, 95, 101, 102, 106, 157–159

ECN executive control network. 11, 12

EEG electroencephalography. xii–xv, xvii, 14–16, 19, 20, 23–26, 32, 35–38, 44–46, 48–55, 58, 64, 65, 70, 75, 81, 82, 85, 93, 99, 100, 104–106, 110, 113, 115–121, 123–125, 127–133, 135–137, 139, 141–145, 147–149, 151, 156–159, 162

EMCS emergence from the minimally conscious state. 8, 25, 26

EMG electromyography. xii, 20, 36, 37, 44–47, 49–51, 53–55, 64, 156

ERD event-related desynchronization. 19, 37, 45, 46, 48, 52, 62, 63, 67

ERP event-related potential. 22, 26, 32, 35, 37, 81, 93, 96, 161

ERS event-related synchronization. 19, 45, 46, 68

FDS flexor digitorum superficialis. 49, 53

FMN functional muscle network. 47

fMRI functional magnetic resonance imaging. 14–19, 23, 24, 26, 36

GM gastrocnemius medialis. 49, 60

GNW global neuronal workspace. 12, 13, 25

HEP heartbeat-evoked potential. xiv, xviii, 32–35, 74–76, 80, 82–84, 87, 89, 91–95, 98, 99, 102–105, 110, 159–162

HER heartbeat-evoked responses. 33, 34

HR heart rate. 85

HRV heart rate variability. 85

ICA independent component analysis. 106, 110

IMC intermuscular coherence. 47

ISC intersubject correlation. xv, xviii, xix, 35, 116, 117, 122, 125–140, 142–144, 148–150, 163–165, 167

ITPC intertrial phase coherence. 87, 95, 96, 103, 104, 166

KC kolmogorov complexity. 89, 91, 93, 98, 105

LDA linear discriminant analysis. 56, 58, 59, 65

LIS locked-in syndrome. 16, 17, 19, 26, 159

LPC late positivity complex. 23

LSM left sensorimotor bipolar channel. 51, 53, 60

MCS minimally conscious state. 7–11, 13, 15, 16, 18–23, 25, 26, 35, 42–45

ME motor execution. 46

MEG magnetoencephalography. 33, 34

MI motor imagery. 43, 46, 54, 64, 67–69

MMN mismatch negativity. 25, 26

mTRF multivariate temporal response function. 123, 130

NMF non-negative matrix factorization. 42, 47, 52, 53, 59, 60, 63

NST nucleus of the solitary tract. 30

PE permutation entropy. 91, 93, 98, 105

PET positron emission topography. 19

PSD power spectral density. 74, 80, 89–91, 93, 97, 98, 109

RepRN repeated random noise. 79–81, 85, 87, 96, 104, 108

RN plain white noise. 87, 106

RSM right sensorimotor bipolar channel. 51, 53, 60

S spectrogram. 124, 125, 127, 134, 141, 148

SMA supplementary motor area. 17, 18

SN salience network. 11

SRepRN structured repeated random noise. 81, 87, 96, 103, 104, 108

TA tibialis anterior. 49, 60

TBI traumatic brain injury. 9

TRF temporal response function. xviii, 116–118, 124, 125, 128–130, 133–135, 141, 166, 167

TZ trapezius. 49, 53, 60

UWS/VS unresponsive wakefulness syndrome/vegetative state. 7–11, 13, 15–23, 25, 26, 35, 42–45, 155, 159

WO word onset. 124, 125, 127, 128, 131, 134

wSMI weighted symbolic mutual information. 91, 95, 98, 105, 161

WU word unpredictability. 123–125, 127, 128, 131, 134, 135, 141, 148

WUr randomized word unpredictability. 125

I am the color I am tasting

Işabela Kami

Chapter 1

General introduction

General introduction

The term consciousness is problematic due to its polysemy (Zeman, 2001; 1997), it can convey multiple meanings depending on the intention of the individual and the context in which it is evoked. As eloquently expressed by Miller, 1962: *Consciousness is a word worn smooth by a million tongues. Depending upon the figure of speech chosen it is a state of being, a substance, a process, a place, an epiphenomenon, an emergent aspect of matter, or the only true reality...* (p.25). From the conceptual cluster that is consciousness (Young, Bodien, et al., 2021), we can start with Posner et al., 2019 definition, *consciousness is the state of full awareness of the self and one's relationship to the environment* (p.3). Under this view, individuals are conscious when they are aware of their awareness, that is, there is a subjective experience of what it is like to be that being (Nagel, 1974) separated from the external world but permeable to it. An individual is self-aware if the object of their reflections is themselves (Morin, 2006). Given this definition, the study of consciousness presents itself as paradoxical. The object of study, the 'thing' we try to assess is pervasive and almost inescapable when we consider our own consciousness, whereas it is inaccessible when we consider everyone else's. We can only see the platonic shadows of the consciousness of others: their behaviors (Young & Edlow, 2021). When we recognize them as behaviors that are adequate and relatable to our own conscious experience, we attribute consciousness to the individual performing those actions (provided we do not subscribe to the concept of philosophical zombies (Chalmers, 2003)). If we recognize an individual as being 'as conscious as us', then we infer that there is some sort of phenomenology associated with that consciousness, we attribute them agency and we interpret the motivations underlying their behavior. The problem of inferring consciousness from behavior at first glance might seem relevant only in philosophical domains and thought experiments, nonetheless, it has significant implications in clinical settings. When a brain lesion

alters cognitive function such that consciousness and behavior lose their tight coupling, and an individual's purposeful or intentional engagement with the environment is absent or unclear, how can we know whether the individual is conscious?

1.1 States of consciousness and the content of consciousness

In a universal manner, humans have good intuitions regarding the existence of different levels or states of consciousness (sometimes referred to as global states) and the distinct contents that can be experienced (or not) in those states (sometimes referred to as local states) (Seth et al., 2022), as we have either directly experienced them throughout our life or have seen, heard, or read their depictions. Common examples are the disappearance and reappearance of consciousness throughout the sleep-wake cycle, the feeling of being lost in thought disregarding the world around us, the ego distortion and other alterations of perception elicited by natural or synthetic compounds, as well as states where consciousness disappears entirely such as during deep anesthesia or coma. States of consciousness can be differentiated by the level of connectedness (Sanders et al., 2012) to external information and to the actual content experienced by the individuals. This gives rise to a two-dimensional model that conceives the states of consciousness in terms of wakefulness, or vigilance, and awareness and has been the focus of the clinical approach to detecting consciousness in brain-injured individuals (Laureys, 2005; Posner et al., 2019).

1.2 A dual view of consciousness: wakefulness and awareness

'Wakefulness', encompassing full alertness, drowsiness, sleep, and coma, is related to an individual's arousal degree. 'Awareness' refers to the mental content of consciousness, which can be divided into awareness of the internal world (inner speech, stimulus-independent thoughts, mental imagery) and awareness of the outside world (perceptions associated with external stimuli) (Laureys, 2005). These two dimensions of consciousness can show a dissociation in healthy and pathological conditions (Figure 1.1). A healthy dissociation is the one experienced during rapid eye movement or paradoxical

sleep. This reversible state is characterized by low arousal, such that the interaction with the environment is limited (Türker, Musat, et al., 2023), but displays a cortical activity that is similar to the one present in states of wakefulness, with frequent dream-like experiences that the individual can access and report (Siclari et al., 2013). Patients with disorders of consciousness described in the next section provide a set of pathological examples where wakefulness and awareness can diverge and are the focus of the current thesis.

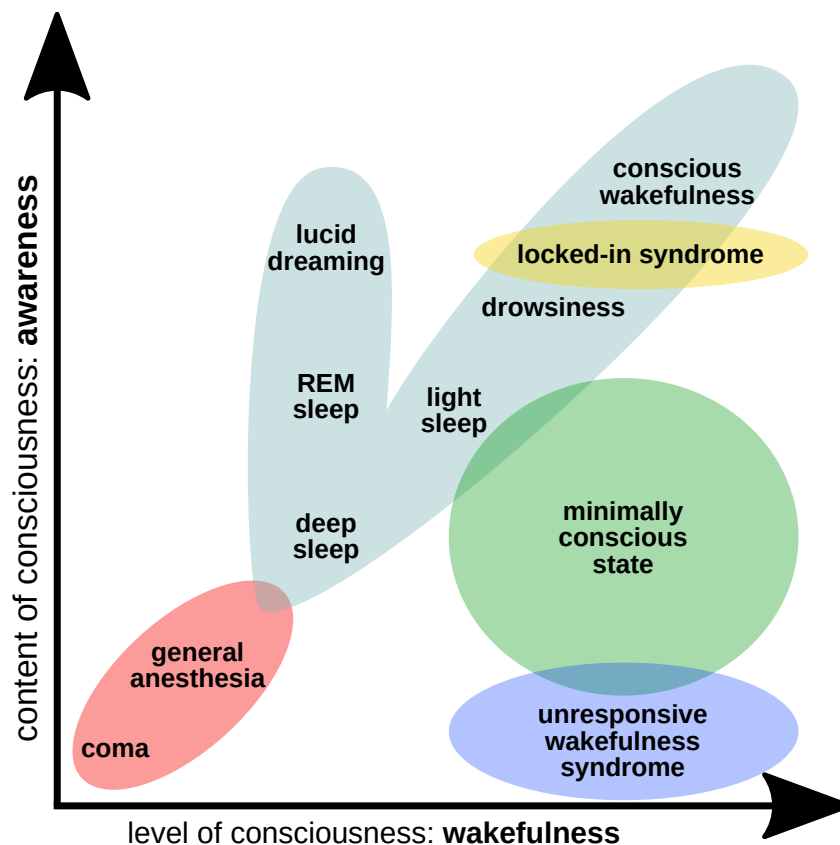


Figure 1.1: A dual view of consciousness. The two major components of consciousness, the level of consciousness (i.e., arousal or wakefulness) and the content of consciousness (i.e., awareness). Adapted from (Jöhr et al., 2015; Laureys et al., 2005)

1.3 Disorders of consciousness

Disorders of consciousness (DoC) refers to a group of related pathological states in which consciousness is affected due to severe injury or trauma to the nervous system transiently or permanently. Coma, unresponsive wakefulness syndrome, originally named vegetative state (UWS/VS), and minimally conscious state (MCS) are three distinct

categories of states of impaired consciousness that can be described in terms of wakefulness and awareness. In this clinical context, wakefulness is defined by eye-opening, whereas awareness is defined by purposeful responses to external stimuli (Laureys, 2005; Young, Bodien, et al., 2021).

After severe brain damage (anoxia, brain trauma, stroke) a patient can experience a state of coma, defined as a continuous unconscious state in which wakefulness and awareness are lacking. No voluntary behavior is observed and patients have their eyes consistently closed despite intense stimulation (Posner et al., 2019). Normally, if the patient survives they transition in a few days to the unresponsive wakefulness syndrome. Patients in UWS/VS show intermittent arousal as indexed by spontaneous eye opening and in response to stimulation, but without signs of reproducible volitional behavior (Jennett, 2002). These patients maintain cardiac, respiratory, and visceral autonomic regulation, produce spontaneous automatic movements, and show preservation of the reflexes supported by the brainstem but are unaware of themselves or their surroundings (Posner et al., 2019). They are awake without being aware (Monti, 2012). The UWS/VS state can be transitory or chronic, when a patient is in this state for more than 1 month it is referred to as being in a persistent vegetative state (Zeman et al., 1997). If any overt and unambiguous sign of knowledge about self or in response to sensory stimuli beyond reflex is observed, the patient is considered to be in a minimally conscious state, a state of impaired consciousness with fluctuating awareness. If the patient shows functional communication or the functional use of objects then a patient is labeled as emerging from MCS (EMCS) (Giacino et al., 2002). Recently, a sub-classification of MCS has been proposed where patients performing non-reflex acts such as orientation to noxious stimuli, visual pursuit to salient stimuli, or willful behavior contingent and appropriate to external stimuli are classified as MCS minus (MCS-) and are distinguished from MCS plus (MCS+), patients that show comparatively more high-level behavioral responses such as command-following, comprehensible vocalization, and gestural or verbal yes/no responses (Bruno et al., 2011). Importantly, MCS patients are a highly heterogeneous group and concerns regarding whether patients in the lower bound of this category have residual consciousness have been raised (Hermann et al., 2021; Naccache, 2018).

In order to classify DoC patients in one of these states repeated clinical assessments are carried out to examine spontaneous and evoked behaviors (Majerus et al., 2005).

Multiple scales can be used to evaluate these patients (Jöhr et al., 2015). Currently, the Coma Recovery Scale-Revised (CRS-R); (Giacino et al., 2004) is the most prevalent instrument to assess these patients. The CRS-R consists of 23 items grouped in six sub-scales: auditory, visual, motor, oromotor, communication, and arousal which try to uncover evidence of awareness of the self or the surroundings, a reproducible and appropriate response to sensory stimuli, and language comprehension (Monti et al., 2010). The responses to the different items allow the physician to locate the patient in the two-dimensional space defined by wakefulness and awareness and monitor their recovery (Figure 1.1). Interestingly, responses to certain items are more prevalent when transitions between states occur (Mat et al., 2022). A crucial problem is that accurately distinguishing patients in UWS/VS from patients in MCS based on behavioral criteria is difficult. Although the level of arousal of a patient is relatively straightforward to assess, signs of awareness can be much more ambiguous, as it requires to differentiate between responses linked to the physician demands and randomly coincidental behaviors (Fischer et al., 2015). In addition, multiple factors have to occur simultaneously during clinical assessment. Patients have to be awake, be motivated to initiate a response contingent to the proposed stimulus, and have no perceptual, attentional, or motor disabilities that could be impeding overt responses (Giacino et al., 2009; Kondziella et al., 2016).

A fundamental question, when faced with a patient with a DoC, is what will their outcome be: will they get better? when? better how?. The answer to these questions has a direct impact on the patient chance of recovery as most of the deaths associated with traumatic brain injury (TBI) are due to withdrawal of life-sustaining therapy (Turgeon et al., 2011). The decision is primarily driven by the low survival probability stated by the medical team and a prognostic scenario that is not compatible with the patient's wishes according to the caregivers. Importantly, half of these end-of-treatment decisions take place during the first three days after the insult (Turgeon et al., 2011). Crucially, research in a cohort of 300 patients shows that half of the patients with severe TBI can function independently 12 months after the event (McCrea et al., 2021). Therefore, there is a level of misdiagnosis that drives the self-fulfilled prophecy of a bad outcome (Izzy et al., 2013; Russell et al., 2024; Van Veen et al., 2021). The trajectories of these patients are not fixed, research focused on reducing the uncertainty surrounding the diagnosis and prognosis of these patients during the acute phase, the first 28 days after injury (Giacino et al., 2018), is of paramount importance to guide optimal care

and avoid the premature withdrawal of assistance.

Because awareness is defined by explicit intentional behavior, the underestimation of the level of awareness in DoC patients is significant. Roughly 40% of DoC patients are incorrectly classified as UWS/VS in comparison to the diagnosis made by experts using the CRS-R, and misdiagnosis is higher in chronic patients (Schnakers et al., 2009). Importantly, MCS patients have a higher probability of regaining cognitive function (Dolce et al., 2008; Faugeras et al., 2018; Hirschberg et al., 2011; Luaute et al., 2010a), which renders vital the importance of an accurate diagnosis. To reduce the level of misdiagnosis between a UWS/VS and MCS diagnosis, assessments have to be carried out by experts and should be repeated multiple times to detect signs of residual consciousness (Wannez et al., 2017).

1.4 Neural correlates of wakefulness and awareness

Disorders of consciousness refer to a heterogeneous clinical population with severe brain injuries produced by diverse etiologies (Estraneo et al., 2021). Different patterns of lesions can give rise to a disorder of consciousness (Posner et al., 2019), hinting that consciousness is not sustained by one specific brain area but by the complex interaction of multiple cortical and subcortical regions. Furthermore, the distinctive behavior of UWS/VS and MCS patients suggests that the neural substrates of wakefulness and awareness are somewhat distinct. Wakefulness is sustained by an overall cortical excitatory activity mediated by nucleus in the brain stem that project to the thalamus and the basal forebrain (Edlow et al., 2013; Fuller et al., 2011; Snider et al., 2019), but the structures supporting the content of consciousness have been more difficult to pinpoint. Neuroimaging data supports the idea that the brain is organized in large-scale functional neural networks (Damoiseaux et al., 2006; Fox et al., 2005; Greicius et al., 2003), that are crucial to sustain internal and external awareness (Heine et al., 2012). The default mode network (DMN) encompasses the ventromedial, anteriomedial and dorsal prefrontal cortex, the precuneus, and the posterior cingulate cortex (Alves et al., 2019; Bressler et al., 2010), shows decreased activation when participants are actively focusing on external stimuli, whereas is more active during stimulus-independent thoughts or when tasks require access to episodic or autobiographical representations (Andrews-Hanna et al., 2014; Mason et al., 2007). The DMN has therefore been associated with

internal awareness. Reduced activation of the DMN is linked to lower levels of consciousness induced by anesthesia (Huang et al., 2014) as well as during sleep (Horowitz et al., 2009). In addition, lower connectivity between areas comprising the DMN has been associated with UWS/Vs diagnosis (Vanhaudenhuyse et al., 2010), while preserved correlations within the DMN have been related to a better functional outcome in DoC patients (Hannawi et al., 2015; Threlkeld et al., 2018). The DMN is believed to interact with the executive control network (ECN) (Chen et al., 2013) consisting of lateral frontoparietal areas, the supplementary motor areas, and the insular cortices (Heine et al., 2012) (although see Witt et al., 2021). The ECN shows increased activation during tasks that demand the processing of external information (Vanhaudenhuyse et al., 2011), and is believed to mediate external awareness. The salience network (SN) encompassing the anterior cingulate cortex (ACC) and the anterior insula (Seeley et al., 2007) is considered to be fundamental in the allocation of attentional resources and to dynamically switch between the DMN and the ECN according to internal or external cognitive demands (Schimmelpfennig et al., 2023). Evidence shows that preserved connections between the SN and the DMN are crucial for an appropriate activity in the DMN (Bonnelle et al., 2012). Importantly, patients with impaired consciousness who show higher connectivity within the DMN together with higher anticorrelations with the ECN and the SN have a better functional outcome one year after (Sair et al., 2018). Furthermore, a dynamical view of brain organization has been proposed showing that the degree of connectivity between and within brain networks spontaneously varies in time (Betz et al., 2016; Preti et al., 2017; Zalesky et al., 2014), and that the brain presents different recurrent long-range connectivity patterns such that conscious individuals exhibit more complex and anatomically distinct patterns compared to MCS and UWS/Vs patients (Demertzi et al., 2019). Under this view, impaired consciousness results from the impossibility of fluctuating dynamically across different brain network configurations in an unprompted manner or in response to sensory stimulation.

Impaired consciousness is believed to be a disconnection syndrome (Schiff et al., 2002). The frontoparietal networks comprised of the DMN and the ECN are normally connected to the anterior forebrain mesocircuit (Edlow et al., 2021), a circuit composed of frontal and prefrontal cortex connections to the thalamus via the globus pallidus and the striatum. Under normal circumstances, the striatopallidal projections act as a negative feedback loop between the thalamus and the frontal cortices. The 'meso circuit' hy-

pothesis postulates that DoC arises from a lack of excitatory outputs from the thalamus to the cortex due to dysfunctions of the frontal cortical-striatopallidal-thalamocortical loops (Schiff, 2010). This view is supported by research showing that improvements in the state of consciousness are correlated to increases in connectivity between the meso circuit and the DMN (Lant et al., 2016) and the ECN (Thibaut et al., 2015).

1.5 The global neuronal workspace theory

Multiple theories to explain how consciousness could be instantiated in the brain have been put forward (Seth et al., 2022). Here we will summarize the theory that has more support in the academic community as assessed by a recent survey completed by researchers in consciousness (Francken et al., 2022).

The Global Neuronal Workspace (GNW) theory was proposed by Dehaene et al., 1998 building on the Global Workspace theory (Baars, 2005), and is focused on explaining 'conscious access' (Baars, 2002), the process by which information becomes conscious, such that an individual can operate on it, integrate it with other conscious information and report it ('I saw this'). The GNW is an integrative theory that postulates that consciousness is required to integrate information from multiple brain networks, has a tight relationship with selective attention (*consciousness is selective* Miller, 1962 (p.38)), and accounts for the cortical processes underlying conscious, preconscious, and subliminal information (Dehaene et al., 2011). The GNW proposes the existence of modular cortical areas that sustain specific processes (perceptual, motor, memory, and evaluative information), and a second space coined 'neuronal workspace' comprised of excitatory neurons from prefrontal and parietal regions (GNW neurons) with long-range feedforward and feedback connections (corticocortical and corticothalamic) that enable the enhancement or suppression of specific groups of neurons (Mashour et al., 2020). Under this theory, a content becomes conscious if it produces a sudden and exclusive activation, an 'ignition', of the GNW neurons in an 'all or nothing' type of response in prefrontal, cingulate, and parietal cortices, and primary sensory cortices associated to that specific stimuli. This sustained and amplified activity is how conscious content is encoded, and can be broadcast to different cortical regions making it available in a global manner thus enabling its evaluation, verbal reports, planning, and goal-directed behaviors associated with that stimuli even after its disappearance

(Dehaene et al., 2003). Evidence supporting this ‘ignition’ concept comes from the distinct cortical activations observed between conscious and unconscious stimuli. An unconscious stimulus elicits a local and short-lived cortical activation, whereas conscious stimuli are associated with later and sustained responses in distributed cortical regions that would be supported by the reciprocal connections of the GNW neurons (Dehaene et al., 2011). Furthermore, pharmacological manipulations to induce states of unconsciousness show a functional disconnection between the prefrontal and the posterior cortices, between the thalamus and the frontoparietal and posterior cingulate cortices (Ranft et al., 2016), and the dorsal anterior insula cortices and frontoparietal areas (Warnaby et al., 2016). In addition, anesthesia disrupts the temporal fluctuations that produce spontaneous connectivity patterns in the brain by affecting specifically the prefrontal, posterior parietal, and cingulate cortices (Barttfeld et al., 2015), which are believed to be mediated via corticothalamic connections (Redinbaugh et al., 2020). Consciousness would be the gateway that enables the integrated processing of information by neuronal modules that would otherwise work in separate ways (Baars, 2002). Consistent with the GNW theory, MCS and UWS/VS patients seem to be differentiated by the extent to which sensory information activates the cortex. Patients in UWS/VS show cortical responses limited to primary sensory areas and no responses in large distributed networks (Bernat, 2006). UWS/VS patients show preservation of metabolic activity in isolated brain networks that can sustain isolated behaviors (Schiff et al., 2002), and show a lack of interaction between associative areas (Laureys et al., 1999), while MCS patients show a conservation of associative frontoparietal networks (Laureys et al., 2004). In MCS patients nocive stimuli evoke cortical responses in areas overlapping with those activated in healthy controls (secondary somatosensory, insular, and anterior cingulate cortices) (Boly et al., 2008), whereas patients in a UWS/VS only display activation of subcortical and primary somatosensory areas (Laureys et al., 2002). Similar results have been found for the auditory modality, as UWS/VS patients only show activation of the primary auditory cortices (Laureys, 2000), whereas MCS patients showed additional activation in BA 22 (Boly et al., 2004). Moreover, MCS patients exposed to auditory stimuli with negative and positive valence show increased activation over cortical regions associated with emotional processing (Laureys et al., 2004).

In summary, for a patient to be conscious under this theory the GNW has to be preserved

and specific contents should be broadcasted to associative areas.

1.6 Covert consciousness

It is challenging to accurately state the level of awareness of DoC patients based on behavioral assessments. Significant effort has been directed toward developing objective markers of consciousness that can reduce the uncertainty surrounding the diagnosis and prognosis (Sanz et al., 2021). Recently, non-invasive techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have been used to explore the level of consciousness in patients who cannot convey overt responses (Laureys et al., 2004; Laureys et al., 2012; Owen et al., 2008). There are different ways to assess residual consciousness in DoC patients, they differentiate on the level of information that a positive or negative result provides, and how demanding they are for participants. Neuroimaging techniques have been used to measure the neural response of DoC patients during resting state and in response to passive and active paradigms. Resting-state paradigms study the brain's response without external stimuli, making them suitable for all patients, regardless of sensory impairments. They can provide information on how preserved the brain dynamics (Alkhachroum et al., 2024; Amiri et al., 2023; Colombo et al., 2023; Engemann et al., 2018; King et al., 2013; Lehenbre et al., 2012) and resting-state networks are (Demertzi et al., 2019; Fischer et al., 2015; Heine et al., 2012). Passive paradigms consist of measuring neural activity in response to external stimuli (auditory (Bekinschtein et al., 2009), visual (Monti et al., 2013), olfactory (Arzi et al., 2020) and tactile (Schiff et al., 2005)) without requiring the active engagement of the patient (Bruno et al., 2010). These tasks give information regarding the processing of low-level sensory information, and in some cases can index the recruitment of association cortices. Nevertheless, a positive response does not necessarily index conscious processing. Active paradigms are based on the premise that although we are unable to measure consciousness directly, awareness is associated with certain contents and that specific contents of awareness can be mapped to brain activity. The rationale is that if a patient is given a task requiring conscious processing and their brain response is consistent with that of healthy controls, awareness can be inferred (Boly et al., 2007; Owen, 2013). While we do not have access to patient reports, we do have access to verbal reports or performances from healthy participants,

confirming they were aware of executing a specific task. This creates a correlation between brain activity and content-behavior that can be used as a subjective-objective measure to index command-following beyond explicit responses in DoC patients.

An important number of patients who display no overt signs of awareness show brain activity consistent with healthy subjects measured with active tasks based on fMRI and EEG. Indeed, a recent meta-analysis on neuroimaging studies comprising more than 1000 patients estimates that 15% of chronic patients clinically diagnosed as UWS/VS show modulation of brain activity consistent with command-following ([Kondziella et al., 2016](#)). There is a heteronymy to refer to patients showing this dissociation between behavior and brain response ([Schnakers et al., 2022](#)). Some of the most frequent names are cognitive motor dissociation ([Schiff, 2015](#)), covert consciousness ([Schiff, 2015](#)), and covert awareness ([Owen et al., 2007](#)), with all uses implying some sort of residual consciousness. In addition, assessments based on passive stimulation have introduced the terms higher-order cortex motor dissociation ([Edlow et al., 2017](#)), and covert cortical processing ([Edlow et al., 2021](#)), when brain activity beyond primary sensory cortices is observed in response to external stimulation. It is not resolved whether these clinical presentations should be considered new clinical categories ([Claassen et al., 2024](#); [Jöhr et al., 2020](#); [Schiff, 2015](#)) or if they are a clinical dimension within the disorders of consciousness through which patients can transition ([Edlow et al., 2021](#)). Evidence accumulation regarding the epidemiology and the functional meaning of these cases will probably result in a consensus on how to label these patients ([Claassen et al., 2024](#)). Following [Claassen et al., 2024](#) and [Edlow et al., 2021](#), patients that show a mismatch between clinical diagnosis and behavior are grouped into three categories: cognitive motor dissociation (CMD), covert cortical processing (CCP) and covert awareness (CA). Patients with CMD are patients who display a dissociation between their residual cognitive abilities and their self-expression. Patients behaviorally categorized as in a coma, UWS/VS, or MCS- that show neural activity in response to commands, typically assessed with motor imagery paradigms (see below), would be CMD patients. The mechanisms underlying CMD are not clear. It has been proposed that CMD is the product of a dissociation between motor planning and motor execution. Supporting evidence for this view comes from a single-patient study where CMD was associated with a disconnection between the primary motor cortex and the thalamus, which would be fundamental for motor execution ([Fernández-Espejo et al., 2015](#)).

CCP refers to patients that behaviorally show no language expression or comprehension (coma, UWS/VS, or MCS- patients), but show brain activation of associative cortices when exposed to music or language. CA patients show response to commands when evaluated with EEG/fMRI assessments but are behaviorally unresponsive (coma or UWS/VS), and therefore overlap with the CMD patients. CMD and CA patients can willfully modulate their brain activity in response to specific instructions, which implies they comprehend language and have preserved executive functions, and are therefore considered to be aware. The experimental paradigms to detect CCP do not demand responses from patients nor necessarily require their attention, and therefore no inferences regarding awareness can be made (Claassen et al., 2024). Nevertheless, passive assessments using speech or music could be sensitive to detect residual consciousness (Cruse et al., 2011; Sokoliuk, Degano, Melloni, et al., 2021). An advantage of this approach, compared to command-following tasks, is that the latter requires the patients to be motivated and attentive to carry the task, comprehend language, sustain the instruction in short-term memory, and execute it. Moreover, in the case of imagery tasks patients have to be able to evoke vivid images, failure at any of these steps would give a negative result (Kotchoubey et al., 2011). These very demanding tasks have high specificity but low sensitivity (Sanz et al., 2021), and possibly underestimate the level of awareness of DoC patients (Kondziella et al., 2016).

Detecting covert cortical processing is not only relevant for the diagnosis but also for prognosis purposes (Claassen et al., 2024). CMD patients identified with a clinical assessment sensitive to subtle movements (Jöhr et al., 2020) or by showing cortical response consistent with command-following (Claassen et al., 2019; Egbebike et al., 2022) show that these patients have better functional outcomes than classical disorders of consciousness patients. Patients with no behavioral responses to commands who were able to perform an item selection task regained consciousness 3 months later in greater proportion than patients who could not perform the task (Pan et al., 2020). Along the same line, research shows that patients with signs of CCP elicited by passive language tasks have a better prognosis (Coleman, Davis, et al., 2009; Di et al., 2007; Fernández-Espejo et al., 2008; Gui et al., 2020; Sokoliuk, Degano, Melloni, et al., 2021; Steppacher et al., 2013).

Finally, another syndrome that is not a disorder of consciousness per se but is closely related is the locked-in syndrome (LIS). Generally produced by a lesion at the level of the

brainstem, the LIS is characterized by a general paralysis that impairs overt responses but with preserved consciousness. The patients are unable to respond to stimuli except by producing vertical ocular movements (Posner et al., 2019) and as a consequence, patients in LIS can be incorrectly diagnosed as in a UWS/VS if the physician does not test for this communication channel (Gallo et al., 1989). Expectedly, command-following tasks have proven useful in detecting covert awareness in patients in a LIS as well (Goldfine et al., 2011; Lesenfants et al., 2016; Stender et al., 2014).

In summary, detecting residual consciousness at the patient level using active and passive paradigms is crucial for diagnosis and prognosis purposes. Currently, if behavioral assessments are not conclusive regarding the level of awareness of a patient, it is recommended to use multimodal evaluations based on neuroimaging (Comanducci et al., 2020; Giacino et al., 2018; Kondziella et al., 2020), although access to these tools is far from widespread (Young & Edlow, 2021).

1.7 Complementary assessments to behavior

This section details the current passive and active methods for probing consciousness in DoC patients using mostly auditory stimulation. While various sensory pathways can be used, auditory stimulation is the simplest. If the auditory system is intact, we can use this method without needing active cooperation from the patient. Although visual stimuli show promise (Vassilieva et al., 2019), the lack of eye-opening and gaze fixation makes this approach challenging (Sangare et al., 2023). Other forms of stimulation, like olfaction (Arzi et al., 2020; Merrick et al., 2014), require specialized equipment not available in most centers and depend on the patient's ability to breathe independently.

1.7.1 Mental imagery and covert command-following

Mental imagery can be defined as the process of evoking a perception in the absence of external sensory stimuli (Krüger et al., 2020). There are numerous studies providing evidence that imagery and actual execution of a movement are sustained by partially overlapping systems (Jeannerod et al., 1999). fMRI and PET studies consistently show an activation of the supplementary motor area (SMA) during motor imagery and motor execution (Decety et al., 1994; Deiber et al., 1998; Fernández-Espejo et al., 2015; Lotze et al., 1999; Naito et al., 2002; Porro et al., 1996; Roland et al., 1980; Roth

et al., 1996). Several parietal areas (Bonda et al., 1995; Deiber et al., 1998; Meister et al., 2004; Nair et al., 2003), the cerebellum, and the basal ganglia are commonly activated as well (Bonda et al., 1995; Decety et al., 1990; Deiber et al., 1998; Li et al., 2004; Lotze et al., 1999; Naito et al., 2002). Furthermore, spatial navigation tasks show activation of the pre-SMA, the parahippocampal cortex, and the precuneus (Boly et al., 2007; Ino et al., 2002).

The use of imagery together with fMRI produced the first evidence of cognitive motor dissociation in a UWS/VS patient. When a patient was asked to imagine herself walking around her house and playing tennis, sustained command-following was observed as indexed by an increase in activity in the SMA, posterior parietal cortex, lateral premotor cortex, and the parahippocampal gyrus (Owen et al., 2006). The tennis task and a variation evoking swimming have been used in further fMRI studies involving groups of UWS/VS and MCS patients, where responses in the SMA (Bardin et al., 2011; Bardin et al., 2012; Gibson et al., 2014; Monti et al., 2010) and premotor cortex (Bardin et al., 2012) have been evidenced. More recently, 75 non-traumatic DoC patients were assessed with the tennis paradigm, 40% of the patients showed significant modulations of brain activity, and MCS patients were more likely to show this behavior (Schnetzer et al., 2023). For a review of studies using mental imagery to detect command-following responses in fMRI see Laureys et al., 2012. Crucially, healthy participants do not always exhibit an fMRI response when asked to imagine complex events (Bodien et al., 2017; Monti et al., 2010), and some patients that have overt responses to commands fail to show a modulation of brain activity during these imagery tasks (Bardin et al., 2011; Gibson et al., 2014; Monti et al., 2010; Stender et al., 2014). The high cognitive demands associated with the imagery of complex tasks could explain the observed inconsistency. Preserved cognitive functionalities among DoC patients may be highly variable as brain injuries are commonly accompanied by other disorders or pathologies, consequently, complex tasks may in some cases underestimate the level of awareness (Bekinschtein et al., 2011). In this line, simpler motor tasks have been proposed to evaluate DoC patients. In a study, a small group of UWS/VS patients asked to move their hand showed fMRI activity in the contralateral dorsal premotor cortex (Bekinschtein et al., 2011). Interestingly, demanding patients to imagine themselves squeezing their hand resulted in a more accurate measure of command-following with fMRI than the tennis task (Bodien et al., 2017).

Although much less explored, EEG has also proven useful in identifying covert responses in DoC patients. As described for fMRI and PET, the brain response to motor execution and motor imagery show similar electrophysiological signatures (Munzert et al., 2009), although a proportion of individuals do not show a modulation of brain activity while attempting motor imagery (Y. Hashimoto et al., 2010; Höller et al., 2013; Pfurtscheller et al., 2009). Movement execution, as well as the mental rehearsal of a movement, requires the coordinated action of cortical and subcortical structures in space and time. It is hypothesized that the synchronization of neural activity (Varela et al., 2001) allows these distributed motor systems to be integrated to provide a specific motor output (Farmer, 1998). Cortical event-related synchronization (ERS) and event-related desynchronization (ERD) have been shown to occur before and during the execution of a movement (Barlaam, 2011; Pfurtscheller, 1981; Pfurtscheller et al., 1997; Salmelin et al., 1994), or during its imagination (Beisteiner et al., 1995; Höller et al., 2013; Lang et al., 1996; Neuper et al., 2010; Pfurtscheller, Scherer, Müller-Putz, & Lopes da Silva, 2008; Pfurtscheller et al., 2009).

Spectral changes assessed in two MCS and one LIS patient in response to a complex motor imagery instruction (imagine swimming), elicited significant responses in one MCS and in the LIS patient (Goldfine et al., 2011). Similarly, in a cohort of 6 MCS patients, mental imagery instructions elicited ERD/S, with a more consistent result when using motor imagery than imagined navigation (Horki et al., 2014). EEG responses have been detected in UWS/VS and MCS patients when asked to imagine simple motor tasks, such as imagining opening and closing their hand (Cruse et al., 2012; Cruse et al., 2011; Gibson et al., 2014) and moving their toes (Cruse et al., 2012; Cruse et al., 2011). A study on 28 DoC patients showed EEG responses to motor imagery in 21 patients, and although the responses were highly variable and different to healthy controls, EEG was as sensitive as fMRI to detect command following (Curley et al., 2018).

Although with different sensitivity, these studies managed to detect command-following responses in MCS patients and crucially in UWS/VS patients, illustrating that the information provided by these evaluations is a significant complement to behavioral examinations.

1.7.2 Motor execution and covert command-following

To score in the motor items of the CRS-R that are associated with a MCS diagnosis a patient has to be able to move their limbs towards a noxious stimulus or manipulate objects. As mentioned earlier, clear overt responses could be impaired in a DoC patient and the CRS-R is not sensitive to subtle motor responses. In this line, it has been shown that the revised Motor Behavior Tool (MBT-r), a scale developed to identify motor behaviors with more granularity, enables the detection of residual cognition that goes unnoticed by using the CRS-R (i.e. increases in the frequency of nonreflexive motor responses, grimaces in response to noxious stimuli) (Pincherle et al., 2019). Furthermore, a study shows that patients who display motor responses overlooked by the CRS-R but that are detected by the MBT-r are associated with better outcomes (Jöhr et al., 2020). In this context, objective measures of movement execution have been a much less explored approach to evaluate command-following in patients without explicit motor or verbal responses. A few studies combining surface electromyography (EMG) and simple motor tasks have shown subthreshold (covert) motor activity in DoC patients who failed to exhibit overt motor behavior. In a study comprising 10 DoC patients, one patient diagnosed as UWS/VS and one as in MCS showed a covert motor response detected by EMG following "try to move your hand" instructions compared to control sentences (Bekinschtein et al., 2008). A subsequent study carried out on 38 DoC patients, and using multiple motor instructions showed EMG responses for a UWS/VS and three MCS patients. Interestingly a more frequent response was obtained to "move your hands" than "move your legs" or "clench your teeth" commands (Habbal et al., 2014). A more recent study in a cohort of 40 patients with impaired consciousness recorded EMG activity while instructing patients to move both right and left hands, single-trial level analysis allowed to successfully detect covert motor responses in MCS-patients (Lesenfants et al., 2016). Therefore, muscular activity evaluated with a generally available and non-invasive tool such as surface EMG can provide complementary information to the behavioral scales typically used for diagnosis. Additionally, EEG has also been combined with simple motor commands to evaluate the level of awareness in DoC patients. Demanding patients to move their feet on cue resulted in an EEG response in 2/6 MCS patients (Horki et al., 2014). In a study comprising 104 patients, instructions to open and close their hands elicited a power modulation in 16 patients. Furthermore, the patients who showed brain activity consistent with following the in-

structions had a better long-term outcome than unresponsive patients ([Claassen et al., 2019](#)).

1.7.3 Language processing and covert cortical processing

Another important approach to assessing DoC patients is testing their language capabilities. Having information regarding the level of speech processing in these patients is fundamental to knowing whether patients can understand the physicians and caregivers, as the lesions that give rise to a DoC can also produce receptive and productive aphasia ([Majerus et al., 2009](#)). Additionally, this information is important to interpret the CRS-R results, as preserved language comprehension is crucial for a good score ([Schnakers et al., 2015](#)).

Speech is a complex signal with specific acoustic properties that have to be properly encoded by the language networks in the brain to extract the multiple levels of meaning that are embedded in the signal ([de Heer et al., 2017](#); [Hickok et al., 2007](#)). Active and passive language-based evaluations in patients with impaired consciousness are mostly focused on measuring the neural processing of the amplitude variations of the speech signal over time, comparing neural responses to speech in contrast to noise, contrasting brain activation to forward and backward speech, using semantic-based manipulations or self-referential stimuli.

It has been shown that increases in the latencies associated with envelope-tracking are correlated to worse behavioral diagnoses and patients that are categorized as CMD by neuroimaging methods present processing latencies similar to the ones displayed by healthy controls ([Braiman et al., 2018](#)). In a cohort of 4 MCS and 3 UWS/VS patients, one MCS and one UWS/VS patient showed significant activation of language network areas during forward compared to backward speech. Importantly, the UWS/VS patient showed a recovery of consciousness 9 months after the assessment ([Fernández-Espejo et al., 2008](#)). In another study, 3/7 patients behaviorally labeled as in a UWS/VS showed increased responses to meaningful speech sounds compared to unintelligible noise with a diverse pattern of activation in temporal regions ([Coleman et al., 2007](#)). In a follow-up study encompassing 41 patients with impaired consciousness ([Coleman, Davis, et al., 2009](#)), 7 UWS/VS and 12 MCS patients showed significant responses to the same contrasts, and the depth of auditory processing (no response, response to sound, response to speech and response to semantic manipulations) was correlated to

behavioral assessments 6 months later. Furthermore, 2 UWS/S and 2 MCS of these patients displayed evidence of semantic processing as indexed by increased activity to semantically ambiguous sentences. Crucially, the UWS/VS patients with signs of semantic processing transitioned to MCS 6 months after the evaluation.

Paradigms based on highly familiar and emotional stimuli have been used to assess DoC patients. Research based on event-related potentials (ERPs) shows that patients in MCS (9/14) have greater P3 responses to their name compared to control names in a detection task in contrast to a passive condition, and this effect was not present in the eight UWS/VS patients that were evaluated (Schnakers et al., 2008). A similar study in 16 patients with chronic DoC (5 UWS/VS and 11 MCS), showed that 3 MCS and 1 UWS/VS patient elicited stronger cortical responses to their own name compared to other names (Kempny et al., 2018). Moreover, 7/12 chronic DoC patients showed a mismatch negativity response to their name during an auditory oddball task. Three UWS/VS and a coma patient exhibiting this attentional response transitioned to MCS (Qin et al., 2008). fMRI studies based on self-referential stimuli revealed that patients who display responses in association cortices to their own name vocalized in a familiar voice were associated with an improvement in clinical outcomes 3 months later (Di et al., 2007). In another study, increased responses in the ACC in response to the patients' name were correlated with the level of consciousness and were predictive of a positive outcome in 2/7 UWS/VS patients (Qin et al., 2010). The ACC has been shown to be activated during self-referential processing independently of the familiarity of the stimuli and it overlaps with the DMN activation during resting state (Qin et al., 2011), which is believed to sustain internal awareness (Demertzi et al., 2013; Vanhaudenhuyse et al., 2011).

Semantic processing has also been evaluated in patients with impaired consciousness through classical ERPs. In a group of 16 DoC patients consisting of half UWS/VS and half MCS, all with preserved auditory functionalities, cortical responses to speech stimuli compared to noise were elicited in 3 UWS/VS and 4 MCS patients, with one MCS patient showing a N400 semantic priming effect (Beukema et al., 2016). In a study of 92 DoC patients, N400 responses elicited by the incongruent ending of short sentences were observed in nearly a third of the UWS/VS patients evaluated (15/53) and it was correlated to the recovery of functional communication in both UWS/VS and MCS patients (Steppacher et al., 2013). A study based on semantic priming using

related and unrelated pairs of words was used to assess the N400 and the late positive complex (LPC) evoked in 15 UWS/VS and 15 MCS patients, compared to healthy volunteers. A group analysis revealed LPC responses only in healthy participants and in MCS patients. Subject-level analysis suggests a relationship between LPC response and recovery of consciousness in MCS patients, nevertheless, authors acknowledge the lack of robustness of ERP individual analysis even in healthy participants (Rohaut et al., 2015). A subsequent study assessed these lexical ERPs during a lexical task in which healthy participants and 19 DoC patients (9 in a UWS/VS and 10 in MCS) had to identify repeated words or pseudowords. The N400 response was present in healthy individuals and patients, in contrast, the LPC response was observed only in controls and MCS patients (Ben Salah et al., 2023). Furthermore, DoC patients have been assessed using fMRI together with factually correct and incorrect sentences. Following healthy individuals, factually incorrect sentences elicited increased activation in mostly left Broca and Wernicke areas in a third of the patients (11/29 UWS/VS and 5/26 MCS patients). Nevertheless, the cortical response did not correlate with their clinical diagnosis, the time since the injury, or the degree of brain damage (Kotchoubey et al., 2013). The authors discuss that language networks could be conserved and the process of semantic information carried out in a modular way independent of conscious awareness. Nonetheless, 4 out of 21 controls did not show the effect which undermines the value of the paradigm as a reliable marker of semantic processing.

A clever non-naturalistic language paradigm (Ding et al., 2016) has been implemented to assess the depth of language processing and the influence of attention on word, phrase, and sentence processing in DoC patients using EEG and inter-trial phase coherence (ITPC) (Gui et al., 2020). When presented with speech stimuli in which the phrasal and sentential boundaries could not be derived from prosodic or statistical cues, both MCS and UWS/VS patients showed signatures of tracking the element-wise rate (word rate). Importantly, responses to higher language structures were informative to distinguish between groups. Furthermore, MCS patients who showed phrase tracking were associated with better outcomes 3 months later, confirming the predictive value of speech comprehension previously reported with fMRI at 6 months (Coleman, Davis, et al., 2009). The same paradigm was carried out in a cohort of acute DoC patients who did not show overt command-following responses. The tracking of phrases and sentences correlated with a better prognosis at 3 and 6 months, stating its relevance

during early evaluation ([Sokoliuk, Degano, Melloni, et al., 2021](#)).

1.7.4 Naturalistic language-based evaluations

Naturalistic stimuli allow probing the brain in a more engaging way while avoiding potential confounds and restrictions faced when constructing controlled linguistic stimuli. Efforts in applying more ecological language paradigms to assess these patients have been recently implemented by capitalizing on intersubject correlation (ISC) measures. ISC during narrative stimuli was first evidenced in fMRI, where it was shown that the responses elicited during movie watching in primary and associative cortices in an individual are correlated to the evoked activity by the same stimuli in other individuals, which could be associated with specific contents of the film ([Hasson et al., 2010](#); [Hasson et al., 2004](#)). Importantly, ISC is increased when attention is directed to the stimuli ([Ki et al., 2016](#); [Rosenkranz et al., 2021](#)), and has been postulated as a marker of engagement to the narratives ([Cohen et al., 2016](#); [Dmochowski et al., 2012](#); [Poulsen et al., 2017](#)). [Naci et al., 2014](#) implemented this naturalistic approach using a suspenseful film to demonstrate synchronized activity in the primary visual and auditory areas, as well as in the frontoparietal associative cortices of both healthy participants and for a non-communicative patient who was later found to show CMD. By combining EEG, narratives, and correlated component analysis ([Parra et al., 2019](#)), it has been shown that although the ISC is generally decreased in DoC patients ([lotzov et al., 2017](#); [Laforge et al., 2020](#)), a few patients display brain activity patterns correlated to the brain activity elicited by the same narratives in healthy controls ([Laforge et al., 2020](#)). In addition, ISC shows a paradoxical behavior during forward and backward speech in DoC patients ([lotzov et al., 2017](#)), which could be related to the diagnosis or the sample size.

Overall, language-based evaluations can capture covert cortical processing of highly familiar stimuli, as well as acoustic and semantic information in fMRI and EEG, for both passive and active paradigms, with an important prognostic value. Indeed, a recent systematic review supports that the level of language processing in DoC patients is correlated to the level of consciousness ([Aubinet et al., 2022](#)).

1.7.5 Attention and covert command following

According to the GNW theory attention is a gateway for consciousness. Selective attention is closely related to consciousness, that which is selected will be made available for broadcasting in a distributed manner (Mashour et al., 2020). Attention and consciousness are considered to be sustained by rather overlapping structures such as the dorsal fronto-parietal network, nevertheless it has been shown experimentally that attention can be manipulated independently of consciousness (Koch et al., 2007; Tallon-Baudry, 2012).

Attention has been described as a general mechanism that allows increasing the detection of a desired signal while suppressing the response to irrelevant stimuli (Harris et al., 2011; Sarter et al., 2001). In general, directing attention to certain features of a stimulus produces increases in neural activity in areas associated with the processing of that specific feature. The modulatory effect of attention on sensory processing has been consistently shown for top-down attention on sound (Hall et al., 2000; Hillyard et al., 1973; Jäncke et al., 1999), touch (Johansen-Berg et al., 2000), vision (Corbetta et al., 1991; Kanwisher et al., 2000), olfaction (Singh et al., 2019), and taste (Q. Luo et al., 2013), and more recently during interoceptive attention to the heart (Petzschner et al., 2019).

Compared to motor imagery, paradigms based on attention to detect command-following responses in disorders of consciousness have been less explored. The capabilities to exert top-down attention and the required structures to carry this was assessed by Monti et al., 2015 in a group of 16 patients with impaired consciousness (8 UWS/VS, 16 MCS, and 4 EMCS) using an auditory word detection task. Patients were instructed to count a specific word and their response was compared to a condition of passive word listening. 3 UWS/VS, 6 MCS, and 1 EMCS patients showed responses consistent with following instructions, and brain activations were increased in connections between the thalamus and the prefrontal cortex in respondents compared to non-respondents.

A few studies have focused on assessing awareness with auditory paradigms based on tones and EEG. The Local Global Paradigm (Bekinschtein et al., 2009) is an auditory task based on repeated sequences of sound with a hierarchical pattern, such that a target sound can deviate from the local or global pattern. EEG responses to a local deviant elicit an early mismatch negativity (MMN) considered to be an automatic process (Chennu et al., 2012; Näätänen et al., 2001) independent of the level of wakefulness

of an individual (Heinke et al., 2004). However identifying a sound that deviates from global regularities is considered to be a conscious process, given that it depends on top-down attentive processes that allow to maintain in working memory the auditory representations. Consistently, global deviants elicit a late ERP referred to as P3b, only when attention is directed to the sounds. The original study showed a consistent dissociation between MCS and EMCS patients who displayed the global deviant effect, and UWS/VS patients who showed only the MMN. In a subsequent study comprising 22 DoC patients, two UWS/VS patients with brain responses to global deviants transitioned to MCS a few days after the evaluation (Faugeras et al., 2011). In addition, although not the most informative markers, ERPs elicited by the local-global paradigm can distinguish between MCS and UWS/VS patients (Engemann et al., 2018; Sitt et al., 2014). In another study, based on a classical auditory oddball paradigm in three attentional conditions: passive, attentive, and distracted attention in 68 DoC patients, 14 patients showed brain responses consistent with complying with instructions during the attentive condition, and responsive patients showed better outcomes than non-respondents (Morlet et al., 2023). A paradigm based on EEG and somatosensory stimulation assessed the relation between selective attention and command-following in 14 patients (7 UWS/VS, 4 MCS, 2 EMCS, and 1 LIS patients) and 15 healthy participants. Although no patient (and not all healthy controls) showed a P3b cortical response to the stimuli, patients who displayed stimulus orientation responses indexed by the early P3a ERP, typically considered an unconscious response (Chennu et al., 2012), also showed covert command following unmasked by fMRI-based assessments (Gibson et al., 2016). In addition, in a study in a small cohort of DoC patients, covert selective attention measured with fMRI allowed patients to respond to binary questions by focusing on specific words presented auditorily (Naci et al., 2013). Overall, cortical responses to attended stimuli can convey information on the level of awareness of DoC patients.

1.8 Bodily signals and consciousness

The idea of imagining a brain without a body (Putnam, 1981) is in some way an impossible exercise to ask to brains with bodies, brain and bodies are intertwined and the percepts that we experience are the result of the complex interaction between the

central and the peripheral nervous systems.

The classification of sensory perception traditionally distinguishes between interoceptive and exteroceptive processes based on the origin and pathways of the afferent signals (Ceunen et al., 2016; Critchley et al., 2017). Under this view, exteroception refers to the sensory perception of stimuli picked up by exteroceptors, while interoception consists of the perception of signals sensed by visceral receptors (Sherrington, 1911). The brain constantly monitors the bodily signals and the environment through interoceptive and exteroceptive pathways which trigger appropriate homeostatic-allostatic and behavioral responses to current changes, as well as in anticipation of task demands (Ceunen et al., 2016; Critchley et al., 2013; Petzschner et al., 2021). The diffuse nature of visceral signals renders them typically not accessible to our conscious experience and therefore totally detached from cognition, or only associated with the emotional domain of awareness (Damasio, 2000; James, 1884; Porges, 1995). Nevertheless, interoception is currently understood in a broader sense as the processing of internal physiological states, their context dependant integration, and representation by the nervous system with a decisive role in perception (Craig, 2002; Joshi et al., 2021; Khalsa et al., 2018). It has been proposed that cardiac, respiratory, and gastric rhythms continuously send information to the cortical and subcortical structures, influencing cognition at multiple time scales (Azzalini et al., 2019; Criscuolo et al., 2022; Draguhn et al., 2022; Engelen et al., 2023). Furthermore, a healthy nervous system has to be able to integrate interoceptive and exteroceptive multisensory information to correctly determine whether a change is elicited within the system or by external influences. Building on this, the implicit 'neural subjective frame' has been put forward as a theory of consciousness which states that bodily signals would provide an anchor to establish a first-person perspective (Park et al., 2019b; Park & Tallon-Baudry, 2014; Tallon-Baudry et al., 2018), which is fundamental for the notion of self-awareness (Craig, 2002; Damasio, 2003; Morin, 2006). The 'neural subjective frame' proposes that the monitoring of the bodily state by the brain is at the root of subjective experience, providing a new framework to assess consciousness.

1.8.1 From mental content to bodily signals and back

The autonomic nervous system (ANS) maintains bodily homeostasis by regulating most of the organs in the human body (Cechetto et al., 2009). It is intuitive to think that the

processing of conscious information can have a direct effect on bodily signals (Lacey et al., 1978; Somsen et al., 2004). We can all relate to daily events having an impact on our heartbeat or our gut: being nervous, getting a surprise, or expecting a reward, are common experiences associated with a 'bodily feeling'. Mental content endogenously generated as well as mental content produced by external stimuli can be detected by measuring changes in peripheral activity. Bolliet et al., 2005 showed an increase in heart rate, electrodermal response, and temperature when participants observed someone perform a movement and the magnitude of the response covaried with the amount of effort perceived. Similarly, increases in respiratory rate are elicited when subjects observe an individual lifting weights or using a treadmill at different speeds (Paccalin et al., 2000). In addition, research shows that the time between heartbeats is modulated by anticipation of sensory stimuli (Jennings et al., 2009), when the feedback given after an error is relevant to adjust behavior (Crone et al., 2003; Skora, Livermore, & Roelofs, 2022; Somsen et al., 2000), and following violations of statistical regularities (Raimondo et al., 2017).

Mentally representing an event can also elicit an autonomic response, and this has been evidenced during motor imagery tasks. Decety et al., 1991 and Wuyam et al., 1995 showed that mentally simulating locomotion elicited a cardiac and respiratory rate increase, which correlated with the level of imagined effort. Likewise, during a leg imagery task, the heart and respiratory rate exhibited an increase, and this response was sensitive to the imagined load on the leg (Decety et al., 1993). In summary, evoking oneself or seeing someone else perform a certain task induces a bodily preparatory effect associated with the task demands (Collet et al., 2013; Collet et al., 2010). Analogously, bodily signals can affect mental content. Several studies have shown that sensory perception is influenced by the phase of the cardiac cycle during target detection of visual (Marshall et al., 2022; Ren et al., 2022; Salomon et al., 2016), somatosensory (Al et al., 2020; Al et al., 2021), and auditory (Edwards et al., 2007; Schulz et al., 2020) stimuli. Hence, external and internal signal processing are intertwined and are sensitive to the state of the body and the state and content of the brain.

1.8.2 The ANS and brain-heart interactions

The ANS, considered part of the peripheral nervous system, encompasses visceral afferent pathways, integration centers at the level of the brainstem and forebrain, and

efferent pathways subdivided into the sympathetic and parasympathetic systems. These systems act tonically to regulate the heart, lungs, glands, and smooth muscles, among other functions. The sympathetic system prepares the body for energy-consuming tasks and dominates during "fight-or-flight" situations. In contrast, the parasympathetic system maintains activity during rest. They have distinct anatomical organization and visceral regulation effects and collaborate to maintain bodily homeostasis (McCorry, 2007).

The cardiac cycle consists of a ~900 ms period composed of two repeating events, the diastole, a somewhat variable period during which the heart fills with blood, and the systole, a more constant period during which the heart pumps sending blood to the rest of the body (Engelen et al., 2023). A cycle can be considered to start during the last part of the diastole with a depolarization of the sinoatrial node, an electrically active tissue localized in the right atrium considered to be the pacemaker of the heart. This produces a contraction of the atrial muscle followed by a ventricular contraction, which marks the onset of the systole. At the end of the ventricular contraction phase, a repolarization of the ventricles occurs which produces a relaxation of the tissue enabling a new diastolic phase to unfold (Berntson et al., 2016). Cardiac activity is controlled by the nucleus ambiguus and the rostral ventrolateral medulla in the brain stem which receive efferent information from central areas and afferent input from mechanical and chemical receptors across the vascular system (Critchley et al., 2013) (Figure 1.2). The cardiac sympathetic innervation is organized in multiple synapses. Preganglionic neurons in the spinal cord receive information from the rostral ventrolateral medulla and send information to neurons in the cervical and thoracic ganglia whose afferents release norepinephrine. The binding of norepinephrine to cardiac beta-1 adrenergic receptors produces a cAMP-mediated depolarization in the myocytes of the sinoatrial node. This results in an increase in cardiac output reflected in increased heart rate, contractility, and conduction velocity (Silvani et al., 2016). The parasympathetic innervation consists of preganglionic neurons in the nucleus ambiguus and the dorsal motor nucleus that sends their fibers via the vagus nerve to ganglia distributed in the epicardium, and to the sinoatrial and the atrioventricular node, where they release acetylcholine. The binding of acetylcholine to M2 muscarinic receptors produces a hyperpolarization and a reduction in cAMP levels, which results in a decrease in heart rate, conduction times, and atrial and ventricular contractility. The parasympathetic and sympathetic systems

affect cardiac activity in complementary but non-linear ways. The parasympathetic system has more control of the heart rate and acts faster, as its effects do not rely on second messengers. In contrast, the sympathetic system has greater control over the contractility of the heart tissue and tends to act more slowly (Silvani et al., 2016).

Multiple central structures in the forebrain and the brainstem are involved in cardiac activity regulation (Benarroch, 1993; Lamotte et al., 2021) through low-level mechanisms such as the baroreceptor heart rate reflex, and higher behavioral processes. The baroreceptor heart rate reflex is produced when increases in blood pressure, typically during the systole, activate stretch-sensitive receptors in the carotid and aorta which send information via the glossopharyngeal and vagus nerves to the nucleus of the solitary tract (NST) (Figure 1.2), the major relay of visceral information in the brainstem and the main target of top-down influences (Critchley et al., 2013). The NST excites parasympathetic nuclei and indirectly inhibits the sympathetic drive of the rostral ventrolateral medulla, producing a decrease in heart rate and contractility. The opposite autonomic effect unfolds when a decrease in blood pressure is sensed by these mechanoreceptors. The NST projects the afferent signals associated with changes in blood pressure to nucleus in the pons, to the hypothalamus, and higher cortical areas via the thalamus, informing the timing and strength of each heartbeat. This information is sent to the amygdala, the anterior cingulate cortices, the prefrontal cortices, the somatosensory cortices, and the insula (Azzalini et al., 2019; Berntson et al., 2016; Cechetto et al., 2009) (Figure 1.2). These structures in the central nervous system involved in integrating autonomic, emotional, and cognitive processes have been coined the central autonomic network (CAN) (Benarroch, 1993; Lamotte et al., 2021), and would sustain the internal representation of the physiological state of the body as well as modulate the baroreflex in a top-down manner in response to effortful cognitive tasks (Critchley et al., 2003; Gianaros et al., 2012) or emotional stimuli (Critchley et al., 2015; Roelofs, 2017).

As mentioned before, some evidence supports the view of cardiac synchrony effects. It has been suggested that the oscillatory nature of the cardiac activity that is afferently fed to the cortex produces a decrease in cortical excitability (Elbert et al., 1995; Lacey et al., 1978) that could affect the processing of external stimuli. One hypothesis is that the systolic period of the cardiac cycle during which baroreceptors are most activated produces a transient cortical inhibition affecting the precision of exteroceptive

signals. Under this view, cardiac deceleration produced by increases in parasympathetic drive would be a mechanism by which to diminish the afferent noise produced by the heartbeat and enhance stimuli processing (Skora, Livermore, & Roelofs, 2022).

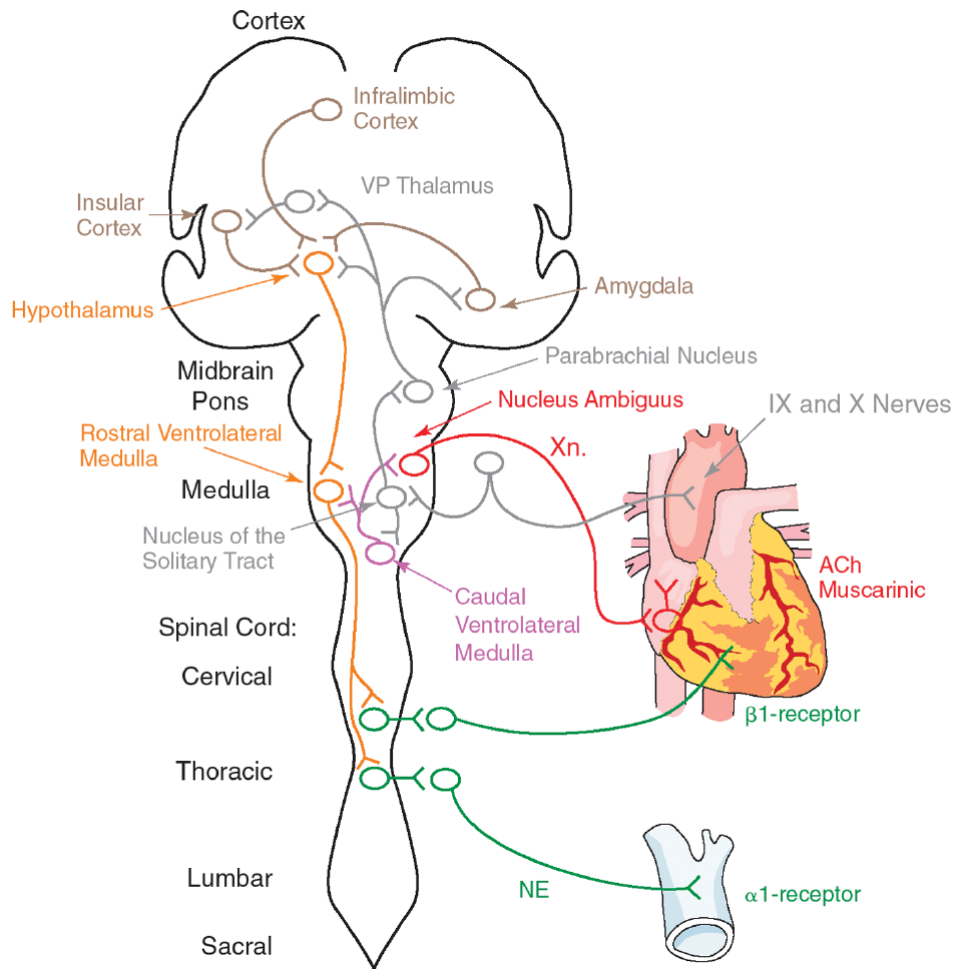


Figure 1.2: Cardiovascular control pathways. Visceral afferent information (gray) arrives from nerves IX and X into the nucleus of the solitary tract. This information is sent to the parabrachial nucleus, which relays it to the forebrain, and to the ventrolateral medulla, which controls cardiovascular reflexes. Inputs to the nucleus ambiguus modulate vagal control of heart rate (red); inputs to the caudal (purple) and rostral (orange) ventrolateral medulla regulate sympathetic outflow to both the heart and the blood vessels (dark green). Forebrain areas that influence the cardiovascular system (brown) include the insular cortex, the infralimbic cortex (a visceral motor area), and the amygdala, which produces autonomic emotional responses. All of these act on the hypothalamic sympathetic activating neurons (orange) in the paraventricular and lateral hypothalamic areas to provide behavioral and emotional influence over the blood pressure and heart rate. ACh, acetylcholine; NE, norepinephrine; VP, ventroposterior. Adapted from (Posner et al., 2019)

1.8.3 Active interoception and the heartbeat-evoked potential

In addition to the modulations of visceral information by mental content or by external stimuli described in previous sections, evidence shows that directing attention toward bodily signals in a process known as interoceptive attention (Joshi et al., 2021) can impact their final encoding. Following other perceptual systems (Adams et al., 2013; Kaya et al., 2014; Rao et al., 1999; Zelano et al., 2011), interoception has been described in terms of the predictive coding theory (Allen et al., 2022; Barrett et al., 2015; Seth et al., 2012). Under the Bayesian inference lens, perception is the result of a dynamic process of error correction between the brain's expectations and the actual sensory input at different levels of a hierarchical organization. Sensory representations are shaped by empirical a priori of what the percept (or 'interocept') should be in terms of content and precision, and how far were they from the afferent inputs, expressed as feedforward prediction error signals. This continuous process of inference based on experience allows the brain to develop hierarchical generative models of the world, as well as of our body, which can better anticipate the perception of new input (Friston, 2009; Hohwy et al., 2020). It has been postulated that the computational operation of attention is to optimize the precision of sensory signals by modulating the gain of the prediction feedforward error at particular levels in the hierarchy (H. R. Brown et al., 2013; Feldman et al., 2010; Friston, 2009; Schröger et al., 2015) which would result in increased neural responses to specific features or stimuli in relevant cortical areas (Ainley et al., 2016).

The heart has been the preferred candidate to manipulate and assess the effects of interoceptive attention at the individual level. The heart acts as a dynamical pacemaker with a rhythmic activity that is continuously fed via ascendant pathways to the brain (Criscuolo et al., 2022; Shaffer et al., 2014), of which subjects are normally unaware. Heartbeat counting (Dale et al., 1978) or heartbeat tapping (Ludwick-Rosenthal et al., 1985) tasks have been proposed to engage attention towards internal stimuli while an objective neural measure of attention to the heart can be acquired. Brain response to the heartbeats can be measured with surface EEG by averaging time-locked EEG activity to the ECG waveform R peak (Schandry et al., 1986). The ERP elicited is called heartbeat-evoked potential (HEP) and is considered to reflect the cortical processing of heart activity with and without awareness (Coll et al., 2021). More generally, the term heartbeat-evoked response (HER) is used to refer to the cortical response to the

heartbeats obtained using other methods such as magnetoencephalography (MEG). The amplitude of the HEP is modulated by directing attention to the heart (Montoya et al., 1993; Petzschner et al., 2019; Schandry et al., 1986; Villena-González et al., 2017; Yuan et al., 2007, see (Coll et al., 2021) for a review), correlates with interoceptive awareness, measured as the accuracy in heartbeat detection (Katkin et al., 1991; Pollatos et al., 2004; Yuan et al., 2007), and decreases with sleep depth (Lechinger et al., 2015). In addition, the cortical response to the heartbeats is modulated by emotional stimuli (Couto et al., 2015; Fukushima et al., 2011) and it has been associated with specific dimensions of spontaneous self-related thoughts in the ventromedial prefrontal cortex and the posterior cingulate cortex (Babo-Rebelo, Richter, et al., 2016; Babo-Rebelo, Wolpert, et al., 2016). Time-frequency analysis suggest that the HEP arises from an increase in intertrial-coherence in the theta band (Park et al., 2018), but the exact brain-heart pathways that sustain the HEP are not entirely understood. Possible origins involve the mechanoreceptors in the heart arteries (Gray et al., 2007), cardiac afferent neurons in the wall of the heart (Tahsili-Fahadan et al., 2017), somatosensory information from the skin (Khalsa, Rudrauf, & Tranel, 2009), and cortical neurovascular coupling (Jammal Salameh et al., 2024). Cortical responses to the heart have been observed in the somatosensory cortex (Kern et al., 2013; Pollatos et al., 2005), the amygdala (Park et al., 2018), the ventromedial prefrontal cortex (Babo-Rebelo, Richter, et al., 2016; Babo-Rebelo, Wolpert, et al., 2016; Park, Correia, et al., 2014), the posterior cingulate cortex (Park et al., 2016), the insula (Babo-Rebelo, Wolpert, et al., 2016; Canales-Johnson et al., 2015; Park et al., 2018; Pollatos et al., 2005), the anterior cingulate cortex (Park, Correia, et al., 2014; Pollatos et al., 2005), the frontal operculum (Park et al., 2018), the orbitofrontal cortex (Canales-Johnson et al., 2015), the right parietal lobule (Park, Correia, et al., 2014), and the precuneus (Babo-Rebelo, Wolpert, et al., 2016). Given the overlap of the areas most consistently associated with the HER, such as the ventromedial prefrontal cortex, the precuneus, and the posterior cingulate cortex, with the DMN, it has been proposed that the neural responses to the heartbeat can influence cognitive functions by modulating the activity in the DMN (Park et al., 2019a).

1.8.4 Brain-heart interactions and internal-external awareness

Internal awareness, consisting of spontaneous thoughts independent of the environment, has been linked to fMRI increases in the anterior cingulate cortex and the medial prefrontal cortex (Vanhaudenhuyse et al., 2011). Self-referential processing, defined as the processing of stimuli that are related to one's own person (Northoff et al., 2006), is associated with midline structures, that overlap with the DMN, (Northoff et al., 2004; Northoff et al., 2006; Qin et al., 2011). In addition, HERs measured with MEG have shown to be increased in ventral ACC when participants detect visual stimuli at threshold with no changes in arousal or afferent cardiac information, which has been related to the first person perspective of the subjective report activity (Park, Correia, et al., 2014; Tallon-Baudry et al., 2018). In addition, the HERs have been shown to covary with self-related thoughts in the ventromedial prefrontal cortex and the posterior cingulate cortex (Babo-Rebelo, Richter, et al., 2016; Babo-Rebelo, Wolpert, et al., 2016). The overlap between the cortical regions associated with the processing of the heartbeats during spontaneous self-related thoughts, and during subjective reports, with the DMN nodes activated during the processing of stimuli related to the self, supports the view that visceral information provides the first-person perspective associated to internal and external awareness (Tallon-Baudry et al., 2018).

1.8.5 Brain-heart interactions and disorders of consciousness

Recent research has focused on exploring whether the interactions between the brain and the heart can be useful for diagnosis and prognosis purposes in patients with impaired consciousness (Candia-Rivera, 2022; Pistoia et al., 2019; Riganello et al., 2019), as brain-heart interactions can be viewed as indirect signals of the state of the cortical and subcortical networks that sustain consciousness (Pistoia et al., 2019). It is common for neurological disorders to be accompanied by neurogenic changes to the ECG probably as a consequence of an autonomic dysregulation produced by lesions to regions that participate in cardiovascular control (Samuels, 2007). In this line, DoC patients can show cardiac pathologies not related to organic heart dysfunction but related to autonomic imbalances (Levy et al., 2011; Pistoia et al., 2015), which are associated with worst outcomes (Pistoia et al., 2015). Moreover, in a group of 68 patients with prolonged DoC, the HEP during resting state was correlated to the level of consciousness inferred from the PET glucose metabolism in DMN areas, and this association

was stronger than the one between brain metabolism and behavioral diagnosis (Candia-Rivera et al., 2021). In a study using EEG and the local-global paradigm (Raimondo et al., 2017), patients in MCS showed a cardiac acceleration in response to global auditory irregularities, which was absent for local irregularities, and this pattern did not occur in UWS/VS patients. Furthermore, this information improved the classification of the state of consciousness of patients compared to classifiers based solely on EEG features. In a subsequent study, the effects of the deviant sounds on the HEP were explored (Candia-Rivera, 2023). The results show that the HEP following the deviant sound together with the concurrent auditory ERPs can be useful in distinguishing between MCS and UWS/VS patients. Additionally, the effects of narratives on the intersubject synchronization (ISC) of heart activity have been explored in DoC patients (Pérez et al., 2021). Compared to controls, patients exposed to common narratives show decreased ISC of heart activity, and the level of ISC was correlated to the fractional anisotropy index of patients, a measure of anatomical integrity. Another study showed that sensory stimulation elicited sympathetic and parasympathetic mediated changes in the heart-rate variability of DoC patients and the level of response was correlated with their recovery (Wijnen et al., 2006).

Overall, brain-heart interactions measured with non-invasive resting state and passive paradigms can provide information on residual cortical processing in DoC patients.

1.9 Research questions and objectives of the present work

Throughout this chapter, we have introduced the complex scenario surrounding patients with disorders of consciousness. In particular, we summarized the evidence regarding the uncertainty in diagnosis based exclusively on behavioral information and the associated impact regarding prognosis and care decisions. In addition, the experimental paradigms used to complement physician examinations were reviewed, stating the relevance of unmasking covert willful behavior and residual covert cortical processing, as positive results are associated with better functional outcomes. Therefore, developing sensitive, precise, and objective patient-level markers of residual consciousness is of the highest clinical and ethical interest.

General objective

The main objective of this thesis was to develop novel experimental paradigms and analyses to assess command-following and residual cortical capacities in brain-injured patients focusing on two promising fields: brain-body interactions and language processing. An important aspect of this work was to enhance equity in healthcare access by creating bedside patient assessments based on widely available tools, such as EEG, EMG, and ECG, which are portable and can be implemented in low-resource settings.

Study 1: Brain-muscle networks: a novel protocol to study covert command-following

Motivation

The command-following assessments from which awareness is inferred are mostly based on motor imagery and fMRI, a technique that is not available in all health centers and is not suitable for all patients. EEG is useful to detect motor imagery and motor execution and a few studies have shown that surface EMG can be used to detect covert movements in DoC patients. In addition, evidence from motor imagery research shows that heart activity is informative on whether a mental task is being carried out.

Objective

To develop a motor imagery task based on EEG, EMG, and ECG that can be useful to detect command following in patients with disorders of consciousness.

Main hypothesis

Evoking a mental representation of movement should elicit specific cortical responses (ERD/S) together with a modulation of bodily signals, such as cardiac activity and potentially muscle tone. The combination of these sources of information should result in an enhanced detection of motor imagery.

Study 2: Predicting Attentional Focus: Heartbeat-Evoked Responses and Brain Dynamics During Interoceptive and Exteroceptive Processing**Motivation**

Most of the command-following tasks implemented to detect awareness in DoC patients are based on motor imagery. The few studies based on selective attention have focused on exteroceptive information and mostly use ERP analysis. Nevertheless, a crucial aspect of consciousness is the awareness of both the internal and external world. Following the processing of external information, attention can affect the encoding of internal signals as shown by the effect of attention on the heartbeat-evoked potential, and could be used as a marker of command-following and self-awareness.

Objective

To develop a task based on sustained selective attention to interoceptive and exteroceptive signals to detect covert attention as a proxy of command-following in patients with disorders of consciousness using EEG and ECG.

Main hypothesis

Directing attention to bodily signals should elicit an increased brain response to internal rhythms and a decreased response to external stimuli, with an opposite pattern during exteroceptive attention. In addition, orienting attention towards different types of information could evoke different brain dynamics as distinct brain networks are postulated

for internal and external awareness. The encoding of the heartbeat-evoked potential and the ongoing brain dynamics elicited during interoceptive and exteroceptive attention should predict attentional focus at a subject level.

Study 3: What drives intersubject correlation of EEG during conscious processing of narrative stimuli?

Motivation

Detecting covert cortical processing (CCP) of language in DoC patients is fundamental in terms of prognosis as patients who show CCP are associated with better outcomes. Assessments based on EEG have either used single words, short sentences, or very controlled stimuli that can produce confounds or restrict their implementation. Researchers have used more ecological methods to measure how the evoked brain activity in patients with DoC correlates with that of healthy controls when exposed to common narrative stimuli. Nevertheless, the meaning of this shared activity is far from clear. Disentangling what information carried in speech elicits the common responses, and whether conscious processing is required to produce them, is crucial to determine the clinical impact of this approach. Furthermore, it would be significant to develop individual markers of speech processing with enough granularity to determine the depth of language processing in patients and to track their improvements over time.

Objectives

To explore which are the speech properties that produce the shared brain responses observed in EEG recordings when participants are exposed to common auditory narratives. To study whether the contributions of low-level acoustic information and higher linguistic features rely on conscious processing.

Main hypothesis

When participants are exposed to the same auditory narratives common brain activity should be elicited during attended and unattended speech processing, with both acoustic and linguistic features contributing to the shared activity. Nevertheless, linguistic information embedded in speech should be particularly affected by attention.

Chapter 2

Brain-muscle networks: a novel protocol to study covert command-following

Brain-muscle networks: a novel protocol to study covert command-following

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2.1 Abstract

In this study, we propose to evaluate the potential of a network approach to electromyography and electroencephalography recordings to detect covert command-following in healthy participants. The motivation underlying this study is the development of a diagnostic tool that can be applied in common clinical settings to detect awareness in patients who are unable to convey explicit motor or verbal responses, such as patients who suffer from disorders of consciousness (DoC). The proposed study will examine the brain and muscle response during movement and imagined movement of simple motor tasks, as well as during resting state. Brain-muscle networks will be obtained using non-negative matrix factorization (NMF) of the coherence spectra for all the channel pairs. We will contrast the configuration of the networks during imagined movement and resting state at the group level, and subject-level classifiers will be implemented using as features the weights of the NMF together with trial-wise power modulations and heart response to classify resting state from motor imagery. The results of this investigation will determine the feasibility of applying this paradigm to individual patients.

2.2 Introduction

Disorders of consciousness (DoC) refers to a group of pathological states in which consciousness is affected as a result of injury or trauma to the nervous system. Unresponsive wakeful syndrome also referred to as vegetative state (UWS/VS), and minimally conscious state (MCS) are two distinct categories of states of impaired consciousness. Patients in UWS/VS are awake (intermittent eye-opening) without reproducible volitional behavior ([Jennett, 2002](#); [Jennett et al., 1972](#)), in contrast, patients in MCS can occasionally show overt signs of awareness or responses to sensory stimuli beyond reflexes ([Giacino et al., 2002](#)), suggesting cortically mediated behavior ([Naccache, 2018](#)). In order to classify patients with DoC in one of these states clinical assessments are carried out to examine voluntary behaviors ([Majerus et al., 2005](#)). Accurately distinguishing patients in UWS/VS from patients in MCS based on behavioral criteria is a challenging task. Indeed, it is estimated that 40% of patients with DoC are incorrectly classified as UWS/VS ([Andrews et al., 1996](#); [Schnakers et al., 2009](#)). The level of conscious awareness of a patient can be underestimated as a consequence of fluctuations in arousal, difficulty in identifying behavior consistent with volition ([Fischer et al.,](#)

2015), as well as patients' impossibility to convey overt responses due to medication, and sensory, or motor lesions (Giacino et al., 2009). Importantly, the diagnosis has a great impact on treatment, prognosis, and end-of-life decisions, as patients in MCS have a higher probability of regaining cognitive function (Dolce et al., 2008; Faugeras et al., 2018; Hirschberg et al., 2011; Luaute et al., 2010b). Therefore, developing sensitive, precise, and objective tools to measure volitional behavior is of the highest clinical and ethical interest.

2.2.1 Command-following beyond behavior

In addition to behavioral evaluation, non-invasive neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have been widely used to assess the level of awareness of patients with DoC. The rationale is that if a patient is faced with a task that requires conscious processing and their brain response is sustained and consistent with the one elicited for healthy controls, then consciousness may be inferred (Boly et al., 2007; Owen, 2013). Motor imagery (MI) has been a recurrently used paradigm since Owen's seminal study, where fMRI together with complex imagery tasks, such as navigating space and playing sports, enabled the identification of sustained command-following responses in a patient clinically diagnosed as in UWS/VS (Owen et al., 2006). MI can be defined as a dynamic mental state during which there is a rehearsal of a motor act without overt body movement (Decety, 1996; Mellet et al., 1998). MI can be divided into kinesthetic imagery, a first-person process that requires one to "feel" the movement or reproduce the sensations that the muscle contractions would produce; and visual imagery, a third-person perspective where one sees oneself performing the movement (Guillot et al., 2005). In practice, the term MI is widely used to refer to the first-person experience (Lotze et al., 2006). Numerous studies have found covert responses in UWS/VS and MCS patients using complex imagery paradigms (see Kondziella et al., 2016; Laureys et al., 2012 for reviews). Although with variable sensitivity, these studies managed to detect covert responses in MCS patients, and crucially in a few UWS/VS patients, illustrating that the information provided by these evaluations is a significant complement to bedside examinations. Nevertheless, some patients that have overt responses to commands fail to show a modulation of brain activity during these imagery tasks (Bardin et al., 2011; Chennu et al., 2013; Gibson et al., 2014; Monti et al., 2010). The high cognitive demands associated with

these events could explain the observed inconsistency. Preserved cognitive functionalities among DoC patients are highly variable as brain injuries are commonly accompanied by other disorders or pathologies, consequently, complex tasks may in some cases underestimate the level of awareness (Bekinschtein et al., 2011). Simpler motor tasks have been shown to be effective in detecting covert responses in UWS/VVS patients (Bekinschtein et al., 2011), and in some cases they even provide a more accurate measure of command-following than complex motor imagery (Bodien et al., 2017), suggesting they could be more appropriate to probe these patients.

2.2.2 Covert responses measured with EEG in patients with DoC

EEG is low-cost, accessible in all health centers, suitable for all patients, and has proven effective to identify covert responses in DoC patients. Power modulations at various frequency bands and channels have been reported in MCS patients instructed to imagine swimming (Goldfine et al., 2011) or a sport of the patient's choice (Horki et al., 2014). Although variable, EEG responses have been detected in UWS/VVS and MCS patients when asked to imagine opening and closing their hands (Cruse et al., 2012; Cruse et al., 2011; Gibson et al., 2014) and moving their toes (Cruse et al., 2012; Cruse et al., 2011). EEG has also been combined with simple motor execution commands to evaluate DoC patients' awareness levels. Demanding patients to move their feet on cue resulted in an EEG response in 2/6 MCS patients (Horki et al., 2014). In a study comprising 104 unresponsive patients, instructions to open and close their hands elicited a power modulation in 16 individuals. Furthermore, responsive patients had better long-term outcomes than unresponsive patients (Claassen et al., 2019). This illustrates that EEG is an adequate tool to detect covert motor execution and motor imagery in non-communicative patients.

2.2.3 Covert responses measured with EMG in patients with DoC

A less explored approach to evaluate awareness in patients without explicit motor or verbal responses is the use of surface electromyography (EMG). Research combining surface EMG with simple motor commands has shown subthreshold motor activity in DoC patients that failed to exhibit overt motor behavior. In a small study, one patient diagnosed as UWS/VVS and one as MCS showed covert motor responses detected by EMG when asked to move their hands (Bekinschtein et al., 2008). A subsequent study

on a bigger cohort of patients and using multiple motor instructions showed EMG responses for a patient in UWS/VS and three patients in MCS (Habbal et al., 2014). Finally, using single-trial analyses of EMG activity, covert responses were detected in MCS patients when instructed to move both their right and left hands (Lesenfants et al., 2016). Therefore, muscular activity evaluated with a generally available and non-invasive tool such as surface EMG can provide meaningful information on a patient's level of awareness.

2.2.4 Corticomuscular coupling

Synchronization between muscle and cortical activity, typically referred to as corticomuscular coherence (CMC) (Conway et al., 1995), arises mainly from the primary motor cortex contralateral to the activated muscle, is somatotopically organized and its magnitude is directly correlated to the extent of the muscle cortical representation (Bourguignon et al., 2019; Liu et al., 2019; Witham et al., 2011). Coupling between EEG and EMG is typically found in the beta band (10-30Hz) during weak contraction (Gwin et al., 2012; Halliday et al., 1998; Mima et al., 2000; Salenius et al., 1997), is maximal when muscle contraction is stable, and disappears during movement (Kilner et al., 2003) or movement preparation (Boonstra et al., 2009; Gilbertson, 2005). At lower frequencies (<10Hz), and mainly during movement, corticokinematic coupling is elicited by afferent sensory information and movement rhythmicity (Bourguignon et al., 2015). Additionally, CMC in the gamma band (31-45 Hz) has been reported (P. Brown et al., 1998; Gwin et al., 2012; Omlor et al., 2007). It is believed that the cortical mu rhythm contributes to the CMC at ~20Hz (Mima et al., 2001; Salenius et al., 1997). Mu rhythm is a somatomotor oscillation that arises from a mixture of frequencies with different neurophysiological origins. Frequencies surrounding the alpha band (mu-alpha ~10Hz) are considered to reflect activity from the somatosensory cortex while frequencies around the beta band (mu-beta ~20Hz) would reflect motor cortex activation (Hari, 1997; Salmelin et al., 1994). The modulation of this rhythm by a movement event is referred to as event-related synchronization (ERS) when an increase of power is observed, or event-related desynchronization (ERD) when a decrease occurs (Barlaam, 2011; Pfurtscheller et al., 1999; Salmelin et al., 1994). Normally, a few seconds before initiation and during movement an ERD is observed followed by a rebound ERS when execution is stopped (Kilner et al., 2003; Pfurtscheller, 1981; Salmelin et al., 1994).

2.2.5 Brain and body response during imagery movement

EEG response during motor imagery (MI) is variable such that a percentage of participants do not show this pattern (Y. Hashimoto et al., 2010; Höller et al., 2013; Pfurtscheller et al., 2009). Nevertheless, when present, MI shows similar brain activity signatures to motor execution (ME) (see Munzert et al., 2009 for a review). Although weaker, ERD of the mu rhythm occurs immediately before (Neuper et al., 2010; Pfurtscheller, Scherer, Müller-Putz, & Lopes da Silva, 2008) and during MI (Beisteiner et al., 1995; Höller et al., 2013; Lang et al., 1996) followed by an ERS initiated by movement termination (Pfurtscheller et al., 2009). In addition to brain activity, bodily signals can serve as a window to detect mental processes. The autonomic nervous system (ANS) elicits changes to maintain bodily homeostasis and to prepare for environmental as well as internal demands. It has a close relationship to processes such as emotion and attention (Porges, 1995) and is also modulated by mental representations of movement, both observed and imagined. Kinesthetic imagery requires accessing stored information related to the sensations elicited by proprioceptors and exteroceptors during actual movement and movement preparation (Collet et al., 2013). In this line, evidence shows an increase in heart rate during motor imagery with a magnitude of the effect related to the level of effort of the imagined movement (Decety et al., 1993; Decety et al., 1991; Oishi et al., 2000; Wuyam et al., 1995); suggesting that the brain is in fact evoking an internal model of the movement comprising its metabolic demands (Collet et al., 2013). On the other hand, evidence of covert contraction of the muscles during MI is not as robust (see Guillot et al., 2012 for a review). Some studies for which brain responses during MI are consistent with movement show no EMG response (Decety et al., 1993; Gentili et al., 2006; R. D. Herbert et al., 1998; Lotze et al., 1999; Naito et al., 2002), while studies for which subthreshold EMG activity is elicited, show that the response is correlated to the level of effort imagined (Bakker et al., 1996; Slade et al., 2002), and the muscles activated are consistent with the muscles involved in the mentally represented movement (Guillot et al., 2007; R. Hashimoto et al., 1999). Crucially, there is evidence of an increase in the excitability of descending motor pathways during MI tasks (Bonnet et al., 1997; Grosprêtre et al., 2016; Irie et al., 2020; Li et al., 2004; Sakamoto et al., 2009).

2.2.6 Functional muscle networks

The musculoskeletal system is characterized by having a great number of degrees of freedom which makes it a very flexible but complex system (Bernstein, 1967). Movement execution, as well as the mental rehearsal of a movement, requires the coordinated action of cortical and subcortical structures in space and time. Muscle synergies have been proposed as the strategy the nervous system has to simplify motor control while ensuring proper motor outputs (W. A. Lee, 1984; Tresch et al., 2002). Muscle synergies can be defined as the coherent activation in space or time of a group of muscles orchestrated by motor areas of the cortex and the afferent systems (Bizzi et al., 2013). In order to explore motor organization, intermuscular coherence (IMC) is computed as the cross-correlation in the frequency domain of the EMG response for each pair of muscles (Challis et al., 1991), and muscle synergies are identified by applying non-negative matrix factorization (NMF) (K. M. Lee et al., 1999) to the IMC spectra. Recently, a new approach that combines NMF and network analysis shows that muscle groups show coupling at different frequencies for different movements, postulating a functional organization of the muscle synergies which they refer to as functional muscle networks (FMN) (Boonstra et al., 2015; Kerkman et al., 2018). Experimental evidence suggests that muscle synergies derive from common neural input (Hart et al., 2010; Overduin et al., 2012; Zandvoort et al., 2019). Therefore, FMN combined with corticomuscular coherence analysis could provide information on cortical descending control (Boonstra, 2013).

2.2.7 This study

Finding markers of concealed command-following in healthy participants is the first step to developing new diagnostic tools for unresponsive patients. Moreover, markers based on equipment that is broadly available in any hospital are of particular importance. In this line, although muscular activity measured with surface EMG has shown some promising results, its potential to detect covert responses remains relatively unexplored. In this study, we propose to evaluate the potential of a network approach to electromyography and electroencephalography recordings to detect covert command-following in healthy participants. We will study the brain and muscle functional network configuration during motor execution, motor imagery, and resting state, and we will test the following hypothesis. (H1) The brain-muscle networks of healthy participants during motor imagery

are different from the resting state networks and engage the same muscles as during motor execution. (H2) Autonomic responses are modulated by motor imagery. (H3) Subjects' cortical responses during motor imagery are correlated to their motor imagery ability. (H4) Brain-muscle networks together with ERD/ERS and cardiac activity can provide information on covert command following at the subject level.

The results of this investigation will determine the feasibility of applying this paradigm in the clinical context to detect persistent covert awareness in unresponsive patients.

2.3 Methods

The task has been conceived with the underlying intention of a future application in the clinical context, and this has determined its design. It is a simple auditory task that requires non-invasive equipment commonly available in health centers that would cause minimal discomfort to patients. Moreover, it is inspired by a similar task that has already been shown to be effective in detecting covert awareness in patients with disorders of consciousness using EEG ([Claassen et al., 2019](#)).

2.3.1 Motor imagery scale

First, participants will be evaluated on their ability to imagine movements. To this aim, the French-validated Movement Imagery Questionnaire-Revised Second version (MIQRS) ([Loison et al., 2013](#)) will be carried out. On top of evaluating participants' motor imagery ability, this scale will serve to exercise participants' kinesthetic imagery for the upcoming task.

2.3.2 Task

The following commands will be presented to the participants:

1. Open and close your hand
2. Flex and extend your foot
3. Open and close your hand and flex and extend your foot
4. Imagine opening and closing your hand
5. Imagine flexing and extending your foot

6. Imagine opening and closing your hand and flexing your foot
7. Stay relaxed without moving or tensing your body

Participants will have to repeat the requested action for 15 s until a stop command is heard. The task is structured in four blocks. In each block, each motor condition is presented 6 times and the resting condition is presented 18 times (54 trials per block), resulting in 72 trials of motor execution, 72 trials of motor imagery, and 72 trials of resting state. The conditions within each block are presented in a randomized fashion. Participants will be asked to focus on the sensations during movement execution and to try to remember them when engaging in kinesthetic motor imagery. Instructions will be presented binaurally through Etymotic ER3C Tubal Insert Earphones and participants will be asked to remain with their eyes closed during the blocks. The inter-trial interval is randomly varied between 4 - 8 s (Figure 2.1). Audio instructions are sent via a custom-built Arduino stimulation box that sends event markers directly to the amplifier.

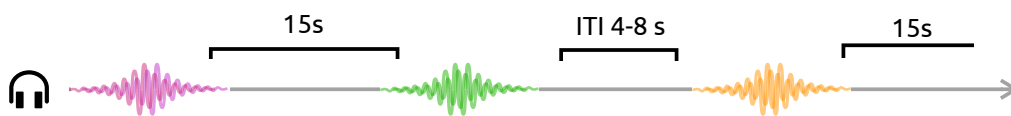


Figure 2.1: Experimental design. Each instruction is presented auditorily. Participants have to execute a movement, imagine a movement or remain relaxed according to the received instruction for the duration of the trial. A stop command is presented 15s after the initial instruction. Trials are separated by a random interval between 4-8s.

2.3.3 Physiological recordings

Participants will be seated in a high Fowler's position and surface EMG electrodes will be applied on their dominant hand (Abductor pollicis brevis - APB), arm (flexor digitorum superficialis - FDS, extensor digitorum - ED, biceps brachii - BB), leg (gastrocnemius mediale - GM, tibialis anterior - TA) and on the back (trapezius - TZ). In addition, a bipolar electrode placed in the left and right collarbone will be used to record cardiac activity. The skin will be prepared by scrubbing with alcohol swabs in order to reduce the impedance and improve the contact between the skin and the electrodes. High-density EEG will be recorded using EGI 256 channels HydroCel GSN net and EMG and ECG activity will be recorded using the Physio16 MR input box. All signals will be acquired with a Net Amps 400 EEG Amplifier from Electrical Geodesics, Inc, digitized at 1000Hz.

2.4 Analysis

2.4.1 Preprocessing

Preprocessing for EMG and EEG data is carried out using MNE 1.0.3 ([Gramfort, 2013](#)) and Scipy 1.8.1 ([Virtanen et al., 2020](#)). MNE and Scipy are open-source Python-based libraries. MNE is dedicated to the analysis of EEG and MEG signals, and much of its code is based on Scipy functionalities, a scientific and numerical tools library.

2.4.2 EMG and Intermuscular coherence

EMG data preprocessing will follow the steps detailed in ([Kerkman et al., 2018](#)). Briefly, the EMG signal is downsampled to 500 Hz and band-pass filtered 0.5-200 Hz (one-pass zero-phase FIR filter with length 6601 samples). The ECG artifact will be removed using independent component analysis (ICA) and a 20 Hz high-pass filtered (one-pass zero-phase FIR filter with a length of 661 samples) will be applied. Data will be epoched from movement onset to stop command. Trials for which EMG activity in any channel is above 3 standard deviations of the mean in a condition and channel-specific manner will be rejected. For this, the mean EMG activity for each channel and condition will be computed. If for a given trial, EMG activity exceeds the threshold specific to that condition and channel for a minimum of 3 seconds of data, the trial will be rejected. In order to ensure no overt movement during the motor imagery conditions, on top of the described criterion, we will reject a motor imagery trial if any channel exhibits EMG activity surpassing the average activity observed for that channel during the corresponding motor condition (i.e. EMG activity during 'open and close your hand' conditions will be used to assess overt movement during 'Imagine opening and closing your hand' conditions), for a duration of at least 1 s of data. The data will be rectified using the Hilbert transform and demodulated to remove slow fluctuations due to movement ([Boonstra et al., 2009](#)). For each subject and trial, power spectral density will be estimated using Welch's periodogram method with a hamming window of 750 ms and an overlap of 550 ms with an fft length of 3 s. Before computing complex value spectral coherence, the autospectra will be smoothed ([Mehrkanoon et al., 2013](#)). Complex value spectral coherence will be obtained for each muscle pair and averaged across trials within each condition for group analysis. The absolute value of the resulting coherence will be squared yielding a magnitude squared coherence (MSC)

value per subject, muscle, and condition. In order to increase the number of trials for subject-level classification, each 15 s epoch will be divided into 3 s epochs, yielding 5 sub-epochs per trial, and MSC will be obtained for each one.

2.4.3 EEG, corticomuscular coherence and cortical coherence

EEG signals will be bandpass filtered 0.5-40 Hz (one-pass zero-phase FIR filter with length 6601 samples). Electrodes over facial muscles will be discarded. ICA will be applied to remove cardiac and eye movement artifacts. Bad channels will be interpolated using Autoreject ([Jas et al., 2017](#)) and data will be referenced to the average of the electrodes before epoching from the onset of movement to the stop command (0:15 s). The high-density EEG will be reduced to 64 channels by interpolating neighboring channels. The decision to reduce EEG data to fewer sensors is motivated by trying to reduce the number of features fed to the classifiers (see below), this optimizes computational time while increasing the observations and features ratio. Following [Roeder et al., 2024](#), a bipolar montage will be used to measure left (LSM: C3-F3 electrodes) and right (RSM: C4-F4 electrodes) sensorimotor activity. CMC will be computed between C4-F4 and each muscle, and between C3-F3 and each muscle, following the same steps as to obtain intermuscular coherence. Cortical coherence (CC) will be assessed between LSM and RSM using imaginary coherence to avoid pseudo-connectivity due to volume conduction ([Nolte et al., 2004](#)). For subject-level analyses, the same procedure as for EMG data will be carried yielding 5 sub-epochs per trial.

2.4.4 Brain-muscle networks

Group-level brain-muscle networks (BMN) will be obtained by decomposing the coherence spectra of the 36 pairs of channels (2 EEG and 7 EMG channels), conditions, and subjects using non-negative matrix factorization (NMF). Reconstruction quality is assessed by increasing the number of components and evaluating the percentage of Frobenius norm of the coherence spectra accumulated by the components. The final number of components corresponds to the number for which a subsequent increase in one component results in less than a 2% increase in the variance accounted for. The decomposition will result in two matrices, one corresponding to frequency components and one to the weights for the different components. The weights matrix can be represented as frequency-specific networks for each condition and subject where the strength

of connectivity for each pair of channels gives the edges of each network. In order to obtain subject-level brain-muscle networks NMF will be applied to the sub-epochs coherence spectra and the above procedure will be carried out to select the number of components (Figure 2.2). The visualization and analysis of the resulting networks will be conducted with NetworkX (Hagberg et al., 2008).

2.4.5 Event-related synchronization/desynchronization

To obtain ERD/S, EEG will be 0.5 Hz high-pass filtered (one-pass zero-phase FIR filter with a length of 1651 samples) and current source density transformation based on spherical spline surface Laplacian (Perrin et al., 1989) will be applied to reduce volume conduction and to obtain less correlated sensors (Kayser et al., 2015). In order to determine subject-specific frequency bands we will use FOOOF (Donoghue et al., 2020) to parametrize the power spectrum of each subject across all trials and obtain the peak frequencies for mu-alpha and mu-beta bands. The bands will be defined as a frequency window of 3 Hz centered at the peak frequencies. Data will be epoched from -3 s before movement to 3 s after stop command (-3 to 18 s), and the epoch from 0 to 18 s will be divided into equally spaced 3 s sub-epochs. Sub-epochs will be band-passed according to the subject-specific frequency bands, Hilbert transformed and the absolute value of the complex signal will be obtained for each sub-epoch. Baseline correction will be applied by subtracting the mean activity of the baseline period (-0.5 to 0 s) from each sub-epoch and dividing by the same value. Finally, ERD/S for each sub-epoch will be computed as the average power from 0 to 3 s for each frequency band.

2.4.6 Heart activity

Raw data for the difference between the channel placed on the left and right collarbone will be processed with Neurokit2 0.2.0 toolbox (Makowski et al., 2021). Data will be filtered with a 0.5 Hz high-pass Butterworth filter (order = 5) and a 50Hz Butterworth notch filter (order = 2). R peaks in each 15 s epoch will be detected using the method 'neurokit'. The HR is computed as the inverse of the average difference between consecutive R peaks (RR intervals). HRV is measured as the mean root square of successive differences between RR intervals. For each participant, a value is considered an outlier and discarded if it is below or above 3 standard deviations.

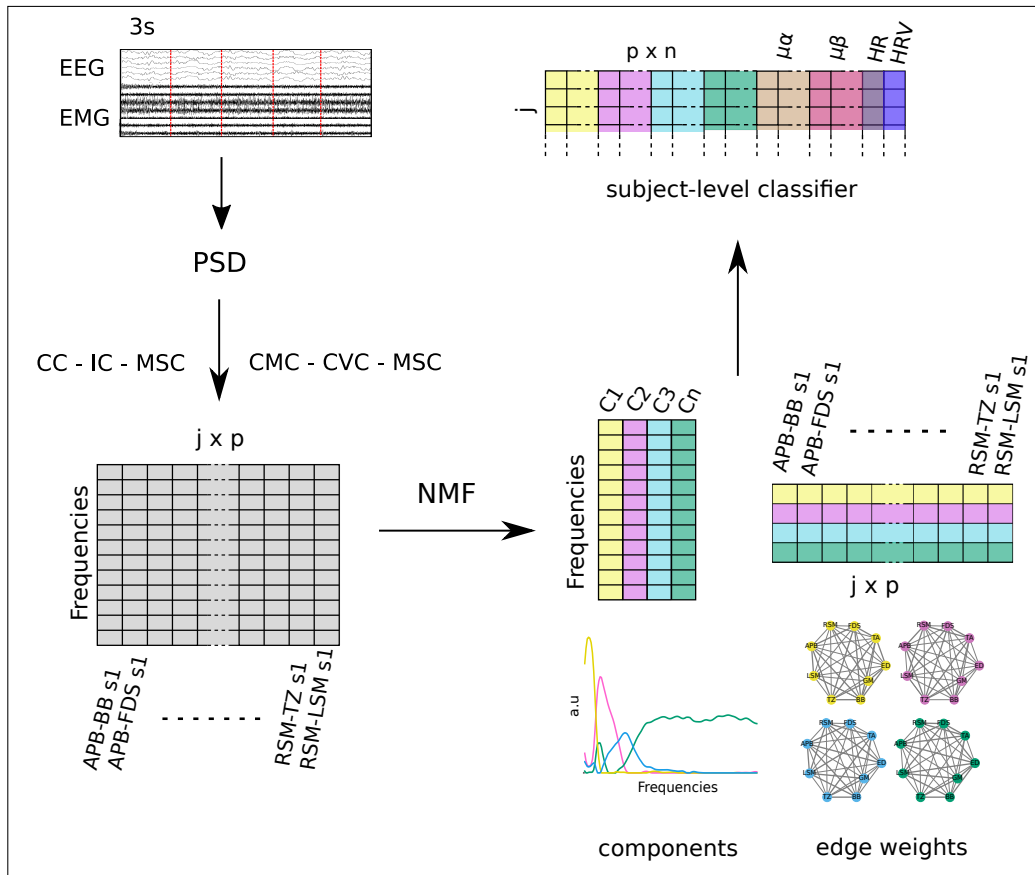


Figure 2.2: Each 15 s trial is subdivided into 3 s sub-epochs. Power spectral density is obtained for each sub-epoch. For corticomuscular coherence and muscle coherence, complex value spectral coherence (CVC) is computed for each EMG-EMG and EEG-EMG pair (p). The absolute value of the resulting coherence is squared yielding a magnitude squared coherence (MSC) value per sub-epoch and channel pair. In order to avoid spurious connectivity for cortical coherence, imaginary coherence (IC) is computed for the EEG channel pair (RSM - LSM). The resulting coherence matrix has dimensions sub-epochs \times number of channel pairs ($j \times p$). Non-negative matrix factorization is used to decompose the coherence matrix. The decomposition results in two matrices, one corresponding to frequency components and one to the weights for the different components. The frequency components matrix is a unique matrix whose final dimensions depend on the reconstruction quality of the original matrix evaluated with the Frobenius norm (n). The weights matrix can be represented as frequency-specific networks for each condition and component where the strength of connectivity for each pair of channels gives the edges of each network (in the figure the networks would correspond to the connectivity for each frequency component for a given condition). For classification purposes, a feature matrix is constructed such that for each sub-epoch the edge weights for each channel pair and frequency component are combined with the heart rate, heart rate variability during the 15 s epoch, and the power for the mu-alpha and mu-beta bands for the 64 channels during the sub-epoch. For group-level networks, the coherence values for each subject are averaged across the same condition trials before computing MSC, and therefore the resulting matrix has dimensions number of subjects \times channel pairs \times conditions, and the NMF factorization results in one network per subject, condition, and component. APB: abductor pollicis brevis, FDS: flexor digitorum superficialis, TZ: trapezius, RSM: right sensorimotor bipolar channel, LSM: left sensorimotor bipolar channel.

2.4.7 Statistical analysis

A1) Edge weights node normalization is carried out for each subject and condition by dividing all networks' edge weights by the maximum edge weight across all the frequency networks. The strength of the nodes in each network and condition is computed by summing the weights of the connecting edges. The strength of each node in each network is assessed for the following contrasts: RS and motor imagery (MI) of hand movement, RS and MI of foot movement, and RS and MI of simultaneous hand and foot movement. Therefore, 27 tests are carried out (3 comparisons for each of the 7 EMG and 2 EEG channels). Two-tailed t-tests are used to evaluate each contrast. FDR correction was applied to the resulting p-values.

A2) Cardiac activity modulations by motor imagery were evaluated by fitting linear mixed-effects models to heart rate and heart rate variability with condition (motor imagery - resting state) as a fixed factor and subject as a random effect using R ([Team RStudio, 2022](#)). The normality of the residuals was tested with a Shapiro-Wilk test, and transformations on the data were applied for normality violations.

A3) Cluster-based permutation analyses were used to assess the group effect of motor imagery on mu-alpha and mu-beta bands. The mean power in the canonical mu-alpha and mu-beta bands were obtained for each participant during the resting state, motor imagery, and motor execution conditions. Differences between conditions are analyzed as follows: i) subject average for motor imagery trials is subtracted from the subject average for resting state trials (or from the motor execution trials), ii) a one-sample t-test is performed on every channel, iii) t values that exceed a dependent samples t-test threshold corresponding to an alpha level (p-value) of 0.025 (two-tailed, number of observations = number of subjects) are clustered according to spatial proximity. The adjacency matrix for a Biosemi 64-channel layout as defined in Fieldtrip is used. iv) t values for each electrode within each cluster are summed in order to obtain a summed t statistic per cluster (t-sum), v) 2000 permutations of the data are computed, and for each permutation, the cluster with the biggest-summed t statistic is kept in order to obtain a null hypothesis distribution, vi) the proportion of clusters from the null hypothesis with more extreme values than the cluster obtained from the observed data yields the p-value for a given cluster. We considered the critical cluster level here to be 0.025.

A4) We conducted Shapiro-Wilk tests to assess the normality of the the kinesthetic and visual imagery scores across subjects, as well as the subject average power for mu-alpha and mu-beta bands. Pearson's correlations were implemented to correlate subjects' scores to power.

A5) Subject-level classifiers were constructed to distinguish between imagery and resting state conditions using Scikit-learn v1.0.2 (Pedregosa et al., 2011). The observations correspond to the sub-epochs for the imagery trials (360) and the sub-epochs for the resting state trials (360). The features are the weights for each component for each channel pair obtained from the spectral coherence decomposition (brain-muscle networks, BMN), the average heart rate and heart rate variability (heart activity features), and the power for the mu-alpha and mu-beta band during the sub-epoch. Random forest were implemented using a stratified group 10-fold cross-validation procedure, where on each fold all sub-epochs from the same trial were grouped together in the train or test data set. The mean accuracy across folds was computed. This procedure is repeated 100 times yielding 100 accuracies per classifier. To test the significance of the classifiers' accuracies we followed standard practice (Combrisson et al., 2015) by evaluating the classifier performance using a non-parametric statistical approach. The labels for the observations are randomly permuted 1000 times and for each permutation, the classifier accuracy is obtained. We compare the mean accuracy of our original data against the empirical null distribution of classification accuracies. The proportion of null classification accuracies that are greater than the AUC of the original data yields our p-values. We used recursive feature elimination to evaluate the impact of the brain-muscle features on the classifiers' accuracies. The level of significance is established at $\alpha = 0.05$ for all the proposed statistical tests.

2.5 Number of participants and power analysis

The main objective of our study is to detect covert command-following at the individual level by combining multimodal information. In healthy participants, motor execution is not impaired, and moving elicits overt behavior easily detected with EEG and EMG. In this study we consider healthy participants imagining movement as a model of unresponsive patients trying to execute a movement. Motor imagery measured with EEG shows intersubject variability in healthy participants, indeed, brain-computer interface

(BCI) literature estimates that 10-30% of people are not able to willfully modify their brain activity by attempting motor imagery (Allison et al., 2010; Dickhaus et al., 2009; Guger et al., 2003). This estimate is likely influenced by differences in individual abilities, training, task, and analysis pipelines. The sampling size of this study has to guarantee that we find participants who are able to perform motor imagery to test the proposed brain-muscle network approach. To address this, we developed a motor imagery classification pipeline based on common spatial filters and linear discriminant analysis (LDA), a usual approach in brain-computer interface (Arpaia et al., 2022), that will be used to determine whether a participant is able to elicit motor imagery. In order to test this pipeline and estimate its power for classifying participants, we used a public dataset (Cho et al., 2017) in which, in a single session and without previous training, 52 subjects performed 100 trials of imagery of the left hand and 100 trials of imagery of the right hand. The data consisted of segments of -2:5 s time-locked to the imagery cue. A 0.5 Hz high-pass filter (one-pass zero-phase FIR filter with length 3381 samples) was applied to remove slow drifts, followed by a 7-40 Hz band-pass filter (one-pass zero-phase FIR filter with length 845 samples). The epochs were cropped from 0.5-2.5 s and as features, we used 4 spatial filters of the common spatial pattern (CSP) using MNE (Gramfort, 2013). A LDA classifier was implemented for each participant's data using a stratified 10-fold cross-validation procedure and the mean accuracy, measured as the area under the curve (AUC) across folds was obtained. This procedure was repeated 50 times yielding 50 accuracies per classifier. To test the significance of the classifiers' accuracies we used a non-parametric approach. The labels for the observations were randomly permuted 500 times and for each permutation, the classification was recomputed. The proportion of null classification accuracies that have higher accuracy than the mean AUC for the original data resulted in the p-value. The level of significance was established at $\alpha = 0.05$. 40 participants were classified above chance with an overall AUC of 0.72 ± 0.16 (Figure 2.3), which is consistent with the population estimates. Given this result in order to obtain at least 20 participants showing motor imagery as detected by our classifier we would have to test at least 26 participants. Importantly, this estimated sample size corresponds to distinguishing different types of imagery, specifically right from left-hand imagery, which has proven difficult as some subjects show poor cortical lateralization (Rimbert et al., 2017). In our analysis, we will try to distinguish trials in which a participant is carrying motor imagery from resting

state trials; our effect size is expected to be bigger than the one associated with the analyzed dataset, so we argue that the sample size is a conservative estimate of the one needed for this study. We propose an initial sample size of 35 participants, in the event that we reach a subject-level classification above chance using CSP information for 20 participants, data collection will be stopped before completing the proposed sample size.

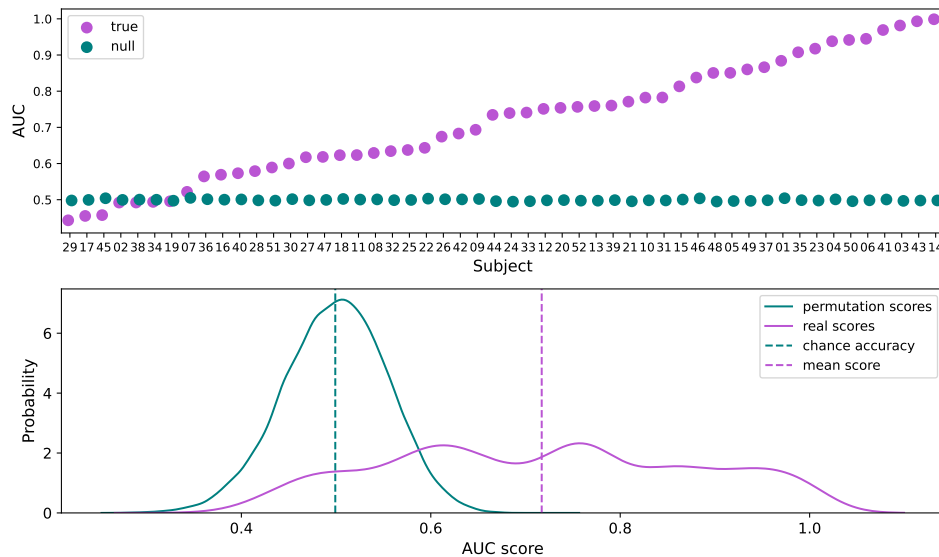


Figure 2.3: Motor imagery of left-hand versus right-hand classification performance across subjects. Top. Mean area under the curve score for each participant (purple). Mean area under the curve for 500 classification accuracies after randomly permutating the trial labels (green). Bottom. Kernel density estimation for the null distribution of AUCs (green) and for the original data (purple) across subjects.

2.5.1 Participants and data replacement

The sample will consist of right-handed healthy individuals without neurophysiological or musculoskeletal disorders between the ages of 18-45 years old. They will be informed about the experimental protocol and objectives, and written consent will be provided. We will replace a given participant if they do not complete any part of the study.

2.6 Predicted outcomes

We expect to find brain responses consistent with motor imagery for at least half of the participants tested, this would be reflected in the number of participants for which the motor imagery classifier is able to distinguish imagery and resting trials. Trials during motor imagery should elicit an increase in HR and HRV in comparison to resting state,

the result of the linear mixed-effects models will provide information on this.

Although we expect a greater correlation between a participant's score in the kinesthetic subscale of the MIQ-RS with the power for mu bands during motor imagery than for the visual subscale, the evidence regarding the predictive value of MIQ-RS on participants' motor imagery abilities is not robust (Rimbert et al., 2019).

At the group level, we expect the motor imagery conditions to elicit an increase in the strength of nodes associated with the specific muscles involved in the imagined movement in comparison to resting state. During imagined movement of the hand, we expect the nodes corresponding to hand (Abductor pollicis brevis) and arm (flexor digitorum superficialis, extensor digitorum, biceps brachii) muscles to show an increase in strength, compared to resting state condition. During imagined movement of the foot, we expect the nodes gastrocnemius mediale and tibialis anterior to exhibit an increase in node strength, compared to the resting state condition.

Motor imagery should elicit an event-related desynchronization for the mu-alpha and mu-beta bands in comparison to resting state, that is, a reduction in power should be observed during the mental representation of movement.

For participants for which motor imagery was detected using the CSP-based classifier, we expect to distinguish resting state from motor imagery with the classifier described in A5. In particular, we expect that the brain-muscle network information results in an improvement in classification accuracy compared to classifiers based only on power modulations.

2.7 Results

A total of 38 participants took part in the study. During one session EEG collection could not be carried out due to a technical issue and the participant was removed from the study. Two participants did not manage to finish the task and were also discarded. The final sample consisted of 35 participants (21 female, age = 25.6 ± 6.0).

2.7.1 Initial motor imagery classification

Running the LDA classifier based on common spatial patterns to discriminate between trials of imagery and trials of rest yielded low AUC values in comparison to the open data set used to estimate our sample size. 15 participants out of 35 were classified

above chance (for one participant the classifier did not converge), with an overall AUC of 0.54 ± 0.11 (Figure 2.4). We selected these 15 participants for the subsequent analysis.

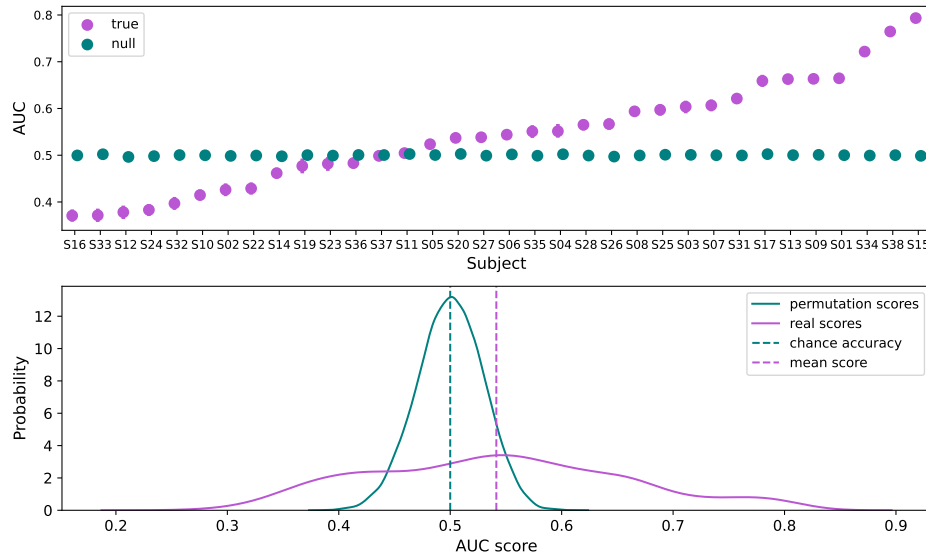


Figure 2.4: Motor imagery versus resting state performance across subjects for the LDA classifier based on CSP. Top. Mean area under the curve score for each participant (purple). Mean area under the curve for 500 classification accuracies after randomly permutating the trial labels (green). Bottom. Kernel density estimation for the null distribution of AUCs (green) and the original data (purple) across subjects.

2.7.2 Brain-muscle networks are not affected by motor imagery

Functional brain-muscle networks were constructed by applying NMF to the magnitude squared coherence computed for pairs of channels during the resting state and motor imagery conditions. Reconstruction quality assessed with the Frobenius norm showed that 4 components accounted for 89.98% of the variance of the MSC matrix, and computing the decomposition for more components resulted in improvements smaller than the 2% established as threshold (3 components: 84.33%, 5 components: 91.34%). The decomposition yielded four separate frequency components (component 1, 0 to 5 Hz; component 2, 5 to 15 Hz; component 3, 15 to 30 Hz; component 4, 30 to 40 Hz; Figure 2.5), which can be considered as four frequency-specific networks. For each network and motor imagery condition, the node strength was contrasted to the node strength during resting state. No significant differences were obtained after FDR correction (Figure 2.6).

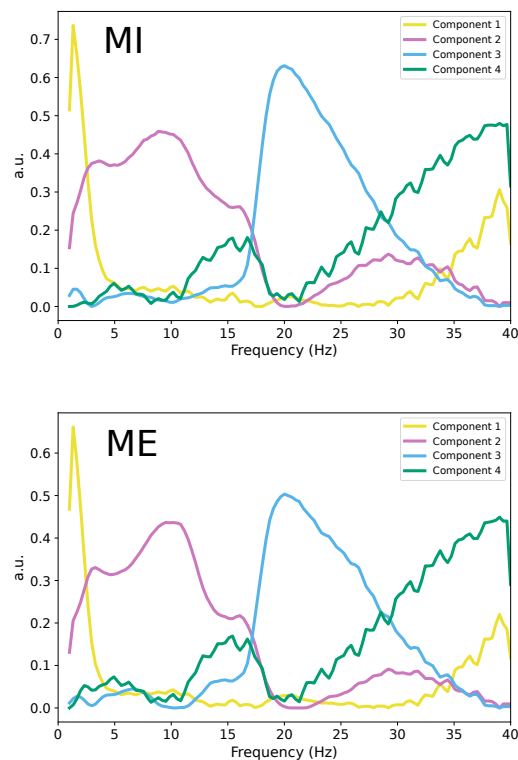


Figure 2.5: Frequency spectra of the four components obtained using NMF. Top. Components obtained from the MSC between electrodes for motor imagery (MI) and resting state trials. Bottom. Components obtained from the MSC between electrodes for motor execution (ME) and resting state trials.

In order to explore the functional brain-muscle networks during motor execution the same procedure was carried out but considering motor execution and resting state trials. The factorization in 4 networks resulted in an accounted variance of 88% (Figure 2.5). The network for component 1 associated to the coherence for lower frequencies showed a behavior that was consistent with a decrease in node strength for muscles involved in the different movement conditions. A decrease in node strength was observed for APB, LSM, and RSM during hand-moving trials, while during foot-moving trials node strength for TA was reduced. Finally, during simultaneous movement of hand and foot, node strength for APB, TA, RSM, and LSM was smaller than during resting state (p values <0.043). For the third frequency network (15 to 30Hz), simultaneous movement of hand and foot, as well as foot movement elicited a decrease in connectivity for TZ, GM, TA, and APB (p values <0.047). Hand movement showed a decrease in strength for nodes APB, TA, and TZ (p values <0.042). No significant differences were observed

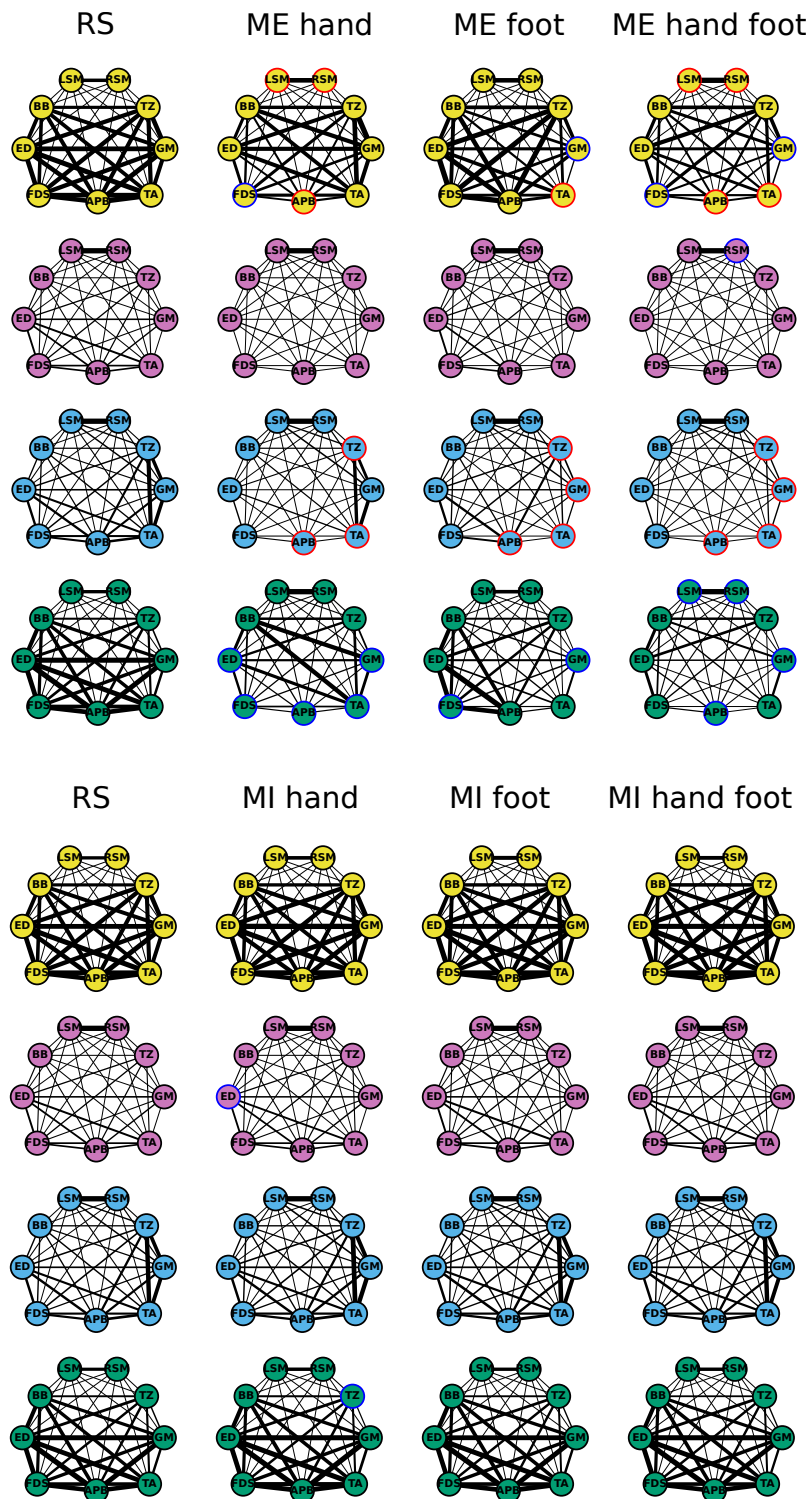


Figure 2.6: Functional brain-muscle networks. Top. Networks during motor execution (ME). Bottom. Networks during motor imagery (MI). Each node strength was contrasted to the strength of the same node during resting state (RS) (leftmost network). Red circles indicate significant differences after FDR correction, blue circles mark significant nodes before FDR correction, and black circles denote no difference to resting state node strength. The thickness of the edges corresponds to the strength of the connections between nodes.

for the networks for frequency components 2 and 4 (Figure 2.6).

2.7.3 Group analysis did not reveal differences in heart activity during motor imagery

Linear mixed models were implemented to test whether heart activity was different between motor imagery and resting state trials. Residuals for both heart rate and heart-rate variability models violated normality, and logarithmic and inverse data transformations did not improve this. The models evaluated on the original data showed that the experimental condition did not explain the variability observed in heart rate ($\beta = 0.01$, $p = 0.98$, $R^2 = 0$) and heart rate variability activity ($\beta = 4.22$, $p < 0.001$, $R^2 = 0$). Similar results were obtained for models on transformed data.

2.7.4 Motor imagery and motor execution produced modulations of the sensorimotor rhythms

Cluster permutation analysis yielded significant differences between motor imagery and resting state for the mu-beta band. A cluster comprised of 35 centro-parietal electrodes showed lower mu-power during motor imagery compared to resting state trials ($t_{sum} = -129$, $p = 0.005$, Figure 2.7A). In addition, motor execution showed increased power in the mu-beta band compared to motor imagery ($t_{sum} = 62$, $p = 0.0015$, Figure 2.7A) in parietal and occipital electrodes. Finally, power for the mu-alpha band was increased for motor execution in contrast to motor imagery in occipital electrodes ($t_{sum} = 67$, $p = 0.0015$, Figure 2.7A).

2.7.5 Kinesthetic motor imagery correlates with power modulations

The motor imagery scale showed an overall score of 73.13 ± 11.3 , with a lower score for kinesthetic motor imagery (30.8 ± 8.6) than for visual motor imagery (42.3 ± 4.7) (paired-samples t-test $t(14) = -5.5$, $p = 7.8e-5$). Normality tests showed that visual scores ($z = 0.74$, $p = 0.69$) and kinesthetic scores ($z = 5.5$, $p = 0.065$) were normally distributed. Average ERD/S values were obtained for each subject by averaging the values for the electrodes taking part in the cluster yielded by the cluster permutation analysis for the mu-beta band. The ERD/S values for the mu-beta band ($z = 5.6$, $p =$

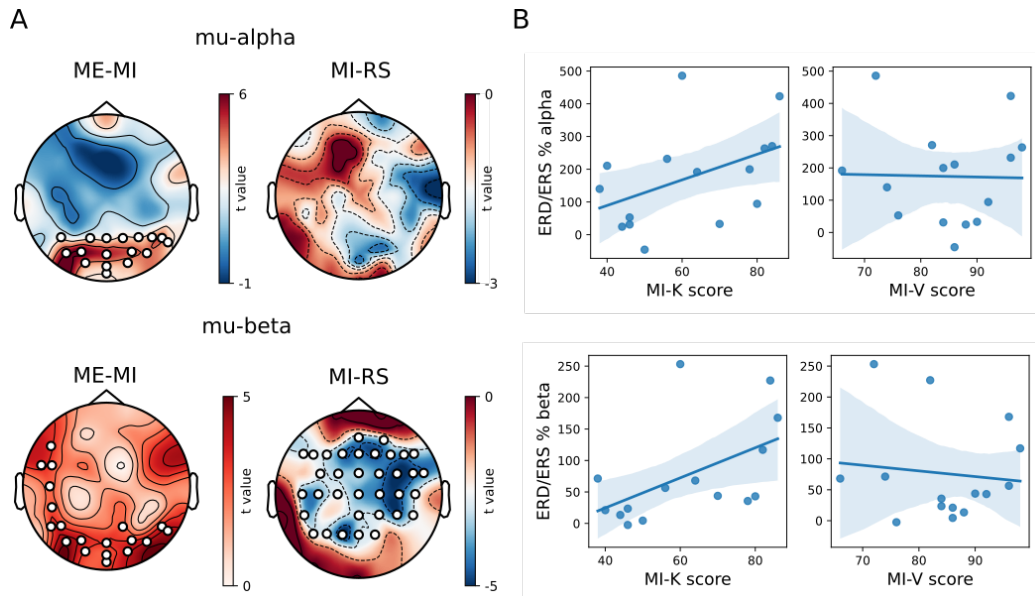


Figure 2.7: **A.** Cluster-based permutation analysis for the mu-alpha power (top) and the mu-beta power bands (bottom). Left: t-values for the contrast between motor execution (ME) and motor imagery (MI). Right: t-values for the contrast between motor imagery and resting state (RS). **B.** Top. Pearson correlations between kinesthetic motor imagery scores (MI-K) or visual imagery scores (MI-V), and the ERD/ERS for the mu-alpha power. Bottom. Correlation between motor imagery scores and the ERD/ERS for the mu-beta power.

0.060) and the mu-alpha band ($z = 1.31$, $p = 0.52$) were normally distributed. For the mu-beta band, a small correlation was found between the kinesthetic imagery scores and the ERD/S values ($r = 0.51$, $p = 0.048$). No correlation was found between the ERD/S and the visual imagery scores ($r = -0.11$, $p = 0.80$). For the mu-alpha power, no correlation was found with the kinesthetic motor imagery scores ($r = 0.45$, $p = 0.092$), nor the visual imagery scores ($r = -0.02$, $p = 0.93$), [Figure 2.7B](#)).

2.7.6 Cortical power and heart rate variability are markers of motor imagery

Subject-level random forest classifiers with decision trees as base estimators were implemented to distinguish between motor imagery and resting state trials. These classifiers were supplied with a set of features including the weights assigned to each channel pair by the NMF decomposition for the four frequency components (36 pairs of channels \times 4 components), heart rate (HR), and heart rate variability (HRV) for the trial, and the power of mu-alpha and mu-beta for the 64 channels (totaling 274 features). The full-feature classifiers successfully classified all participants with an overall AUC

of 0.63 ± 0.07 , no different from the AUCs obtained for the LDA-CSP classifier for the same 15 participants ($AUC = 0.64 \pm 0.07$, $t = -0.47$, $p = 0.648$). We then systematically removed groups of features (BMN, HR, HRV, mu-beta, and mu-alpha) to evaluate their specific impact on classification and compared their performance to the full-feature classifiers. Removing the BMN features showed a slight increase in classification performance, with 15 participants classified above chance ($AUC = 0.64 \pm 0.07$, paired t-test $t = -2.65$, $p = 0.019$). Removing heart rate did not affect the overall accuracy ($AUC = 0.63 \pm 0.07$, paired t-test $t = 1.85$, $p = 0.086$). However, excluding heart rate variability features led to a significant decrease in classification, with only 10 participants classified above chance ($AUC = 0.60 \pm 0.09$, paired t-test $t = 3.30$, $p = 0.005$). Similarly, excluding mu-alpha power resulted in a reduction in the number of participants classified without a significant change in the overall AUC (9 participants classified above chance, $AUC = 0.60 \pm 0.08$, $t = 2.10$, $p = 0.053$). Removal of mu-beta features did not affect the overall AUC, but one participant could not be classified above chance (14 participants classified, $AUC = 0.63 \pm 0.07$, $t = 0.11$, $p = 0.91$). Lastly, we implemented a classifier using only the BMN features to explore their potential to distinguish motor imagery from resting state trials. However, only one subject was classified using this approach ($AUC = 0.50 \pm 0.06$, $t = 7.34$, $p < 0.001$) (Figure 2.8).

2.8 Discussion

The aim of the present study was to evaluate the potential of a network approach to EMG and EEG recordings to detect covert command-following in healthy participants. Data from subjects that showed brain modulations consistent with motor imagery (MI) was further assessed by computing intermuscular coherence between muscles and scalp electrodes, EEG power for the mu bands was extracted, and heart activity was analyzed. Subject-level, as well as group analysis, were performed to evaluate the behavior of these variables during MI compared to resting state.

The task was performed by 35 healthy participants. Fewer than half of the individuals exhibited brain activity consistent with motor imagery as indicated by the CSP-based classifier accuracies. The relatively low accuracy in classification could stem from multiple factors. In typical BCI experiments, motor imagery is elicited on cue and measured

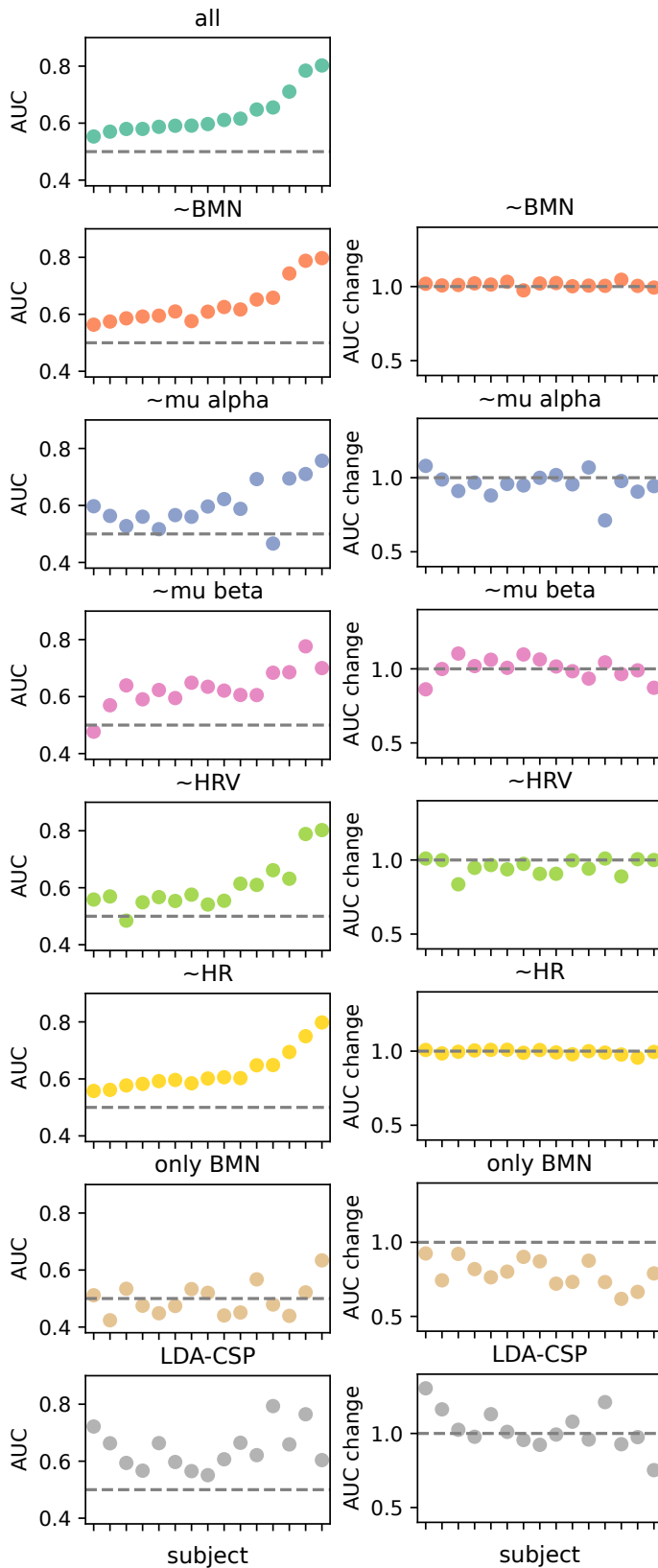


Figure 2.8: Subject-level classifiers based on brain-muscle networks, EEG power, and heart activity features. Left: average AUC across folds with 95% bootstrap confidence interval for each subject and classifier. Subjects are sorted considering the AUC for the full classifier. Right: Ratio between the mean AUC for the classifiers lacking groups of features (or the LDA-CSP) and the mean AUC for the full classifier. \sim BMN: without the brain-muscle networks features. \sim HR: without the heart rate, \sim HRV: without heart variability, \sim mu-alpha: without the mu-alpha power for the 64 channels, \sim mu-beta: without the mu-beta power for the 64 channels, only BMN: classifier fed with only the brain-muscle networks features, and LDA-CSP: LDA classifier based on common spatial patterns.

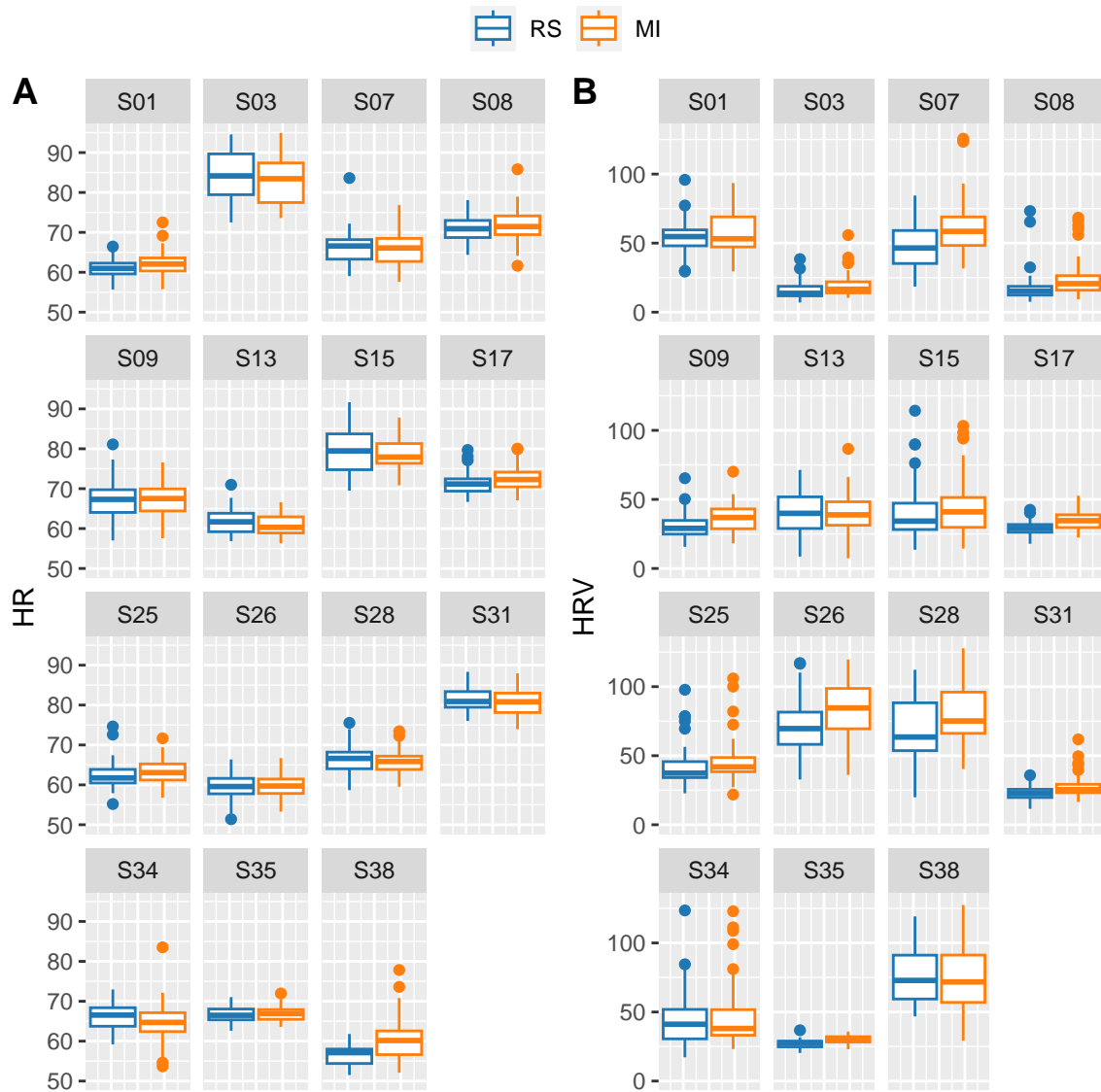


Figure 2.9: Subject-level heart activity during motor imagery (MI) and resting state (RS). **A.** Heart rate. **B.** Heart rate variability.

within the first seconds after the cue onset, as responses are higher closer to the initiation of the mental task (Fazli et al., 2012; Pfurtscheller, Scherer, Müller-Putz, & Lopes Da Silva, 2008). However, our study differed in that we assessed MI carried over extended periods during which participants repeatedly imagined the movements. The multiple initiations of motor imagery within a trial, coupled with the fact that the motor imagery trials consisted of different movements, likely introduced increased variability in our data resulting in a more challenging classification. Indeed, MI detection is sensitive to the time interval analyzed (An et al., 2014) and imagination of feet and hand movement have been shown to elicit different ERD/S cortical profiles (Grimann et al., 2009; Pfurtscheller et al., 2000). Furthermore, the extended duration of the task may have led to fatigue among participants, consequently impacting their performance as the task progressed. Although our task departs from the conventional motor imagery experiments, we argue that it represents a more ecological approach, particularly in light of its application to individuals with disorders of consciousness. The expectation that DoC patients can readily evoke motor imagery immediately after cue can be unrealistic, and allowing the individuals to engage and repeat the mental rehearsal of movement freely could help capture temporally variable responses. In addition, a task with a similar design has been successfully implemented to detect CMD in DoC patients (Claassen et al., 2019). Importantly, the classification of 15 participants was successful and provided us with a significant sample over which to test the hypothesis of our study.

Kinesthetic motor imagery elicited a decrease in the mu-beta band compared to resting state with a widespread distribution over central and parietal electrodes. Normally, MI in the mu-beta band elicits a contralateral ERD during imagined movement initiation (Pfurtscheller et al., 1997; 2001), nevertheless, modulations have also been observed in central (Neuper et al., 2005) and ipsilateral regions (Porro et al., 2000), especially for MI of the feet (Grimann et al., 2009). Although no differences were obtained for the mu-alpha band at the group level, the subject-level analysis showed the relevance of the mu-alpha power to MI, as excluding this information hindered the classification for more than one-third of the participants. Importantly, in this analysis, the mu-alpha central frequency was determined individually for each participant, which probably enabled better results. One of the hypotheses of our work was that ERD/S in the mu-alpha and mu-beta bands would correlate with the subjective perception of a participant's motor imagery capabilities as measured with the MIQ-RS. Consistent with previous research

([Marchesotti et al., 2016](#)), we found a small correlation between the mu-beta power and the scores for the kinesthetic items of the scale. This further supports the notion that engaging in kinesthetic motor imagery elicits a cortical profile more consistent with motor execution than visual motor imagery ([Guillot et al., 2009](#)). MI and motor execution are believed to activate partially overlapping areas, with a weaker activation during MI. fMRI and PET studies consistently show an activation of the supplementary motor area during MI and motor execution ([Decety et al., 1994](#); [Deiber et al., 1998](#); [Fernández-Espejo et al., 2015](#); [Lotze et al., 1999](#); [Naito et al., 2002](#); [Porro et al., 1996](#); [Roland et al., 1980](#); [Roth et al., 1996](#)), and several parietal areas are commonly activated as well ([Bonda et al., 1995](#); [Deiber et al., 1998](#); [Meister et al., 2004](#); [Nair et al., 2003](#)), with a controversial involvement of the primary motor cortex ([Hétu et al., 2013](#); [Munzert et al., 2009](#)). In our study, ME and MI did not show differences in central regions but an increase in the mu-beta band in parietal electrodes was obtained, suggesting a more robust ERS during actual movement. In addition, occipital power was increased during motor execution for both mu power bands, which could be related to top-down inhibition of cortical areas irrelevant to the task ([Klimesch, 2012](#)), which has been reported for the mu-alpha band during repetitive movements ([Gerloff, 1998](#)). In addition, greater activation of the occipitotemporal cortex has been observed during motor execution compared to motor imagery following a topographic representation of bodily parts ([Orlov et al., 2010](#)).

The main hypothesis of our work was that the functional network configuration during motor imagery would be different from the resting state networks and that muscles activated during a specific motor imagery condition would be consistent with the muscles that are activated when the same movement is actually executed. Unfortunately, no differences were found in node strength for any of the muscles and motor imagery conditions. Moreover, classifiers built on only these features did not prove useful in distinguishing motor imagery from resting state trials, and excluding the brain-muscle network features from the subject-level classifiers yielded overall better performances. Overall, motor imagery did not elicit significant changes in the brain-muscle network configurations. Evidence of muscle activation during motor imagery is far from consistent, and it remains to be explained whether the contradictory results are related to intersubject variability ([Dickstein et al., 2005](#); [Li et al., 2004](#)), or methodological differences such as signal processing, electrode placement, and task demands ([Guillot](#)

et al., 2010). To our knowledge, no other studies have evaluated corticomuscular and intermuscular coherence during motor imagery using NMF at a group or subject level. Our network approach may not have been sensitive enough to detect changes in coherence during the mental rehearsal of movement. Future exploratory analyses could compare changes in EMG during motor imagery to the resting state using other methods, such as assessing changes in the mean and median values of the power spectra for each muscle (Lebon et al., 2008; Thongpanja et al., 2013). During motor execution decreases in corticomuscular coherence in low frequencies (<5 Hz) between the sensorimotor cortices and the different muscles were observed as a reduction in node strength. This aligns with the findings in Roeder et al., 2024 for the gait cycle using a similar methodological approach. Corticomuscular coherence for low frequencies was increased during the static phases of gait and reduced during movement. In our study, the reduction was only observed for motor conditions involving hand movement, possibly due to the hand's broader cortical representation (Graimann et al., 2009; Hlustik, 2001; Lotze et al., 2000). Additionally, we observed decreases in node strength for muscles involved in each movement for the 15-30 Hz component. Intermuscular coherence for this frequency band is typically decreased during the dynamic phase of movements (Kilner et al., 1999), this is consistent with evidence on peripheral and cortical rhythms showing a reduction in coupling between muscle and cortical activity during movement execution (Kilner et al., 1999; Kilner et al., 2003; Salenius et al., 2003).

Supporting our second hypothesis we show that bodily responses are informative of MI. Although we failed to model the effect of motor imagery on HR and HRV on grouped data, heart rate variability was modulated in a subject-specific manner during the mental rehearsal of movement, as these features were particularly relevant to distinguish MI from RS at the subject level. HR acceleration has been shown during the first seconds of motor imagery initiation (Pfurtscheller et al., 2013), and increases in heart rate have been reported during MI (Papadelis et al., 2007), particularly when imagined motor activity is perceived as effortful (Decety et al., 1993; Decety et al., 1991; Oishi et al., 2000). It has been posited that the brain constructs internal models of the environment as well as of our body and can access these models not only via action but also during mental tasks (Grush, 2004). In our study, the direction of the effect of motor imagery on HRV was variable across subjects (Figure 2.9). This could be linked to the individual mental effort elicited by the task (Luft et al., 2009), and is possible that different

patterns of sympathetic and parasympathetic control may be underlying the observed profiles. This intersubject variability in heart response could potentially explain previous findings where no discernible group differences were detected (Mulder et al., 2005). Finally, while the performance metrics of both the LDA-CSP-based classifier and the novel classifier proposed in this study showed no significant differences, subject-level variations in the AUC were observed. Notably, certain participants demonstrated enhanced classification efficacy with one classifier over the other (Figure 2.9). Hence, future investigations should focus on elucidating how to optimally combine the distinct information captured by the different approaches, improving overall classification accuracy and reliability.

2.8.1 Limitations

Our work has methodological limitations that should be taken into consideration for future studies. Firstly, participants imagined movement freely during the 15 s of each trial, therefore the onset and offset of each instantiation were undetermined and the changes in power and coherence observed at the group and subject level are the result of the averaged activities in that time span. Together with the fact that simultaneous motor imagery conditions were jointly analyzed probably impacted our results, limiting the classification of motor imagery and the interpretation of the topographies for the mu power effects.

2.8.2 Conclusions

Overall, while brain-muscle functional networks were not modulated by motor imagery of hand and foot movements, heart activity and cortical power were crucial to detect when a participant was mentally rehearsing a movement. Our work highlights the importance of combining EEG and peripheral measurements to detect command-following, which could be important for improving the detection of covert responses consistent with volition in unresponsive patients.

Chapter 3

Predicting Attentional Focus:
Heartbeat-Evoked Responses and Brain
Dynamics During Interoceptive and
Exteroceptive Processing

Predicting Attentional Focus: Heartbeat-Evoked Responses and Brain Dynamics During Interoceptive and Exteroceptive Processing

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3.1 Abstract

Attention shapes our consciousness content and perception by increasing the probability of becoming aware and, or, better encode a selection of the incoming inner or outer sensory world. Engaging interoceptive and exteroceptive attention should elicit distinctive neural responses to visceral and external stimuli and could be useful to de-

tect covert command-following in unresponsive patients. We designed a task to engage healthy participants attention towards their heartbeats or auditory stimuli and investigated whether brain dynamics and the heartbeat-evoked potential (HEP) distinguished covert interoceptive-exteroceptive attention. Exteroceptive attention yielded an overall flattening of the PSD, whereas during interoception there was a decrease in complexity, an increase in frontal connectivity and theta oscillations, and a modulation of the HEP. Subject-level classifiers based on HEP features classified the attentional state of 17/20 participants. Kolmogorov complexity, permutation entropy, and weighted symbolic mutual information showed comparable accuracy in classifying covert attention and exhibited a synergic behavior with the HEP features. PSD features demonstrated exceptional performance (20/20). As a proof of concept, command-following was assessed in 5 brain-injured patients with a modified version of the task. Two patients, one with Unresponsive Wakefulness Syndrome/Vegetative State and another with locked-in syndrome, showed attention-driven changes in the HEP. These changes, along with the brain markers explored, suggested they were following task instructions. Our findings underscore the importance of attentional mechanisms in shaping interoceptive and exteroceptive sensory processing and expand the framework of heart-brain interactions employed for diagnostic purposes in patients with disorders of consciousness.

3.2 Introduction

The brain continuously monitors the bodily and environmental signals, and the interplay between interoception and exteroception determines whether a change in state comes from within or from outside, triggering and shaping appropriate allostatic and behavioral responses (Ceunen et al., 2016; Critchley et al., 2013; Petzschner et al., 2021). Although visceral signals are typically diffuse and not accessible to our conscious experience, interoception is considered to have a decisive role in perception, homeostatic responses, and motivational behaviors (Craig, 2002; Joshi et al., 2021; Khalsa et al., 2018; Quadt et al., 2018). Recent research has demonstrated that bodily rhythms contribute to general brain dynamics impacting the processing of external information (Azzalini et al., 2019; Criscuolo et al., 2022; Draguhn et al., 2022). Notably, target detection of visual (Marshall et al., 2022; Ren et al., 2022; Salomon et al., 2016), somatosensory (Al et al., 2020; Al et al., 2021), and auditory (Edwards et al., 2007)

stimuli is sensitive to the cardiac cycle phase. Conversely, external information can directly affect bodily signals as shown by modulations of the interbeat interval in anticipation of sensory stimuli (Jennings et al., 2009) and after informative feedback error (Crone et al., 2003; Skora, Livermore, & Roelofs, 2022), as well as following violations of statistical regularities (Raimondo et al., 2017). Hence, external and internal signal processing are intertwined and are sensitive to the state of the body and the state of the brain.

3.2.1 Interoceptive attention

Attention has been described as a general mechanism that increases the detection of a desired signal while suppressing the response to irrelevant stimuli (Harris et al., 2011; Sarter et al., 2001). The modulatory effect of attention on sensory processing has been consistently shown for top-down attention on sound (Hall et al., 2000; Hillyard et al., 1973; Jäncke et al., 1999), touch (Johansen-Berg et al., 2000), vision (Corbetta et al., 1991; Kanwisher et al., 2000), olfaction (Singh et al., 2019), and taste (Q. Luo et al., 2013). Crucially, visceral information can not only be passively filtered by the brain but attention can be directed toward bodily signals in a process known as interoceptive attention (Joshi et al., 2021) impacting its cortical representation, which has been evidenced during interoceptive attention to the respiratory cycle (Farb et al., 2013), and to the heartbeat (Petzschner et al., 2021).

3.2.2 The heartbeat-evoked potential

The heart has been the preferred candidate to assess the effects of interoceptive attention at the individual level. The heartbeat is triggered by a dynamical pacemaker that is modulated by efferent brain pathways and inform the brain by ascendant pathways (Crisuolo et al., 2022; Shaffer et al., 2014), of which subjects are normally unaware. Brain response to the heartbeats can be measured by averaging time-locked EEG activity to the ECG waveform R peak (Schandry et al., 1986). The resulting heartbeat-evoked potential HEP is considered to reflect the cortical processing of heart activity with and without awareness (Coll et al., 2021). The amplitude of the HEP is modulated by directing attention to the heart (Montoya et al., 1993; Petzschner et al., 2019; Schandry et al., 1986; Villena-González et al., 2017; Yuan et al., 2007) (see Coll et al., 2021 for a review), correlates with interoceptive awareness, measured as the accuracy in heartbeat

detection (Pollatos et al., 2004; Yuan et al., 2007), and decreases with sleep depth (Lechinger et al., 2015).

3.2.3 Brain dynamics during interoception and exteroception

Multiple processes related to top-down attention such as resource allocation, dynamical focus, inhibition, and selection have been associated with cortical oscillations and their entrainment (Calderone et al., 2014; Clayton et al., 2015; Henry et al., 2014; Klimesch, 2012; Schroeder et al., 2009). While brain dynamics of sensory processing have been extensively studied in the context of top-down attention for various exteroceptive modalities, investigations specifically comparing the electrophysiological response during interoceptive attention to the heart and exteroceptive attention, remain limited. Two studies based on visual and heartbeat detection tasks reported a trade-off between the HEP amplitude and visually evoked potentials during interoceptive attention, accompanied by an increase in parieto-occipital alpha power (Kritzman et al., 2022; Villena-González et al., 2017). In addition, using intracranial recordings García-Cordero et al., 2017 showed an increase in high-frequency oscillations (35-110 Hz) in interoception-related cortical regions during heartbeat tapping, and an increase in lower frequencies (1-35 Hz) when participants were tapping following an external rhythm. Together, these results suggest that time-locked and ongoing brain dynamics during interoceptive and exteroceptive attention can provide information on whether attention is oriented towards the internal or the external world.

3.2.4 Perceptual learning and attention

Casting attention to a specific sensory channel may also enhance the representation of a stimulus that individuals are not actively scanning or may even be unaware of. An interesting case is posited by the perceptual learning of statistical regularities in noise. In the auditory modality, it has been shown that cross-trial repetitions of identical white noise fragments can result in persistent memory formations as indexed by participant's detection accuracy (Agus et al., 2013; Agus et al., 2010), memory evoked potentials (MEPs) (Andrillon et al., 2015), and intertrial phase coherence (ITPC) in the delta band (Andrillon et al., 2015; H. Luo et al., 2013). Although the random white noise snippets used in the noise-memory paradigm have no semantic information or salient spectral features, their encoding is long-lasting (Agus et al., 2010), and brain signatures

of a mnemonic response are elicited even when the repetitions are unbeknownst to the participants (Andrillon et al., 2015; Ringer et al., 2023; Wang et al., 2019). Evidence on the effects of attention on implicit learning of these random acoustic patterns suggests that diverted attention hinders perceptual learning of the repetitions (Ringer et al., 2023). Accordingly, orienting attention towards bodily rhythms should result in a worse encoding of these inconspicuous regularities, reflecting interoceptive or exteroceptive attention despite stimuli being hidden and orthogonal to task demands.

3.2.5 Covert attention in unresponsive patients

As specified above, cortical and cardiac responses to external and internal stimuli are influenced by attention, and could therefore be used to detect covert attention. Developing measures of covert attention at the individual level can have major clinical implications as it could be applied to improve the detection of command-following responses (Claassen et al., 2019; Cruse et al., 2011; Owen et al., 2006) in non-communicative patients, such as patients who suffer from disorders of consciousness (DoC) (Giacino et al., 2014). Assessing the level of conscious awareness in these patients poses a significant challenge as expertise is required to differentiate between reflexes and volitional behavior (Fischer et al., 2015) and overt responses may be impaired (Giacino et al., 2009). Indeed, the distinction of unresponsive wakeful syndrome, also referred to as vegetative state (UWS/VS), characterized by arousal without purposeful responses, from the minimally conscious state (MCS), where signs of intentional behavior are occasionally present, leads to significant misdiagnosis rates (Schnakers et al., 2009). Moreover, some patients show a dissociation between behavior and brain response, referred to as cognitive motor dissociation (CMD) (Schiff, 2015), where residual consciousness can only be detected by functional neuroimaging methods. Finally, patients with Locked-In Syndrome (LIS), who are conscious but cannot show responses due to severe paralysis of almost all voluntary muscles except the eyes, may initially be misdiagnosed as UWS/VS (Laureys et al., 2005). In this clinical scenario, active paradigms that measure command-following but that do not demand motor or verbal responses are especially appropriate, and a positive result provides significant information on the level of consciousness (Bruno et al., 2010). Crucially, certain theories posit that the foundation of the sense of self hinges on defining the limits between oneself and the outside (Craig, 2002; Damasio, 2003; Park et al., 2019a; Park, Correia, et al., 2014). Therefore, prob-

ing the ability to recognize external and internal signals would give essential information on the level of self-awareness of these individuals.

3.2.6 This study

We propose a novel task based on sustained selective attention to compare the effects of interoceptive and exteroceptive attention on the encoding of heartbeats, and salient auditory targets, as well as their effect on the perceptual learning of inconspicuous repetitions of white noise. We hypothesized that increased attention towards bodily signals should elicit an increased brain response to internal rhythms and a decreased response to external stimuli, with an opposite pattern during exteroceptive attention. Directing attention to external stimuli or internal rhythms should be characterized by specific brain dynamics, and should influence the ability to learn regularities passively. Importantly, we elaborated this study with the underlying motivation of applying this paradigm to obtain insights about the nature of attentive processes, and therefore our main goal was to investigate the suitability of different cortical and bodily measurements as markers to predict attentional focus at the individual level. Finally, we probed the clinical potential of our task on a small cohort of brain-injured patients.

3.3 Materials and methods

3.3.1 Healthy participants

Twenty-two healthy volunteers participated in the task (13 females, average age, 30.63 ± 3.39). All participants reported having normal hearing and had not been exposed to the stimuli before the experiment. The study was approved by the ethics committee of the Facultad de Psicología, Universidad de la República (Uruguay). All participants gave informed consent and were not awarded any economic or academic retribution, according to the nationally established guidelines (Decree N379/008).

3.3.2 Experimental design

The task consisted of 64 trials of 31 s of continuous white noise with bursts of amplitude-modulated noise (AmN) at random times. At the beginning of each trial, participants were instructed binaurally to close their eyes and focus their attention on the white noise (32 trials) or their heartbeats (32 trials), and to count the number of AmN

or heartbeats, respectively. At the end of each trial, participants were audio-visually instructed to open their eyes and report the number using the keypad. Participants were not given any specific instruction on how to count their heartbeats but were exhorted to not measure their pulse. Half of the trials had embedded snippets of repeated white noise within and between trials (RepRN) that were not disclosed to participants (Figure 3.1A). At the beginning of the experiment, an 8-trial practice took place to ensure that participants understood the task. The practice stimuli were not repeated during the task and the noise repetitions were different from the ones used in the experiment. Stimuli presentation was coded in Psychopy 3.2.0 (Peirce, 2007), and audio files were played using the sound library PTB in Windows 7 together with the Focusrite Scarlett 4i4 USB audio interface. Stimuli were presented binaurally through Etymotic ER3C tubal insert earphones and sound amplitude was adjusted for each participant during practice trials. The trials were presented in a randomized fashion and the inter-trial interval was randomly varied between 5 - 10 s.

3.3.3 Stimuli construction

AmN was constructed by multiplying 0.5 s of the running white noise background with a 40 Hz sinusoid at a modulation depth of 30%. For each trial, between 0 and 4 AmN were randomly included. Half of the trials (32 trials) included a concatenation of 5 copies of a structured noise repetition composed of a 0.2-s-long white noise snippet (RepRN) seamlessly concatenated to 0.3-s-long fresh noises. Eight different RepRN were created using different random seeds, such that four appeared during trials in which participants had to focus their attention on the sound (RepRN-Sound) and the other four RepRN were only included in trials of heart-directed attention (RepRN-Heart). The RepRNs assigned to each attentional condition were counterbalanced across participants. In each trial, the four RepRN concatenations were repeated twice, resulting in eight RepRN structured repetitions (SRepRN) within each trial (Figure 3.1A).

3.3.4 Physiological recordings and preprocessing

EEG and ECG signals were recorded using a Biosemi Active-Two system. Sixty-four Ag-AgCl scalp electrodes were placed on a head cap following the location and label of the 10-20 system, flat-type channels were placed on the left and right mastoid bones, and on the left and right collarbones to record cardiac activity. The signals were

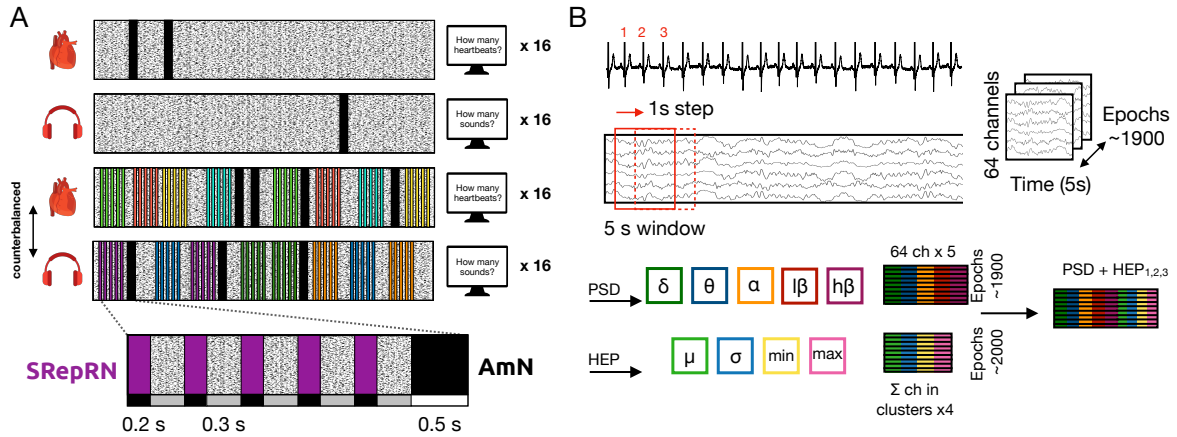


Figure 3.1: Experimental design and subject-level analysis. **A.** The task consisted of 64 trials of 31 s of continuous white noise with bursts of amplitude-modulated noise (AmN) at random times (represented with black lines over noise). On each trial, participants were instructed to focus their attention on the white noise (32 trials) or their heartbeats (32 trials) and were asked to report the counted number (AmN or heartbeats) at the end of each trial. Half of the trials had embedded snippets of repeated white noise within and between trials (SRepRN). Half of the participants were exposed to a set of four RepRN during the sound condition (represented with darker colored lines) and to another set of four RepRN during the heart attention condition (represented with lighter colored lines), this was counterbalanced across participants, such that each participant was exposed to a specific noise repetition in only one attentional condition. **B.** For the heartbeat-evoked potential (HEP) classifier, for each participant, a cluster permutation analysis was carried out to test for differences in HEP in the remaining participants. The channels and time points in the canonical clusters were used to extract the HEP features on the left-out subject data. For each electrode taking part in the clusters, the mean (μ), the standard deviation (std), the minimum (min), and the maximum (max) voltage in the time window spanning the cluster were extracted for each epoch of the subject withheld from the clustering analysis. For the PSD subject level classifier, each trial was segmented into 5 s sub-epochs with a sliding window of 1 s resulting in an overlap of 4 s between epochs. Power was obtained for each sub-epoch and averaged over the delta, theta, alpha, low-beta, and high-beta bands, resulting in five spectral features per channel. As an example of the combined classifiers, the PSD + HEP classifier combining both spectral and time-locked features is represented. The HEP features were derived from the average brain response to the heartbeats occurring within the 5-second sub-epoch, from which the spectral features were also extracted (i.e. heartbeats 1, 2, and 3 for the time window in red).

referenced online to the common mode sense (CMS, active electrode) and grounded to a passive electrode (Driven Right Leg, DRL). Data were digitized with a sample rate of 512 Hz with a fifth-order low-pass sinc filter with a -3 dB cutoff at 410Hz. As a backup, a second ECG recording was obtained following the same configuration but with a ground electrode positioned below the neck on the back of participants, and a respiration belt was used to record breathing. Both signals were recorded with a PowerLab 4/30 (ADInstruments) at a 400Hz sample rate. For two participants the backup ECG recording was used for the analyses. The analyses were conducted using MNE 1.0.3 ([Gramfort, 2013](#)).

3.3.5 EEG preprocessing

EEG data were processed according to the stimuli and the level of granularity of the analysis of interest, this resulted in 7 types of epochs: (1) For the heartbeat-evoked potential, data was filtered with a 30 Hz low-pass filter (one-pass zero-phase FIR filter with length 227 samples), epoched -0.5:0.8 s time-locked to the R peak of the ECG waveform, linearly detrended and referenced to the average of all channels. Epochs were not baseline corrected to avoid any contamination from the PQ component of the heartbeat. Heartbeats matching the moment of the AmN presentation were not included. (2) For the AmN, to remove alpha oscillations due to participants having their eyes closed, data was filtered with bandpass filter 0.2-7 Hz (one-pass zero-phase FIR filter with length 8449 samples), referenced to the average of all channels, epoched -0.1:0.85 s relative to sound onset, linearly detrended and baseline corrected 100 ms before sound onset. For the white noise repetitions, data was filtered following the preprocessing for the AmN but referenced to the average of the two mastoid electrodes. Subsequently, data underwent two types of epoching: (3) -0.4:3 s relative to sound onset thus comprising the 5 noise repetitions (SRepRN), and (4) from -0.05:0.5 s relative to each repeated noise (RepRN). For the ERP analysis of the SRepRN and for each RepRN, 0.2 s and 0.05 s to sound onset, were respectively used as a baseline. (5) In order to have a standard against which to compare the activity evoked by the noise repetitions, analog epochs to (3) and (4) were obtained from trials with plain white noise. This was carried out avoiding EEG data matching AmN presentation. (6) For the subject-level analyses, raw data was filtered with a bandpass filter 0.1 Hz - 30 Hz (one-pass zero-phase FIR filter with length 16897 samples), and referenced to

the average of all channels. The interval between 1:30 s of each 31 s trial (to avoid onset/offset sound artifacts) was segmented into 5 s epochs with an overlap of 4 s. This procedure resulted in a comparable number of trials for the classifiers using ongoing brain activity as features, and HEP-based classifiers, as well as the combination of different families of features (see below). (7) Finally, the 30 s epochs were segmented into 5 s sub-epochs without overlap for group-level analyses of complexity, connectivity, and power. For all epoch types, autoreject 0.3.1 ([Jas et al., 2017](#)) was used to reject bad epochs and interpolate noisy channels. For all the analyses and participants, the number of observations was equalized between conditions taking into consideration temporal proximity and thus avoiding data imbalance. The ECG artifact ([Dirlich et al., 1997](#)) could not be completely removed using independent component analysis. Therefore we decided to keep the potential ECG contributions in the EEG but carry out analyses to check for potential differences in cardiac activity that could be driving our results. We tested for changes in heart-rate and heart-rate variability as well as differences in the ECG waveform across conditions.

3.3.6 Subject-level EEG analysis

In order to classify the attentional focus for each participant, evoked, connectivity, information theory, and spectral markers were extracted and fed to subject-level classifiers. The evoked features were computed from each brain response to the heart, and the rest of the features were extracted from the 5 s sub-epochs. Adaboosts classifiers with decision trees as base estimators ([Freund et al., 1997](#)) were implemented using Scikit-learn v1.0.2 ([Pedregosa et al., 2011](#)). The number of decision trees was set to 1000 and the maximum depth of each decision tree was set to 1. The splitting criteria used for each decision tree was set to 'gini'. To avoid data leakage, we followed a grouped stratified k-fold cross-validation procedure with 8 folds where on each fold all sub-epochs (or brain response to the heartbeat) from the same trial were grouped either in the train or test data. For each classifier, the mean accuracy across folds, measured as the area under the receiver operating characteristic curve (AUC), was obtained and significance was evaluated using a non-parametric statistical approach ([Combrisson et al., 2015](#)). The labels for the observations were randomly permuted 500 times and for each permutation, the mean classifier accuracy was obtained. We compared the mean accuracy of our original data against the empirical null distribution of classification accuracies. The

proportion of null classification accuracies greater than the AUC of the original data yielded our p-values. The level of significance was established at $\alpha = 0.05$. The resulting p-values were corrected using the false discovery rate method (Benjamini et al., 1995).

3.3.7 HEP features

In order to obtain the HEP features a leave-one-out approach was implemented as follows. Cluster permutation analyses were carried out on all subjects except the subject for which the feature extraction and subsequent classification were going to be computed. For the canonical clusters obtained, clusters with p-values < 0.05 were selected. For each electrode taking part in the selected clusters, the mean, the standard deviation, the maximum, and the minimum voltage in the time window spanning the cluster were extracted for each epoch of the subject withheld from the clustering analysis. This resulted in 4 features per channel in the clusters. As a control, the same temporal windows were used to extract analog features from the ECG channel resulting in four features per cluster.

3.3.8 Spectral, complexity, and connectivity features

For each subject, a Laplacian transformation (Kayser et al., 2015) was applied on the channels of the 5 s sub-epochs to reduce the effect of volume conduction and obtain less correlated sensor signals. Power spectral density for frequencies between 1:30 Hz was obtained using multitapers as implemented in the PSD_multitaper function in MNE. Power was averaged across delta (1:4 Hz), theta (4:8 Hz), alpha (8:14 Hz), low-beta (14:20 Hz), and high-beta (20:30 Hz) bands for each channel, resulting in 320 spectral features per sub-epoch. To assess brain dynamics during interoceptive and exteroceptive attention, permutation entropy (PE), symbolic weighted mutual information (wSMI), and Kolmogorov complexity (KC) markers were computed. The selection of these complexity and connectivity markers was driven by previous work showing their efficacy in classifying conscious states in DoC patients (Engemann et al., 2018; Sitt et al., 2014). Furthermore, these metrics capture non-linear dynamics and complement spectral and time-locked features (see supplementary material for details).

3.3.9 Time-locked and dynamical features

In order to evaluate a synergistic effect of the time-locked and dynamical features to classify attentional focus, combined classifiers were implemented joining the HEP features with each of the dynamical features (power, KC, PE, and wSMI). Brain responses to heartbeats arising during the 5 s sub-epochs were averaged, and from the evoked activity the HEP features (mean, std, min, max) were extracted as detailed above (Figure 3.1B). If for a sub-epoch all concurrent heartbeats were discarded during epoch rejection, the median across all the observations was used to replace missing data.

3.3.10 Brain-injured patients

Seven brain-injured patients participated in the study, three patients were assessed at the IRCCS Santa Maria Nascente Fondazione Don Carlo Gnocchi ONLUS, Milan (Italy), and four patients at the Pitié-Salpêtrière Hospital, Paris (France) in the context of the EU-funded multicentric project Perbrain (Willacker et al., 2022). Two Milan patients could not complete the task due to technical issues and were discarded from the analysis. The demographics and clinical information for the remaining five patients are listed in Table 3.1. All patients were in a subacute state (0.5:1.5 months since injury), except for M1 (8 months since injury), a chronic DoC patient. The assessment was performed following the ethical standards of the Helsinki Declaration (1964) and its later amendments and was approved by the local committees of each center (Comité de protection des personnes Ile de France I, #2013-A00106-39 and ethics committee section "IRCCS Fondazione Don Carlo Gnocchi" of ethics committee IRCCS Regione Lombardia, protocol number 32/2021/CE.FdG/FC/SA). Informed consent was obtained from the legal guardians of the patients before enrolling them in the study. The Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004) was performed by experienced neurologists on the same day as the task. All patients had behavioral responses to sound or cortical auditory responses assessed with the local-global paradigm (Bekinschtein et al., 2009).

3.4 Results

We presented white noise with embedded salient auditory targets only, or with the same targets together with specific white noise repetitions to which participants were naive.

Exteroceptive attention or interoceptive attention was elicited by asking participants at the beginning of each trial to report the number of targets or the number of heartbeats they felt. EEG, ECG, and respiration were recorded. Event-related potentials, oscillations, complexity, and connectivity were assessed at the group level, and subject-level classifiers were used together with time-locked and dynamical features to classify attentional focus.

3.4.1 Task performance of healthy participants: heartbeats and AmN count

Healthy participants were able to focus their attention on the sound during sound attention trials, as shown by the proportion of AmN reported (Figure 3.2A). The performance during interoceptive attention showed greater variability across participants but a correlation between interoceptive and exteroceptive accuracy was found ($\rho(20) = 0.63$, $p = 0.002$), suggesting an overall engagement in the task (see supplementary materials). In order to maximize brain responses to the noise repetitions, trials had a high density of RepRN, importantly, the RepRN did not interfere with participants' ability to detect their own heartbeats, as interoceptive accuracy did not differ between trials with plain white noise and trials with embedded noise repetitions (ANOVA $F(1,21) = 0.056$, $p\text{-value} = 0.82$) (SFigure 3.9). The detection of AmN was effortless for participants, therefore the low performance of subjects 1 and 2 ($< 70\%$) was interpreted as a lack of engagement in the task, leading us to exclude them from further analyses.

3.4.2 Heart activity and respiration are not modulated by exteroceptive and interoceptive attention

Mean Heart rate (HR) and mean heart rate variability (HRV) were measured for each 31 s trial and were contrasted during heart and sound attentional conditions (see supplementary materials). There were no differences in heart rate (HR heart = 75.13 BPM, HR sound = 75.44 BPM, $t = 0.94$, $p = 0.36$, $\beta = 0.26$, 95% CrI = [-0.43,0.96], BF = 0.14), nor in heart rate variability (HRV heart = 32.88 ms, HRV sound = 33.15 ms, $t = 0.32$, $p = 0.75$, $\beta = 0.39$, 95% CrI = [-1.38,2.17], BF = 0.12) between conditions (Figure 3.2B). In order to assess whether the AmN prompted a cardiac deceleration, the interbeat interval for the first, second, and third heartbeat following sound onset were compared to baseline (see supplementary materials). Independently of condition,

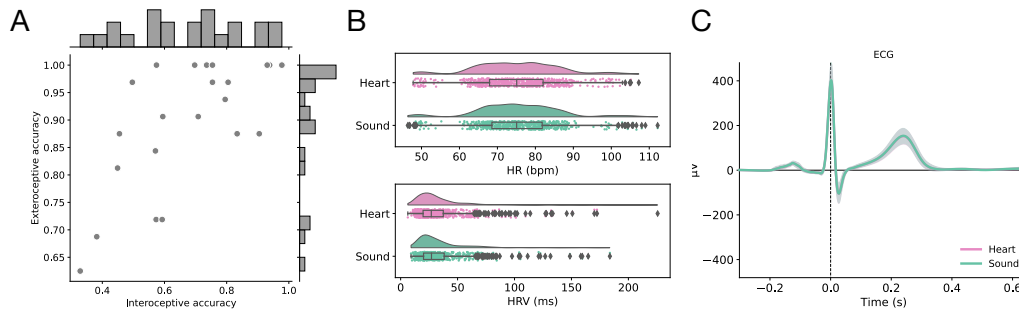


Figure 3.2: Task performance across subjects and heart activity. **A.** Correlation between exteroceptive accuracy as the percentage of AmN reported over the total number of AmN presented during trials of sound-directed attention) and the mean interoceptive accuracy across trials of heart-directed attention. Subjects 1 and 2 were discarded from further analysis due to low exteroceptive accuracy ($< 70\%$). **B.** Heart rate (top) and heart rate variability (down) for all trials during heart and sound-directed attention. **C.** Average ECG waveform for all subjects during sound and heart attention conditions with a 95% bootstrap confidence interval.

there was no effect of AmN presentation on the interbeat intervals post target ($\Delta\text{IBIB0} = 2.13$, $t = 0.85$, $p\text{-value} = 0.39$, $\Delta\text{IBIB1} = 0.67$, $t = 0.27$, $p\text{-value} = 0.79$, $\Delta\text{IBIB2} = -1.88$, $t = -0.75$, $p\text{-value} = 0.45$) (SFigure 3.7B). Moreover, attention did not affect the ECG waveform as suggested by the negative results obtained for a point by point analysis (SFigure 3.7A) as well as a by a temporal cluster analysis (minimum cluster $p\text{-value} = 0.46$). Furthermore, we tested whether our task prompted changes in respiratory activity which could influence brain response to internal and external signals. Respiratory frequency did not differ across conditions (BR heart = 0.249 Hz, BR sound = 0.247 Hz, $t = -0.61$, $p\text{-value} = 0.54$), nor were there differences in the coefficient of variation of the breathing rate (CVBR heart = 0.174, CVBR sound = 0.166, $t = -1.28$, $p\text{-value} = 0.20$) (SFigure 3.8).

3.4.3 HEP and AmN evoked responses are oppositely modulated by interoceptive and exteroceptive attention

The effects of attention on the cortical response to the heartbeats (HEP) was evaluated with a cluster permutation analysis. The analysis revealed two significant clusters. A posterior cluster comprised of 26 channels spanning from 179 to 318 ms ($t_{sum} = 1382$, $p\text{-value} = 0.022$) such that voltage was higher during heart-attention condition, and an anterior cluster comprised of 20 electrodes from 175:316 ms ($t_{sum} = -1398$, $p\text{-value} = 0.022$), for which voltage was more negative when attention was directed towards

the heart (Figure 3.3B). The difference in amplitude for the HEP did not correlate with subject's interoceptive accuracy, and not all participants showed this modulation (SFigure 3.10AB). An increase in ITPC for the delta band was observed in posterior electrodes ($t_{sum} = 7480$, $p\text{-value} < 0.001$, $\text{time} = -25:600$ ms) (SFigure 3.10C), and for ITPC in the theta band ($t_{sum} = -1381$, $p\text{-value} = 0.049$, $\text{time} = 344:600$ ms). Moreover, no differences in power were obtained for the frequency bands tested, suggesting that the changes in the HEP are a result of phase modulations at low frequencies. Differences in brain response to amplitude-modulated noise targets (AmN) during the attentional conditions were also assessed using cluster permutation analysis. An increased response to AmN was observed when attention was directed to the sound (Figure 3.3A) as indexed by five significant clusters spanning from 68 to 850 ms. We report here two of the clusters that summarize the topography of the effect. A later posterior cluster from 377 to 675 ms ($t_{sum} = -13983$, $p\text{-value} < 0.001$) and an early anterior cluster spanning the interval between 68 and 367 ms ($t_{sum} = -8184$, $p\text{-value} < 0.002$).

3.4.4 Interoceptive-exteroceptive attention and perceptual learning

In order to assess the effects of interoceptive and exteroceptive attention to inconspicuous noise repetitions, evoked responses to the repetitions (RepRN) and plain white noise (RN) were compared within each condition. Voltage differences were found between the RepRN and RN during sound attention as indexed by a widespread cluster ($\text{time} = 0\text{-}209$ ms, $t_{sum} = 5586$, $p\text{-value} = 0.003$). In addition, ITPC coherence in the delta band was higher during sound attention to the structured repetitions (SRepRN) compared to trials with plain white noise ($\text{time} = 1.40\text{-}2.57$ s, $t_{sum} = 23072$, $p\text{-value} = 0.009$, SFigure 3.11C), and no difference in power was found (clusters $p\text{-values} > 0.13$). Conversely, no differences were obtained for the analog analyses between RepRN during trials of heart-directed attention and trials in which attention was directed to the heart but plain white noise was presented (SFigure 3.11D). In order to assess perceptual learning during heart and sound attention, evoked responses to the 1st to the 5th RepRN forming the SRepRN stimuli were separately averaged. Nevertheless, no positive results were obtained from the comparison of the 1st to 5th RepRN against plain white noise within each condition (SFigure 3.11B).

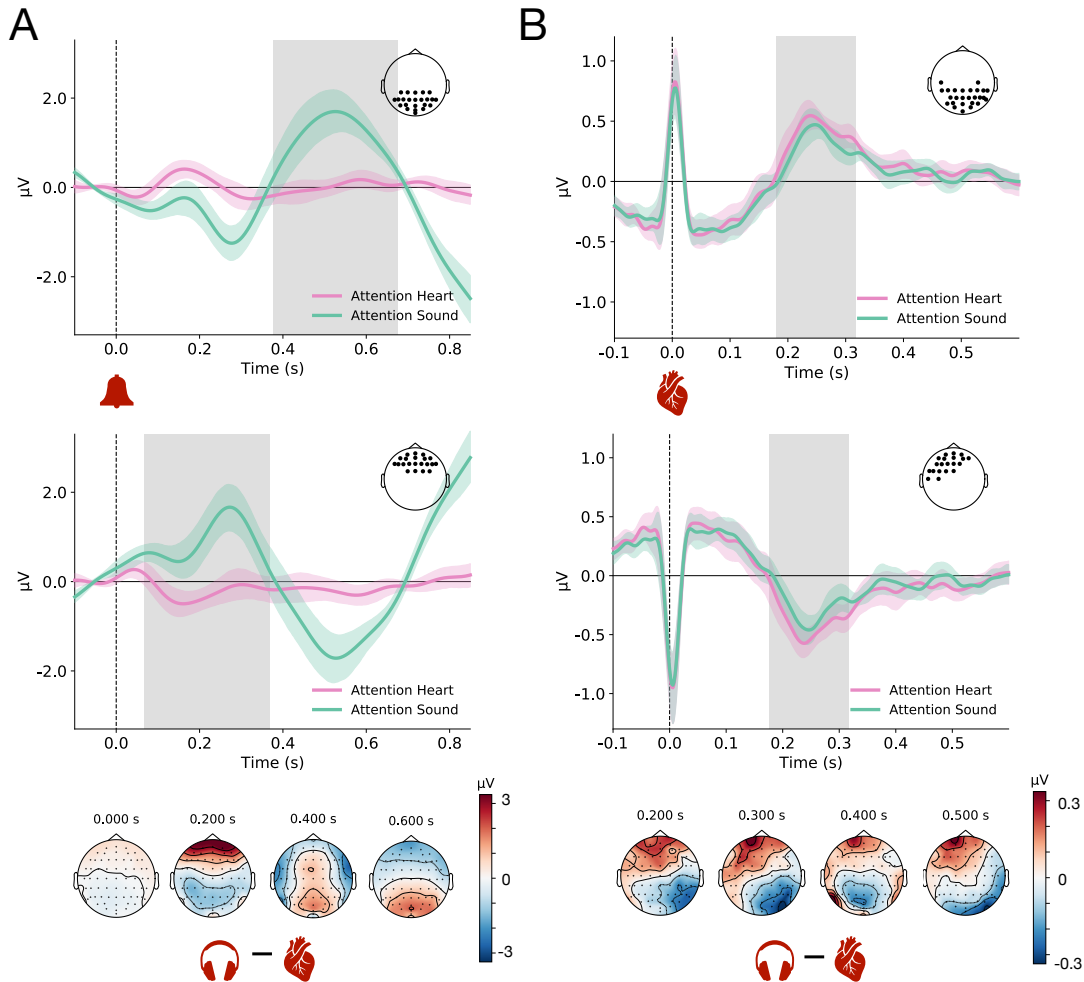


Figure 3.3: HEP and AmN evoked are oppositely modulated by interoceptive and exteroceptive attention. **A.** Brain response to amplitude-modulated noise. An early anterior (68 to 375 ms, $t_{sum} = -9415$, p -value < 0.001) and a later posterior (377 to 675 ms $t_{sum} = -13983$, p -value < 0.001) significant clusters were found. **B.** Heartbeat-evoked potential during heart and sound attention. Two significant clusters were obtained. A posterior cluster spanning from 179 to 318 ms ($t_{sum} = 1382$, p -value = 0.022) and an anterior cluster from 175 to 316 ms ($t_{sum} = -1398$, p -value = 0.022). The topography below each plot is the voltage difference between heart and sound conditions. Grey shading marks the temporal span of clusters and black dots indicate channels in clusters. The ERPs shown are the average voltage across channels for each cluster with a 95% bootstrap confidence interval.

3.4.5 Rhythmic and aperiodic activity during exteroceptive and interoceptive attention

Brain oscillatory and aperiodic dynamics were contrasted between heart and sound-directed attention trials. A group effect of attentional condition was found for the aperiodic activity. Specifically, during interoceptive attention, the aperiodic exponent of the power spectrum was lower than during exteroceptive attention, and this effect was centrally localized in the scalp ($t_{sum} = 24.37$, $p\text{-value} = 0.007$). In addition, differences were found in the oscillatory activity. The bandwidth of the beta band peak was smaller ($t_{sum} = -8.25$, $p\text{-value} = 0.014$), and frontal theta power was higher during heart-directed attention ($t_{sum} = 9.80$, $p\text{-value} = 0.028$, [Figure 3.4A.C](#)).

3.4.6 Time-locked activity, power, connectivity, and complexity classifiers

Adaboost subject-level classifiers were implemented using as features the time-locked and dynamical markers as well as integrated classifiers. Classifiers based on power across the delta, theta, alpha, low, and high-beta showed the best performance, accurately classifying all participants' attentional conditions with an overall $AUC = 0.75 \pm 0.10$, with a performance superior to the one obtained for per-band classifiers ([Figure 3.5A](#), [SFigure 3.12](#)). The classifier based on the HEP features classified above chance 17 out of 20 participants with a mean $AUC = 0.55 \pm 0.03$, and the AUC score was correlated to the number of epochs ($\rho(18) = 0.46$, $p\text{-value} = 0.043$) which was not the case for the PSD classifier ($\rho(18) = 0.19$, $p\text{-value} = 0.41$), suggesting that increasing the amount of data would yield more accurate results for HEP based classifiers. The ECG classifier only classified above chance 6 participants ($AUC = 0.50 \pm 0.06$), which was unsurprising as no differences in cardiac activity were found in the group analyses. Complexity and connectivity-based classifiers showed comparable performance to the HEP-based classifier. The PE-based classifier was able to classify 17 participants ($AUC = 0.59 \pm 0.06$), the wSMI-based classifier resulted in 16 participants being classified above chance ($AUC = 0.57 \pm 0.07$) and the classifier based on Kolmogorov complexity accurately classified 18 participants ($AUC = 0.59 \pm 0.06$) [Figure 3.5A](#)). No significant improvement in classification was obtained for the combination of spectral and HEP features ($AUC = 0.75 \pm 0.09$, $t = -1.48$, $df = 19$, $p\text{-value} = 0.92$) nor when combined with KC features ($AUC = 0.60 \pm 0.06$, $t = 1.57$, $df = 19$, $p\text{-value} = 0.066$). Neverthe-

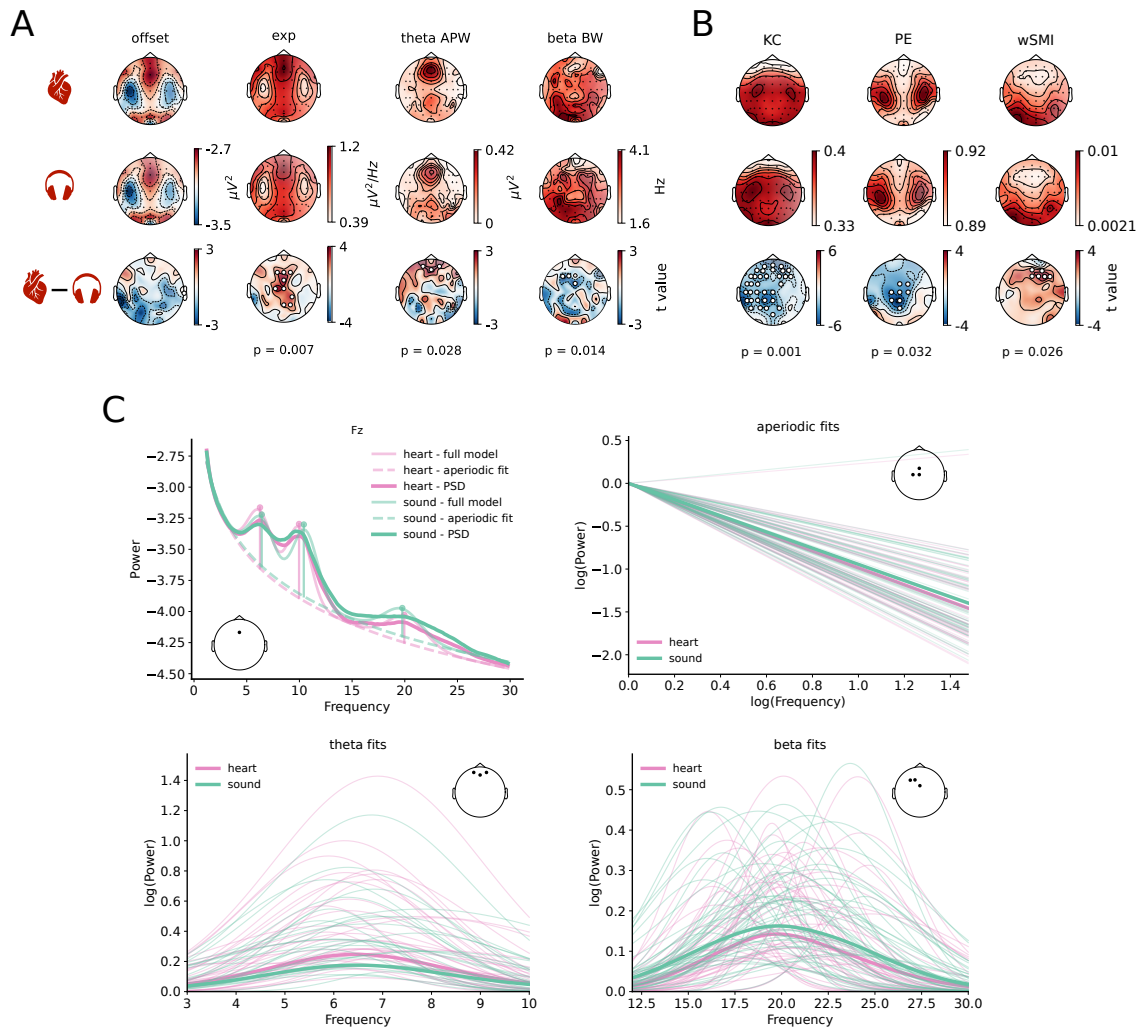


Figure 3.4: Interoceptive and exteroceptive attention show different brain dynamics. **A.** Periodic and aperiodic components of the power spectrum model fit during heart attention trials (top), sound attention trials (middle), and t-values for the difference between the components during both conditions (bottom). From left to right: offset value (off), aperiodic exponent (exp), and aperiodic-adjusted power (APW), and bandwidth (BW) for theta and beta bands. **B.** Kolmogorov complexity (KC), permutation entropy (PE), weighted symbolic mutual information (wSMI). Top. Markers topography during attention to the heart. Middle. Markers topography during sound attention. Bottom. T-values for the difference between markers during heart attention and sound attention trials. White dots indicate sensors in significant clusters. **C.** Left top: average PSD for channel Fz with aperiodic and periodic model components for each condition. Right top: aperiodic fits for all subjects and conditions for Cz, C1, and FCz channels. Bottom left: periodic fits for the theta range (4:8 Hz) for all subjects and conditions for channels Fp1, Fp2, and AFz. Bottom right: periodic fits for the beta range (15:25 Hz) for all subjects and conditions for channels F3, FC1, and FCz.

less, an increase in overall classification was obtained when combining the time-locked features to PE ($AUC = 0.61 \pm 0.05$, $t = 3.63$, $df = 19$, $p\text{-value} < 0.001$) and wSMI ($AUC = 0.59 \pm 0.07$, $t = 3.01$, $df = 19$, $p\text{-value} < 0.001$) features, with three (total: 20 out of 20 participants) and two more participants (total: 18 out of 20 participants) being classified above chance, respectively [Figure 3.5B](#)).

3.4.7 Complexity and connectivity group analysis

Interoceptive and exteroceptive attention effects on brain dynamics were contrasted using Kolmogorov complexity, permutation entropy, and weighted symbolic mutual information. A significant difference was obtained for KC ($t_{sum} = -112.77$, $p\text{-value} = 0.001$) such that complexity was lower during interoceptive attention as shown by a widespread frontocentral parietal cluster. In addition, the analysis yielded differences in connectivity as indexed by a frontal cluster ($t_{sum} = 17.87$, $p\text{-value} = 0.026$) for which wSMI was higher during attention to the heart trials. Finally, permutation entropy was lower during interoceptive attention in centro-parietal electrodes ($t_{sum} = -23.39$, $p\text{-value} = 0.032$) ([Figure 3.4B](#)).

3.4.8 Brain injured patients patients show a modulation of the HEP and ongoing activity consistent with command-following

Three UWS/Vs, one MCS- and a LIS diagnosed patients were presented with a modified version of the task (see supplementary materials for a description). Feature extraction was carried out and fed to classifiers to differentiate between trials of heart-directed or sound-directed attention as a proxy measure for command-following. For the LIS patient, we expected a brain response consistent with interoceptive and exteroceptive attention as these patients are conscious. Although, UWS/Vs are patients who clinically do not show responses to the external world, and MCS- patients are individuals who show basic cortically mediated behaviors, such as visual fixation and pursuit and automatic responses ([Bruno et al., 2011](#); [Naccache, 2018](#)), in a misdiagnose scenario covert volitional responses could be present. UWS/Vs patient P1 was only classified by KC ($AUC = 0.56 \pm 0.03$, $p = 0.014$, all rest $p > 0.09$). P2, also a UWS/Vs patient, was classified above chance by the PSD features ($AUC = 0.56 \pm 0.03$, $p = 0.029$), and although the HEP features were not sufficient for an above chance classification ($AUC = 0.51 \pm 0.01$, $p = 0.38$), combining these time-locked features to the spectral and KC

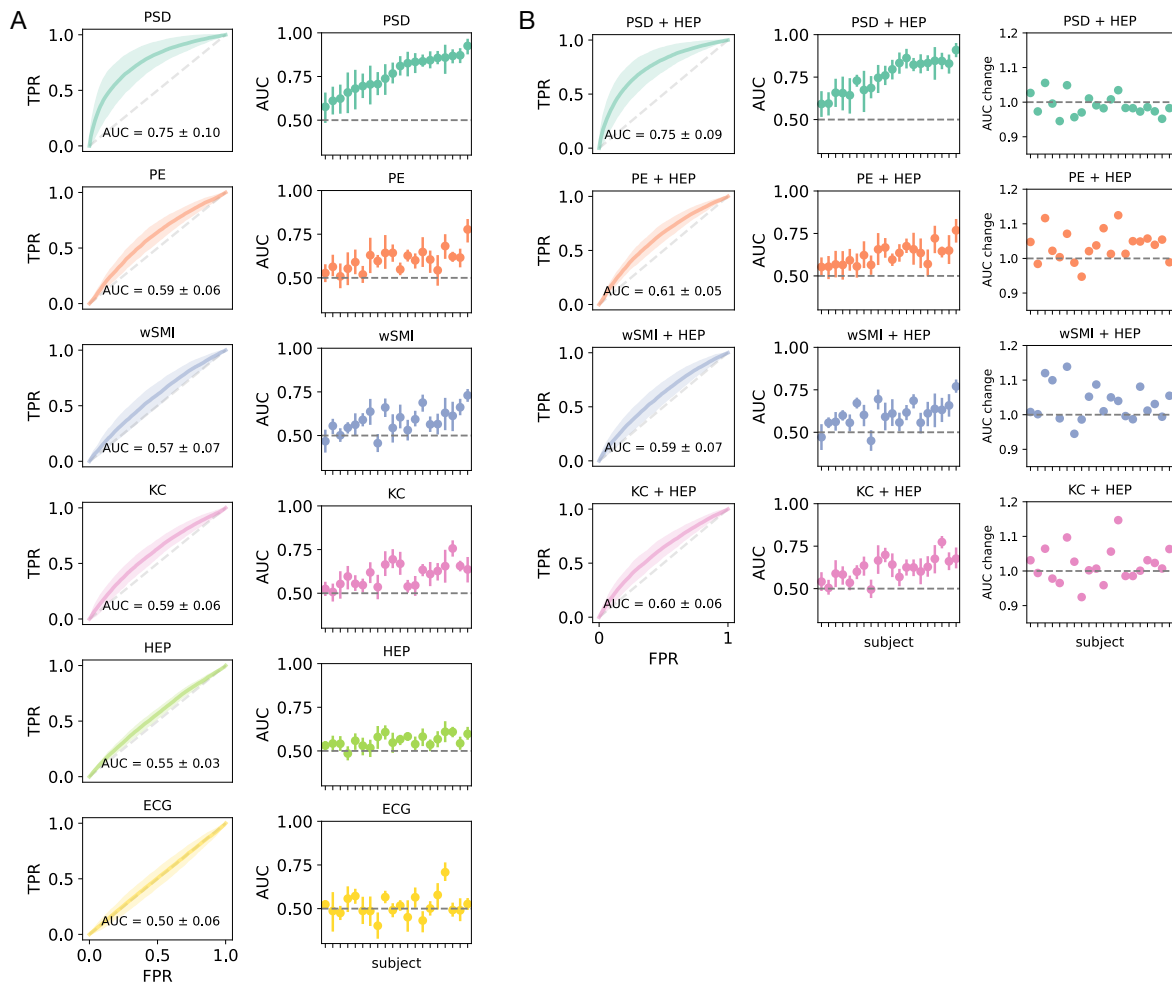


Figure 3.5: Brain dynamics and brain response to the heart are informative of attention orientation at the individual level. **A.** Subject-level classifiers for power spectral density (PSD), permutation entropy (PE), weighted symbolic mutual information (wSMI), Kolmogorov complexity (KC), heartbeat-evoked potential (HEP) and cardiac activity (ECG) features. Left. Average receiver operating characteristic (ROC) curves across cross-validation folds and subjects. Shading corresponds to the standard deviation. Right. Average AUC across folds with 95% bootstrap confidence interval for each subject and classifier. Subjects are sorted considering the AUC for the spectral density classifier. **B.** Combined classifier of dynamical features and HEP features. Left. Average receiver operating characteristic curves across cross-validation folds and subjects. Shading corresponds to the standard deviation. Middle. Average AUC across folds with 95% bootstrap confidence interval for each subject and classifier. Right. Ratio between the mean AUC for the individual classifier and the mean AUC for the combined classifier. Subjects are sorted considering the AUC for the spectral density classifier (not combined with HEP features).

information improved the AUC scores (PSD: $AUC = 0.58 \pm 0.03$, $p = 0.002$; KC: $AUC = 0.60 \pm 0.03$, $p = 0.002$) yielding a successful classification. No EEG marker could differentiate between attentional conditions for UWS/VS patient P3. The attentional state of patient in LIS (P4) was not classified by the single marker classifiers, but combining the HEP features with the PSD, KC and PE resulted in an above chance classification (PSD+HEP: $AUC = 0.54 \pm 0.02$, $p = 0.042$; KC+HEP: $AUC = 0.55 \pm 0.02$, $p = 0.013$; PE+HEP: $AUC = 0.55 \pm 0.02$, $p = 0.026$). Finally, MCS- patient tested at the Milan center (M1) was successfully classified only by the PE features (PE: $AUC = 0.56 \pm 0.02$, $p = 0.007$) (Figure 3.6A). Both patients who showed increased AUC scores when incorporating the HEP features (P2 and P4) show a modulation of this ERP on a time window and electrodes consistent with healthy participants response (Figure 3.6B). A modulation of the HEP was not observed for the rest of the patients.

3.5 Discussion

The aim of the present study was to develop and test an experimental paradigm that would allow to infer the attentional focus of an individual from brain and bodily responses to internal and external stimuli. The hypothesis underlying this work is that attention has an impact on our consciousness content and perception, such that it enhances the probability of becoming aware and, or, of better encoding a selection of the incoming inner or outer sensory world. For this purpose, we designed a task to engage interoceptive and exteroceptive attention by orienting participants to their heartbeats or to salient auditory stimuli, and measured their cortical, cardiac, and respiratory activity, while the effects of attention on passive encoding were probed using concealed noise repetitions.

3.5.1 Interoceptive attention modulates cortical response to heartbeats

In agreement with previous findings (García-Cordero et al., 2017; Petzschner et al., 2019), our results show that directing attention to the heartbeat yields a modulation of the cortical response to the heartbeats. In addition to replicating the group effect on the HEP during interoceptive attention, we have shown the strong nature of this modulation, such that it is sufficient to accurately classify the attentional state at the

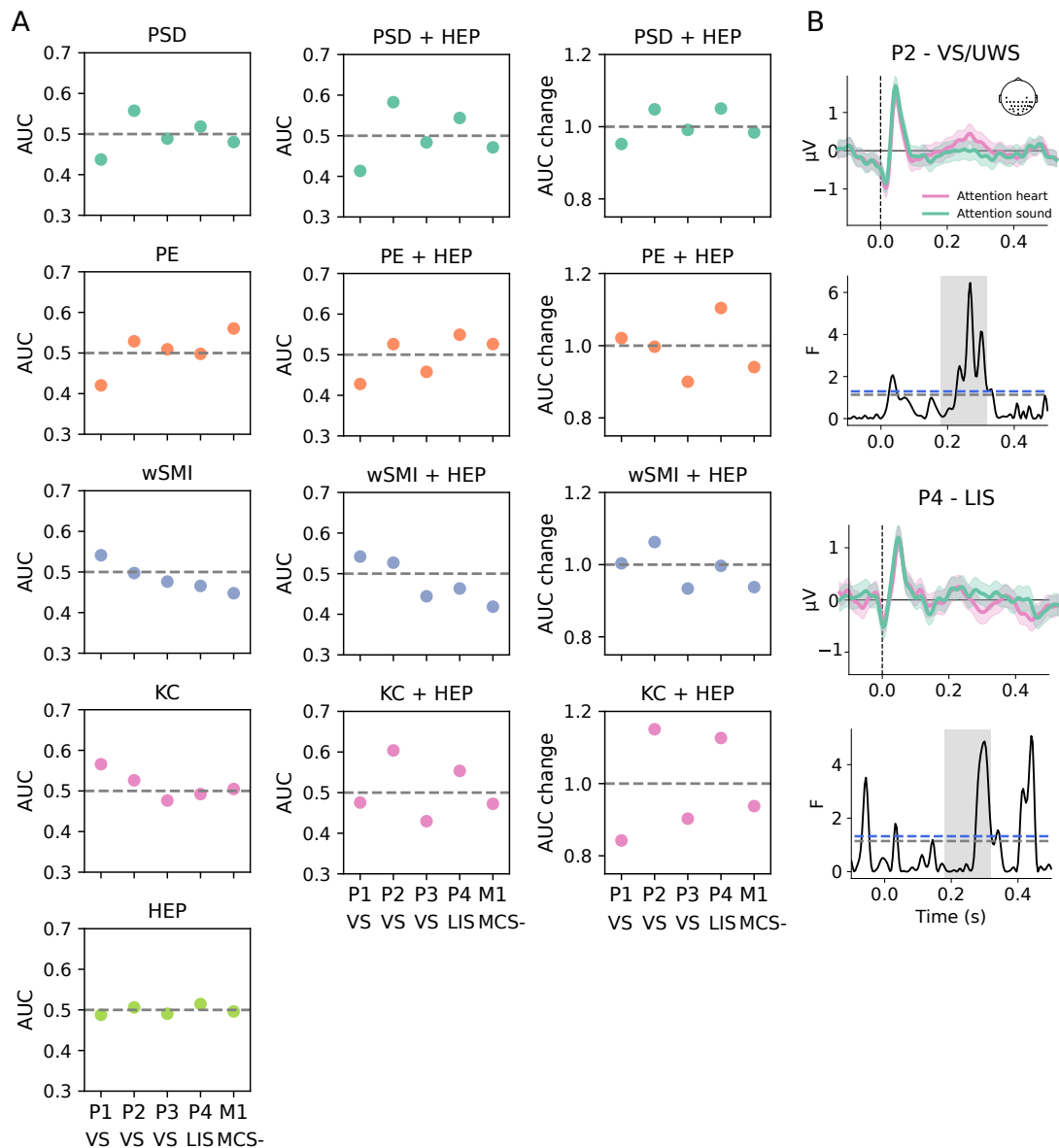


Figure 3.6: Brain dynamics and brain response to heartbeats to detect command following in non-communicative patients. **A.** Left: Subject-level classifiers for power spectral density (PSD), permutation entropy (PE), weighted symbolic mutual information (wSMI), Kolmogorov complexity (KC) and heartbeat-evoked potential (HEP) features. Average AUC across folds with 95% bootstrap confidence interval for each patient and classifier (VS: Unresponsive Wakefulness Syndrome/Vegetative State, LIS: Locked-in Syndrome, MCS-: Minimally conscious state minus). Middle: Combined classifier of dynamical features and HEP features. Average AUC across folds with 95% bootstrap confidence interval. Right: Ratio between the mean AUC for the individual classifier and the mean AUC for the combined classifier. **B.** HEP modulation by attention for patients P2 and P4. Top: average HEP response for electrodes for which an effect of attention is observed in healthy participants. Bottom. F values for point-by-point one-way ANOVA analysis between heartbeat-evoked responses during attention to heart and attention to sound. Black dotted lines represent $p < 0.05$. Blue dotted lines represent $p < 0.05$ after Bonferroni correction. Grey shading indicates the time window for the observed effect of attention on healthy participants.

single-subject level. Although HEP amplitude can be modulated by the respiratory cycle (Zaccaro et al., 2022) exhalation and inhalation showed no differences between attentional conditions. Moreover, no modulation of the cardiac rhythm or the ECG waveform was found at the group level. In addition, cardiac activity was not effective for detecting covert attention. Together, our results suggest that the cortical differences were not driven by changes in the afferent signals but are a result of a top-down modulation on the cortical processing of the heartbeats consistent with predictive coding accounts (Allen et al., 2022; Barrett et al., 2015; Seth et al., 2012). The HEP voltage modulation was accompanied by an increase in ITPC in the delta and theta band, with no differences in power, hinting at a phase-locking reset effect of attention on ongoing neural dynamics. It has been reported that increases in HEP amplitude are associated with increases in ITPC in these frequency bands (Lechinger et al., 2015; Park et al., 2018), and that during resting state the heartbeat induces a cortical synchronization in the theta band (Kim et al., 2019). In this line, we found an increase in connectivity in frontocentral electrodes during interoceptive attention as measured by wSMI for this low-frequency band. The amplitude modulation of the HEP was not correlated to interoceptive accuracy scores. This is not surprising, as multiple criticisms for heartbeat counting as a measure of interoceptive awareness have been raised. Crucially, responses are influenced by the knowledge participants have of their own heart rates, and as these tasks are typically measured during rest, the heart rate variability is very small and therefore hard to perceive and report (Körmendi et al., 2022). Moreover, it has been reported that the belief about one's own heart rate is a better predictor of the number counted than the actual quantity of heartbeats (Ring et al., 1996). Hence, the heightened encoding of this internal state could have occurred without participants being aware of their heartbeats. Furthermore, HEP modulation was variable across participants which may explain why some subjects were not successfully classified only with the HEP features. This intersubject variability is not surprising given the fact that individual differences in heartbeat awareness have been widely reported in the literature, and have been linked to body mass index (B. M. Herbert et al., 2014), sex (Prentice et al., 2022), age (Khalsa, Rudrauf, Feinstein, et al., 2009), emotion (Critchley et al., 2017), and even sensory deprivation (Radziun et al., 2023).

3.5.2 Exteroceptive attention induces an overall gain in auditory processing

Brain response to AmN was substantially affected by attention. This was expected as participants had to detect an infrequent and salient sound, which typically elicits a P300 response (Linden, 2005). Although the effect of attention on perceptual learning of noise repetitions was not as prominent, the white noise repetitions were better encoded during sound attention trials, as shown by the ERP and ITPC results. No cortical response was found for the first repetition of the SRepRN, which would have indexed the long-term learning of the snippets and not a within SRepRN short-term learning effect. Our outcome could be the result of a lack of power, and increasing the number of repetition presentations in future work would clarify this. In fact, although an increased response is visually noticeable for the 3rd repetition during sound attention and the 4th repetition during heart attention in comparison to plain white noise (SFigure 3.11B), no statistical differences were obtained, supporting the hypothesis that we lacked power. From our results, we can only infer that during exteroceptive attention there was a discernable enhancement of auditory processing, leading to an overall increase in the brain response to the RepRN. Unlike previous research, our experimental design holds a distinctive advantage. Modulating attentional focus within the same task with all RepRN presented in both conditions across participants makes it less likely that results are driven by some seeds being more easily perceived than others and enables measuring concurrent learning effects.

3.5.3 Brain dynamics during heartbeat and sound awareness

Multiple studies have focused on comparing the effects of internal attention (Chun et al., 2011) on the processing of external stimuli using paradigms based on mental operations such as mind wandering (Baird et al., 2014; Barron et al., 2011; J. W. Y. Kam et al., 2011; J. W. Y. Kam et al., 2021; Villena-González et al., 2016) or mental imagery (Villena-González et al., 2016), showing a decrease of sensory evoked potentials during attention to internal information, consistent with our findings. Concerning brain dynamics, these paradigms show increases in alpha power (Ceh et al., 2020; Cooper et al., 2003; Ray et al., 1985) associated with a top-down inhibition of cortical areas that would process distractor-relevant information (Foxy et al., 2011), modulations of theta power reflecting working memory demands (J. W. Kam et al., 2018; Magosso

et al., 2021), and increases in the theta-beta ratio during internal thought production and low-alertness (Braboszcz et al., 2011; Van Son et al., 2019). However, scarce studies have directly compared brain dynamics during interoceptive and exteroceptive attention. In our study, and following previous research (García-Cordero et al., 2017), power was lower during interoceptive attention compared to exteroceptive attention for frequencies between 1 and 30 Hz. Our methodological approach allowed us to attribute this difference to an overall change in aperiodic activity such that power at lower frequencies is increased in relation to power at higher frequencies during the interoceptive task. An overall steepening of PSD has been shown during anesthesia (Colombo et al., 2019; Gao et al., 2017; Lendner et al., 2020) as well as during sleep (Lendner et al., 2020), and has mechanistically been attributed to changes in the excitation-inhibition ratio in the brain (Gao et al., 2017; Voytek et al., 2015). Functionally, increases in PSD slope have been observed during response inhibition (Pertermann, Bluschke, et al., 2019; Pertermann, Mückschel, et al., 2019), and interpreted as a marker of top-down control required to sustain goal representations (Zhang et al., 2023). During both interoceptive and exteroceptive attention participants were demanded to carry out a detection operation. Nevertheless, the heartbeats and the auditory stimuli we employed have intrinsically different properties and probably elicited different behaviors. Cardiac activity is a rhythmic stimulus, therefore counting heartbeats was a repetitive and sustained operation. On the contrary, AmNs occurred randomly and scarcely, and participants would incur in counting none or a few times on each trial. Finally, given the lack of salience of heartbeats, interoceptive-attention trials were probably more demanding for participants, which could explain the observed aperiodic activity differences. In addition, our results show that interoceptive attention was characterized by less complex or regular brain dynamics, with a topographical widespread pattern. Brain signal complexity is associated with the number of independent functional sources, such that the higher the complexity the less correlated the neural sources sustaining the overall activity (Stam, 2005). Lower complexity during interoceptive attention is consistent with a more overall stable brain configuration compared to the exteroceptive attention condition. Together with changes in the background activity, the beta band peak was narrower, and theta power was higher during heart-attention trials. As mentioned, previous research has associated a higher theta-beta power ratio with episodes of mind wandering (J. Kam et al., 2022) which are typically elicited during sustained

and repetitive tasks. Considering that the HEP was positively modulated by interoceptive attention, we argue that participants were actively engaged during the task making stimulus-independent thought unlikely, and the rhythmic changes observed would be a reflection of cognitive effort. In line with this, frontal theta has been associated with target detection (Missonnier et al., 2006), fatigue (Wascher et al., 2014), and overall cognitive control (Cavanagh et al., 2014). PE and wSMI features combined with the HEP features enhanced the classification, signaling that they convey mutual information. This behavior was not observed in the case of spectral features or Kolmogorov complexity. For KC there was an improvement but it did not reach significance. Possibly the increase in information could not compensate for the detrimental effect of having a larger number of features in the resulting classifier. In the case of the spectral features, probably, the time-locked information is already embedded within the signal power decomposition, rendering both groups of features redundant and leading to no improvement. Including all spectral bands as features yielded a better classifier than using each power band by itself, which is consistent with an overall change in brain dynamics during our interoceptive-exteroceptive attention manipulation.

3.5.4 HEP and dynamical features act synergically to classify the attentional state of two brain injured patients

The potential of this tool to detect command-following was probed in a small group of brain-injured patients. Classification by the proposed features showed very different behaviors across patients which is expected in a small sample with such heterogeneous etiologies. P1 showed inconsistent results across classifiers, with PE and PSD classifiers showing a below-chance performance, and KC an above-chance performance. This can occur when the models fit to noise in the training sets and is suggestive of no difference in neural activity during both attentional conditions. P3, behaviorally diagnosed as UWS/VS, did not show AUC values above chance for any of the markers, and M1, a MCS(-) patient, was only classified by the PE features, likely indexing no command-following behavior. Crucially, the brain responses of the LIS patient (P4) and a patient with a UWS/VS diagnosis (P2) were reliably classified by combining dynamical and HEP features. Although the classification accuracies were lower in these two patients, probably due to less sustained attention and a more noisy environment, the consistency across classifiers together with changes in the cortical responses to heartbeats topographically

and temporally consistent with healthy participants' responses, suggests that patients were complying with task instructions. The detection of command-following in the LIS represents a positive control of our task as consciousness is preserved in these patients and command-following is therefore expected. Importantly, our assessment suggests that P4 had higher levels of residual consciousness than conveyed behaviorally, and this would mean a mismatch between the patient's conscious level and the clinical diagnosis. Our results expand the framework of heart-brain interactions employed for DoC diagnostic purposes (Candia-Rivera et al., 2021; Candia-Rivera et al., 2023; Raimondo et al., 2017), by showing for the first time the willful modulation of the HEP in two brain injured patients patients with severe impairments of sensory, motor and executive functions. Compared to other command-following tasks (Claassen et al., 2019; Owen et al., 2006), our paradigm possesses the advantage of contrasting brain responses to two active instructions (instead of active instructions versus resting state), which in addition are less demanding compared to executing complex imaginary behaviors or actual movements. Beyond command-following, we argue that the ability to distinguish between internal and external signals in DoC patients could be interpreted as a signature of preserved self-awareness. Moreover, the proposed task can provide information on different levels of information processing independently of the patient following the instructions, as passive cortical responses to sounds, and heartbeats can be measured, as well as assessing EEG markers that have already proven robust in indexing the state of consciousness in DoC patients (Engemann et al., 2018; Sitt et al., 2014). Our results are a proof of concept of the potential of this novel tool to detect command-following among patients who are unable to convey explicit behavioral responses and the feasibility of its application in clinical settings. Future work assessing a bigger cohort of patients should be carried out to comprehensively evaluate its diagnostic as well as prognostic capabilities.

3.5.5 Limitations

Some aspects of our study should be considered to improve future work. Introducing a resting state condition against which to compare the brain markers obtained during both types of attention would be a good strategy to allow a more mechanistic interpretation of the results. Furthermore, the implementation of trials with varying lengths would prevent participants from offering similar responses on a trial-by-trial basis on the num-

ber of heartbeats simply due to their expectation of a consistent heart rate. Another limitation is that an exhaustive analysis of the effects of interoceptive-exteroceptive attention on heart activity comprising frequency domain and non-linear measures could not be conducted as the length of trials was too short to provide reliable results ([Castaldo et al., 2019](#); [McNames et al., 2006](#)).

3.5.6 Conclusions and future directions

In this work, we explored the modulatory effects of interoceptive-exteroceptive attention on the cortical processing of bodily and external signals. We report an overall gain in auditory processing during exteroceptive attention, as indexed by an increased cortical response to target sounds as well as a better encoding of noise repetitions, and a heightened cortical response for heartbeats during interoceptive attention. Exteroceptive attention was characterized by an overall power increase across the frequency range of 1-30 Hz, whereas during interoceptive attention there was a decrease in complexity, together with an increase in theta, and a decrease in beta oscillations. Our findings demonstrate that directing attention to bodily rhythms and the external world elicits distinct neural responses that can be employed to track covert attention at the individual level. Importantly, we show that the brain markers studied in this work can be useful in detecting EEG proxy of command-following in unresponsive patients. Crucially, the proposed paradigm provides multiple layers to explore information processing and awareness in these patients and requires equipment commonly available in clinical environments, rendering its application across centers straightforward.

3.6 Supplementary material

3.6.1 ECG analysis

Raw data for the difference between the channel placed on the left and right collarbone was processed with Neurokit2 0.2.0 toolbox (Makowski et al., 2021). Data was filtered with a 0.5 Hz high-pass Butterworth filter (order = 5) and a 50 Hz Butterworth notch filter (order = 2). R peaks in each 31 s epoch were detected using the method 'neurokit'. Ectopic heartbeats were automatically identified and discarded and wrongly detected peaks were corrected by setting a specific minimum height for the R peak individually for each subject. Mean heart rate (HR) in beats per minute and heart rate variability as the root mean square of successive differences between normal heartbeats (RMSSD) were obtained for each epoch (Baek et al., 2015; Munoz et al., 2015; Salahuddin et al., 2007). For each participant, a value was considered an outlier and discarded if it was below or above 3 standard deviations. To test for differences between conditions, linear mixed-effects models were fitted to heart rate and heart rate variability with condition (heart - sound) as a fixed factor and subject as a random effect. Bayesian hierarchical models were implemented to quantify the probability that our data supported a difference in heart rate activity over a null model. Two analyses were conducted to test for differences in the ECG waveform between conditions. First, point-by-point two-tailed one-sample t-tests on the subjects' difference between the mean ECG waveform during attention to the sound and attention to the heart were conducted, and Bonferroni corrected for multiple comparisons. Secondly, a cluster permutation analysis was carried out by comparing the temporal cluster obtained for the observed t values against an empirical null distribution of clusters obtained for 2000 instances after randomly flipping the signs of the differences between conditions. The cluster-forming threshold value for a critical alpha of 0.025 was obtained for a t distribution with 20 observations (two subjects were discarded due to low performance, see below). Linear models were implemented in R Studio (77) with R version 3.6.3 (Team, 2017) using lme4 (Bates et al., 2015), rstan (Stan Development Team, 2023), and brms (Bürkner, 2017) libraries.

To test whether the sound presentation elicited a heart rate deceleration, heart rate variability was assessed by comparing the interbeat interval (IBI) for the first, second,

and third heartbeat after AmN onset to the IBI for the beat immediately before the target presentation. The IBIs were referenced to the average IBI before the target onset (Skora, Livermore, Nisini, et al., 2022). The resulting differences were z-scored and values were rejected if below or above 3 standard deviations. The effect of target presentation on heart rate variability was evaluated with a linear mixed-effect model contrasting the IBI for the different heartbeat positions with subject as a random factor.

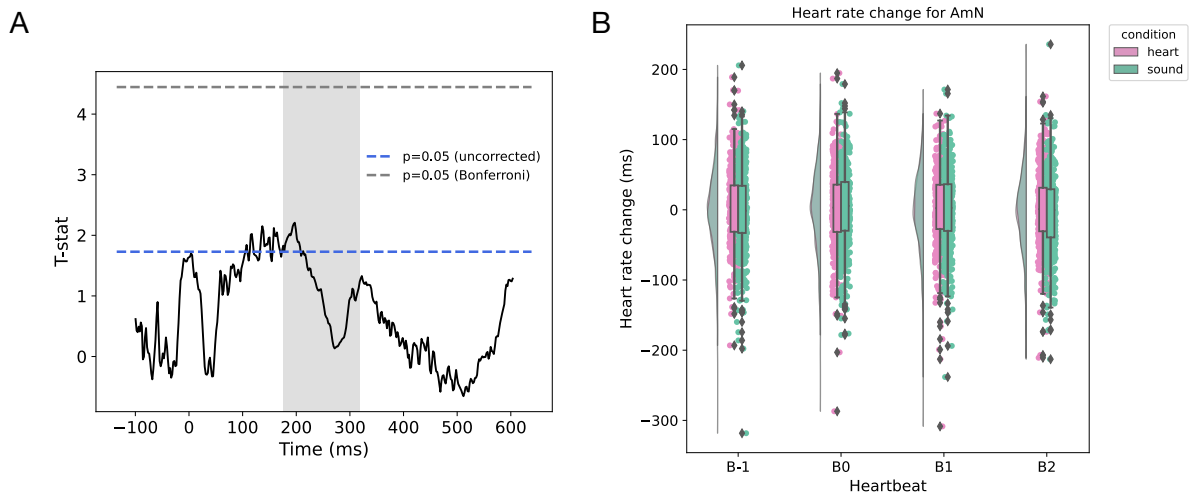


Figure 3.7: Heart activity controls. **A.** ECG waveform analysis. T-values were obtained from a two-tailed one-sample t-test on the subjects' difference between the mean ECG waveform during attention to the sound and during attention to the heart. The grey dotted line marks the threshold of significance after Bonferroni correction. Grey shading marks the HEP significant time points obtained from the cluster permutation analyses on the ERP. **B.** Target effect on cardiac activity. Heart rate change in relation to the average interbeat interval for heartbeat previous (B-1) to noise modulated in amplitude (AmN) onset. B0, B1, and B2 are the first, second, and third heartbeats after stimulus onset. No differences in Δ IBI were found between B0, B1, B2, and B-1.

3.6.2 Respiration analysis

Using breathmetrics toolbox (Noto et al., 2018) implemented in MATLAB 9.7 (2019b) the interbreath interval (IBrI), breathing rate (BR), and the coefficient of variation of the breathing rate (CVBR), measured as the standard deviation of the difference between inhale onsets divided by the average difference between inhale onset, were obtained. To test for differences between each of these independent variables and attentional condition, linear-mixed models were carried with condition (heart - sound) as a fixed factor and subject as a random effect.

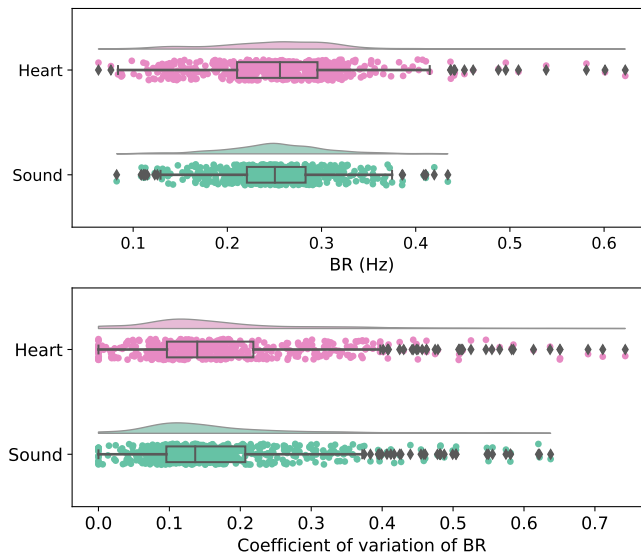


Figure 3.8: Attention effects on respiratory activity. Top: respiration frequency during heart-attention trials did not differ from sound-attention trials. Bottom: the coefficient of variation (standard deviation of the difference between inhale onsets over the average difference between inhale onsets) did not differ between attentional conditions.

3.6.3 Interoceptive and exteroceptive accuracy

Interoceptive accuracy (IAcc) was measured for each trial according to the following equation: $1 - \frac{|realheartbeats - countedheartbeats|}{realheartbeats}$. Values close to 1 indicate high similarity between reported heartbeats and actual heartbeats. Exteroceptive accuracy (EAcc) was defined as the percentage of AmN reported in relation to the total number of AmN presented across the entire experiment. The correlation between interoceptive and exteroceptive accuracy was evaluated using the Spearman correlation.

3.6.4 Power and intertrial coherence ERP

Time-frequency analyses were carried out on ERPs using the multitapers method to extract intertrial phase coherence (ITPC) and power in theta (1:4 Hz) and delta (4:8 Hz) for the heart time-locked epochs, and for 1:5 Hz for the SRepRN, with a 0.2 Hz resolution. The number of cycles used for each taper was set to two for the SRepRN analysis and to one for the HEP, with four as the time-half bandwidth of the multitapers. For the HEP power analysis decibel baseline conversion was carried on the subjects' average power using the interval -300:-150 ms relative to the R peak, and for ITPC the mean phase value of that interval was used as a baseline (Park et al., 2018).

3.6.5 Group-level EEG analysis

Cluster-based permutation analyses were used to assess differences between attentional conditions for the AmN, the HEP, RepRN, and the SRepRN. For the noise repetitions, comparisons between the brain response to the noise repetitions and to plain white noise during the same attentional condition were also carried out. The time points tested for the HEP were -0.1:0.6 s, for the AmN the entire epoch was evaluated, for the RepRN the time interval 0:0.5 s was analyzed and for the SRepRN the time window evaluated was -0.3:3 s. Differences between conditions for all channels in the specified time windows were analyzed as follows: i) subject average for sound attention trials is subtracted from the subject average for heart attention trials (or the subject average response to RepRN during sound/heart attention trials is subtracted from the subject average to plain white noise during sound/heart attention condition), ii) a one-sample t-test is performed on every sample, iii) t values that exceed a dependent samples t-test threshold corresponding to an alpha level (p-value) of 0.025 (two-tailed, number of observations = 20) are clustered according to temporal and spatial proximity. The adjacency matrix for a Biosemi 64 channel layout as defined in Fieldtrip was used and 1 was the maximum distance between samples to be considered temporally connected. iv) t values for each data point within each cluster are summed to obtain a summed t statistic per cluster (t_{sum}), v) 2000 permutations of the data are computed, and for each permutation, the cluster with the biggest-summed t statistic is kept to obtain a null hypothesis distribution, vi) the proportion of clusters from the null hypothesis with more extreme values than the cluster obtained from the observed data yields the p-value for a given cluster. For the AmN the critical alpha level was set to 0.01 to avoid one extreme cluster. The same analyses were carried out for power and phase obtained from the HEP (the time window evaluated was -0.3:0.6 s) by averaging over the delta, theta, and alpha frequency bands. Likewise, for the SRepRN we evaluated ITPC over the -0.3:3 s interval by averaging the ITPC values across 1:5 Hz. Cluster permutation analyses were conducted for subject-average periodic and aperiodic spectral components, complexity, and connectivity measures obtained from the non-overlapping 5 s epochs following the methods described below. The level of significance was established at $\alpha = 0.05$.

3.6.6 Aperiodic and oscillatory dynamics

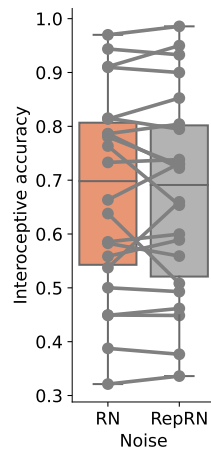
The FOOOF 1.0 library ([Donoghue et al., 2020](#)) was used to model the subject-average power spectrums for the frequency range 1:30 Hz to properly characterize the ongoing rhythmic and aperiodic activity during both attentional conditions. Model fitting was performed with the following parameters: aperiodic mode was set to 'fixed', peak width limits = [1,5], the maximum number of peaks = 4, peak threshold = 1.5, minimum peak height = 0.05. The overall average power spectrum showed peaks on the theta (4:8 Hz), alpha (8:14), and beta range (14:25 Hz). Therefore, for each model, we extracted the center frequency (CF), aperiodic-adjusted power (APW), and bandwidth (BW) for those oscillatory components. If for a given fit no oscillatory component was found, it was replaced with zero.

3.6.7 Spectral, complexity, and connectivity features

PE ([Bandt et al., 2002](#)) quantifies the irregularity of the signal in each channel by examining the distribution of ordinal patterns within the data after transforming the EEG signal into symbolic representations. KC is another measure of complexity that assesses the predictability of the sensor signal by quantifying its compressibility. Finally, wSML ([King et al., 2013](#)) estimates the connectivity between channel pairs by transforming the signal following the method for PE and computing the joint probability of the symbols in the signal. To avoid a disproportion between the number of observations and the number of features, for the wSML classifier, we used only 32 channels in a 1020 configuration (496 features). These markers were obtained using the nice python library ([Engemann et al., 2018](#)), and PE and wSML were evaluated in the theta band which has been shown to provide a more accurate classification of patients and is the frequency band linked to the HEP generator ([Park et al., 2018](#)).

3.6.8 Correlation between HEP amplitude and interoceptive accuracy

For each subject, the average voltage across channels and time points for each cluster resulting from the group analysis was correlated with their interoceptive accuracy using Spearman correlation. No correlation was found for the posterior cluster ($\rho(18) = 0.13$, p -value = 0.58) ([SFigure 3.10A](#)) nor for the anterior cluster ($\rho(18) = -0.03$,



SFigure 3.9: Noise repetitions and interoceptive accuracy. Mean interoceptive accuracy for each participant during trials with plain white noise RN and trials with embedded noise repetitions (RepRN).

p-value = 0.89) (SFigure 3.10B).

3.6.9 Adaptation for unresponsive patients

Modifications were introduced to the original experiment to render the task more adequate for patients. The trial length was reduced to 18 seconds and delivered to patients in blocks of 28 trials separated by 2 min pauses. Each block was composed of 14 trials of heart-directed attention and 14 trials of sound-directed attention. Trial presentation was randomized within each block and a jitter of 1.5-2 s was introduced between trials. The AmN was 450 ms long and could appear between 1 and 3 times per trial, and the same 4 noise seeds were presented during both types of trials. Instructions were recorded in French and Italian and the task was presented via a custom-built Arduino stimulation box that sends the audio through Etymotic ER3C earphones and event markers directly to the amplifier. No report was asked after each trial and therefore no interoception or exteroception accuracies were computed. Paris patients were recorded with EGI 256 channels HydroCel GSN net and ECG activity was recorded using the PIB box. Signals were acquired with a Net Amps 300 EEG Amplifier from Electrical Geodesics, Inc, digitized at 256Hz. In Milan, patients were recorded with a 64-channel BrainAmp DC amplifier (Brain Products) including 60 EEG channels and 2 bipolar derivations for the ECG and EOG activity (sampling rate 1000Hz, low cutoff 0.1 Hz, high cutoff 250 Hz). EEG processing differed in the following steps. ICA was performed on 1:30 Hz filtered data to remove movement and ocular artifacts. Component rejection was carried out

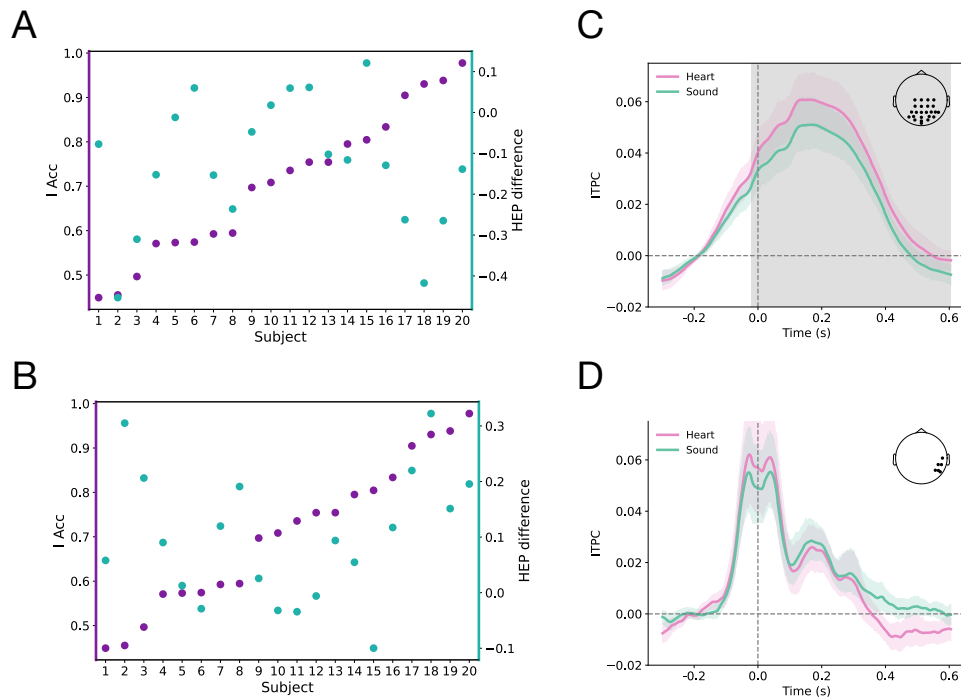


Figure 3.10: Correlation between mean amplitude for the time points and electrodes in the group level significant clusters for each subject and the mean interoceptive accuracy across the task. **A.** Mean amplitude for the time points and electrodes in the group level significant posterior cluster. **B.** Mean amplitude for the time points and electrodes in the group-level significant anterior cluster. **C.** Inter-trial phase coherence in the delta band for the heartbeat-evoked potential during attention to the heart (pink) and attention to the sound (green). Grey shading marks the temporal span of the significant cluster ($t_{sum} = 7480$, p-value < 0.001 , time = -25:600 ms) and black dots indicate channels in clusters. **D.** Inter-trial phase coherence in the theta band for the heartbeat-evoked potential during attention to the heart (pink) and attention to the sound (green). Grey shading marks the temporal span of the significant cluster ($t_{sum} = -1381$, p-value = 0.049, time = 344:600 ms) and black dots indicate channels in clusters. The ERPs shown are the average voltage across channels for each cluster with a 95% bootstrap confidence interval.

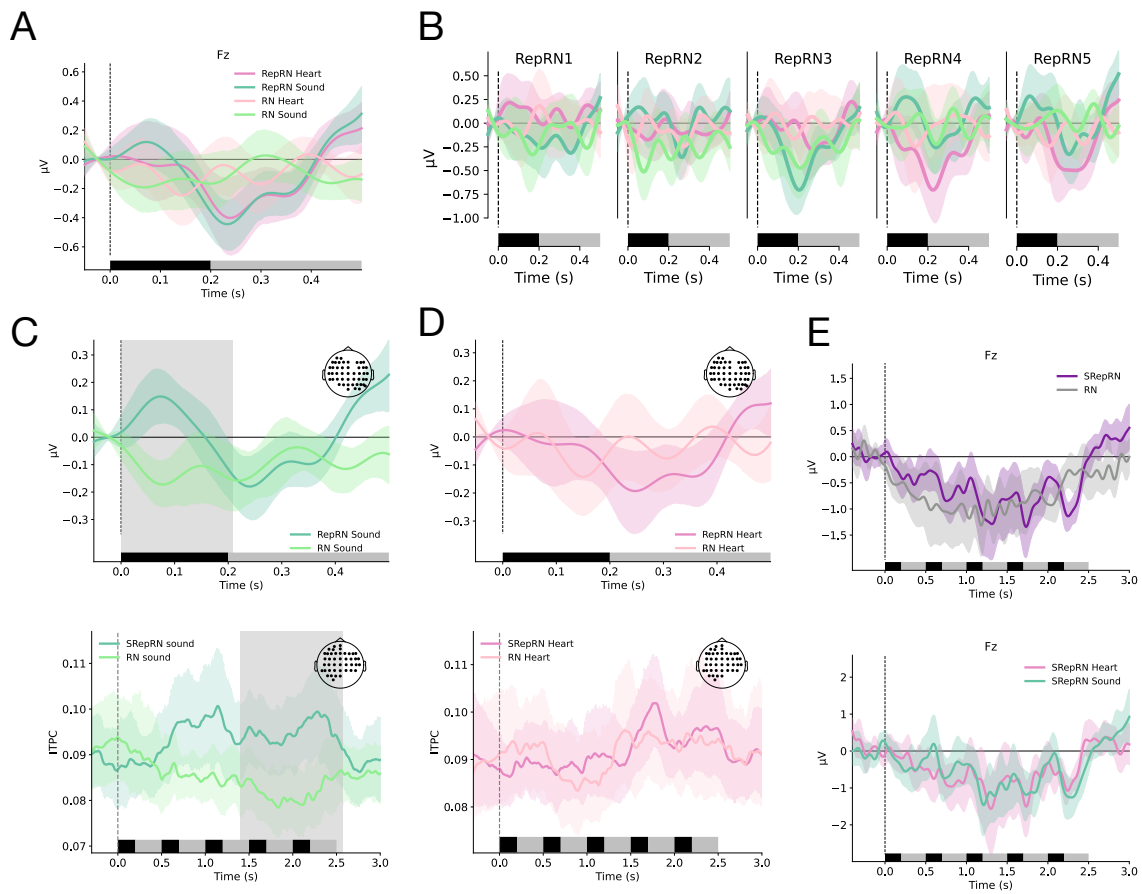


Figure 3.11: Noise repetitions are better encoded during sound attention trials. **A.** Average brain response for all noise repetitions (RepRN) for Fz electrode. **B.** Average brain response for each of the five repetitions comprising the structured repetition (SRepRN) across channels shown in C. **C.** Top. Average response across channels that form the significant cluster for the difference between RepRN-Sound and RN-Sound. Bottom. Average inter-trial phase coherence in the delta band for RepRN-Sound and RN-Sound. Grey shading marks the temporal span of clusters and black dots indicate channels in clusters. The ERPs shown are the average voltage across channels for each cluster with a 95% bootstrap confidence interval. **D.** Top. Average response across the same channels as in C but for RepRN-Heart and RN-Heart. Bottom. Average inter-trial phase coherence in the delta band for the same channels as in C for RepRNHeart and RN-Heart conditions. **E.** Top. Average brain response for the structured repetition (SRepRN-Heart and SRepRN-Sound) in purple and for segments of random noise (RN-Heart, RN-Sound) in grey for Fz electrode. Bottom. Average brain response for the structured repetition during attention to sound in green (SRepRN-Sound) and during attention to heart in pink (SRepRN-Heart) for Fz electrode. RepRN-Heart: random noise seeds presented during heart attention, RepRN-Sound: random noise seeds presented during sound attention, RN-Heart: plain white noise during heart attention trials, RN-Sound: plain white noise during sound attention trials.

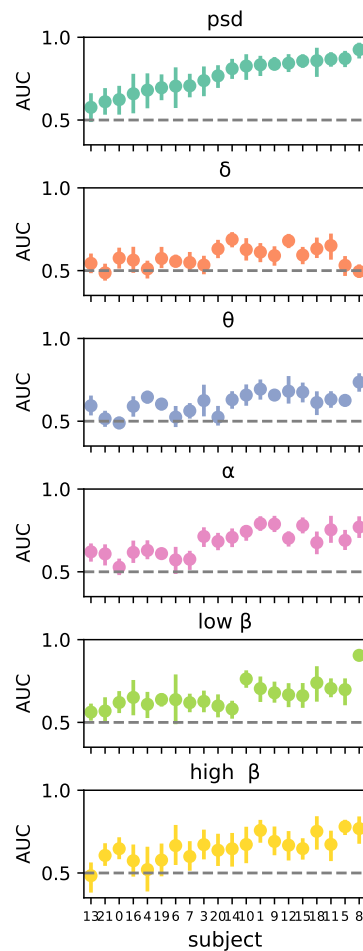


Figure 3.12: Power band-specific classifiers. Subject-level classifiers for each frequency band (delta, theta, alpha, low-beta, and high-beta). **A.** Average receiver operating characteristic curves across cross-validation folds and subjects. PSD: 0.75 ± 0.10 , delta: 0.57 ± 0.06 , theta: 0.60 ± 0.06 , alpha: 0.67 ± 0.08 , low-beta: 0.65 ± 0.07 , high-beta: 0.64 ± 0.07 . **B.** Average AUC across folds with 95% bootstrap confidence interval for each subject and classifier. Subjects are sorted considering the AUC for the classifier with all the frequency features (PSD).

on data filtered between 0.1:30 Hz before obtaining epochs for the HEP and the sub-epochs for classifier purposes. Each 18 s epoch was segmented into five 4 s epochs with an overlap of 3 s. ICA was performed on 1:7 Hz filtered data and the components were rejected from data filtered between 0.1:15 Hz, before epoching to obtain AmN (-0.1:0.9 s). Finally, data was combined into a 64-channel Biosemi layout configuration. For the classifiers involving the HEP, the canonical cluster obtained from the healthy participants' group analysis was used to select the features. Each classifier for each patient was run 100 times and the mean value across runs was compared to 1000 runs of surrogate classifiers. Finally, patient differences in the HEP were evaluated by averaging the EEG response to heartbeats across electrodes in the canonical clusters obtained for healthy participants. The averaged response was subjected to a point-by-point one-way ANOVA for time points -0.1:0.5 s, and Bonferroni corrected for multiple comparisons.

Code	Age at injury	Sex	Injury type	Days since injury	CRS-R						Total	Diagnosis
					Au	V	M	OM	C	Ar		
P1	61	M	Hypoglycemia	14	0	0	0	0	0	1	1	VS/UWS
P2	40	M	CA	48	2	1	2	1	0	1	7	VS/UWS
P3	22	F	Encephalitis	43	1	1	1	1	0	0	4	VS/UWS
P4	38	F	Brainstem stroke	34	4	5	2	1	1	2	15	LIS
M1	50	M	TBI	238	1	4	2	1	0	2	10	MCS-

Table 3.1: Notes: P: patients assessed in Paris center, M: patients assessed in Milan center, CA: cardiac arrest, TBI: traumatic brain injury, Au: auditory functions, V: visual functions, M: motor functions, OM: oromotor/verbal functions, C: communication scale, Ar: arousal scale, VS/UWS: vegetative state/unresponsive wakefulness syndrome, LIS: locked-in syndrome, MCS-: minimally conscious state minus

Chapter 4

What drives intersubject correlation of EEG during conscious processing of narrative stimuli?

What drives intersubject correlation of EEG during conscious processing of narrative stimuli?

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4.1 Abstract

When participants are engaged with narrative stimuli, physiological and neural signals show a temporal correlation between subjects. Narrative stimuli allow probing of the brain in a naturalistic setting. Recent clinical work shows that patients with disorders of consciousness (DoC) exposed to narratives produced EEG evoked responses similar to healthy controls. Here we ask if the intersubject correlation (ISC) is driven by low-level acoustic or higher-level linguistic information, which may serve to assess residual language capabilities in DoC patients. In this study, we combine temporal response functions (TRFs) for acoustic and linguistic features, as well as correlated component analysis (CorrCA) to assess how much each feature contributes to the ISC in two groups of healthy participants. TRFs obtained for acoustic features resulted in higher predicted accuracy than linguistic features and were the main contributors to the ISC. The increase in ISC commonly observed with increased attention was driven by all features. Word unpredictability had a specific effect on the second correlated component, with timing and scalp distribution that is consistent with language processing. Notably, the linear responses captured by TRFs only explained a small amount of the overall ISC, suggesting that ISC is largely driven by nonlinear responses to the narratives. Based on these results, we offer some recommendations on how to practically assess language processing in DoC patients with these tools.

4.2 Introduction

When participants are exposed to common narrative stimuli heart rate, pupil size, and neural activity show a temporal correlation between subjects ([Hasson et al., 2004](#); [Madsen et al., 2022](#); [Naci et al., 2014](#); [Pérez et al., 2021](#); [Türker, Belloli, et al., 2023](#); [Wilson et al., 2008](#)). In EEG recordings, this intersubject correlation (ISC) is increased when attention is directed to the stories ([Ki et al., 2016](#); [Rosenkranz et al., 2021](#)) and is diminished during stimuli repetition ([Dmochowski et al., 2012](#)), suggesting that the source of covariation in brain and bodily signals arises from a similar processing of narratives. The synchronization of brain activity in EEG is best measured using correlated component analysis (CorrCA), a statistical procedure that reduces the dimensions of EEG data from electrodes to a subset of components that maximize the correlation of the evoked responses across all subject pairs ([Parra et al., 2019](#)).

It has been suggested that the obtained ISC components reflect sensory processing (Cohen et al., 2016; Poulsen et al., 2017), memory retention (Cohen et al., 2016), meaning integration (Ki et al., 2016), and overall engagement (Cohen et al., 2016; Dmochowski et al., 2012; Poulsen et al., 2017). Nevertheless, to our knowledge, no study has explored the contribution of specific features of the speech stimuli to the ISC, nor how contextual demands modulate their effects. Whether ISC is driven by basic acoustic stimulus features or language processing is important to interpret some recent clinical results. Two studies have assessed EEG responses of patients with disorders of consciousness (DoC) when exposed to narratives, showing that some, but not all, patients present brain activity patterns correlated to the evoked responses of healthy controls (Laforge et al., 2020). In addition, ISC is generally decreased in these patients and the strength of the ISC differs during forward and backward speech (lotzov et al., 2017), a phenomenon that may relate to the clinical diagnosis. Understanding which speech properties elicit these common brain responses is crucial to understand what language capabilities, including conscious comprehension, are retained by a DoC patient who exhibits ISC.

Speech is a complex natural stimulus for which humans are specially tuned to parse and comprehend. The brain processes involved in understanding speech are likely shared among individuals, and could be driving the observed common neural responses to auditory narratives. Speech is a continuous signal with a hierarchical structure such that sentences can be decomposed into words, words into phonemes, and phonemes into moment-to-moment spectral variations. This hierarchy is reflected in the spatial and temporal unfolding of speech processing in the brain (de Heer et al., 2017; Hickok et al., 2007; Lerner et al., 2011). Speech comprehension is the result of our brains decoding these different levels of information intertwined in the continuous signal. Linear encoding models (Holdgraf et al., 2017) can be used to study the relationship between multiple embedded levels of information in complex naturalistic stimuli and neural activity. In our case, properties of the speech signal can be extracted from the stimulus to train a model on a given feature or set of features. Then, a stimulus-response function is obtained that can be used to predict the neural response for a new stimulus. Here we use temporal response functions (TRFs) (Crosse et al., 2016; Ding et al., 2012), linear encoding models that take into account the delays in neural processing. TRFs quantify the linear dependency between neural activity and a speech feature, which can

be interpreted as a measure of how well the evoked neural response is time-locked to the speech feature (Brodbeck et al., 2020). This method demonstrates a temporal locking of EEG to the acoustic features of speech such as the envelope (Prinsloo et al., 2022), the spectrogram (Di Liberto et al., 2015; Ding et al., 2012), the spectral information of individual phonemes (Daube et al., 2019), and phoneme categories (Di Liberto et al., 2017; Di Liberto et al., 2015; Teoh et al., 2022). In addition, TRFs are sensitive to linguistic features such as the semantic dissimilarity of a word relative to the previous context (Broderick et al., 2018; Broderick et al., 2019; Broderick et al., 2022), word segmentation (Gillis et al., 2021), and lexical properties (Gillis et al., 2021). Directing attention to speech enhances the responses to these features, suggesting a stronger tracking of the features when participants are engaged with the stimuli (Broderick et al., 2018; O’Sullivan et al., 2015; Power et al., 2012; Teoh et al., 2022). Importantly, responses to linguistic features show a stronger correlation to speech comprehension than acoustic information (Shyanthony R. Synigal et al., 2023).

In this study, we use univariate and multivariate TRFs and correlated component analysis to investigate the contributions of low-level acoustic information and higher linguistic features to the intersubject correlation elicited during passive listening, as well as during directed and undirected attention to narrative stories in healthy participants. Finally, we discuss the potential of combining these tools to assess language processing and awareness in non-communicative patients and provide some methodological suggestions for a successful implementation.

4.3 Materials and methods

4.3.1 Experiment 1: passive listening of auditory narratives

Participants

Twenty-seven native English speakers (22 females, age range 18-26, median 21 years old) participated in this study. The experiment was conducted at the Centre for Human Brain Health, University of Birmingham, England, and was approved by the STEM ethics committee of the University of Birmingham, England. All subjects provided written informed consent.

Stimuli and procedure

The participants listened to a 16-minute extract of an audiobook (20,000 Leagues Under the Sea. Author: Jules Verne. Read by: David Linski. Public Domain (P) 2017 Blackstone Audio, Inc.). The audiobook extract was taken from the first chapter and half of the second chapter. The story was presented in segments of 1 minute each, yielding 16 trials. The instructions given to the subject were 'to listen to the story and look at a fixation cross'. The stimuli were delivered by headphones - ER1 Insert Earphones (Etymotic Research), using Psychopy v3.1.2 (Peirce, 2007).

Recording and preprocessing

EEG was recorded with 128 channels with a Brainvision amplifier with a sampling frequency of 250 Hz referenced to CPz. Heart activity was also recorded and results have been already published (Pérez et al., 2021). Data was filtered between 0.1 and 40 Hz with a bandpass filter (one-pass zero-phase FIR filter with a length of 8251 samples). Channels were rejected if their variance was above 3.5 standard deviations from the mean channel variance, this was iteratively performed 4 times. ICA was performed to remove ocular artifacts, bad channels were interpolated, and data was segmented into 16 trials. Sparse artifact removal (De Cheveigné, 2016) was carried out using the meegkit library (<https://github.com/nbara/python-meegkit>). Finally, EEG channels were combined into a 64-channel Biosemi layout configuration to be comparable to 'Experiment 2'. For EEG preprocessing MNE 1.0.3 (Gramfort, 2013) was used.

4.3.2 Experiment 2: attended and unattended listening of auditory narratives

Participants

Thirty-two native English speakers took part in the experiment (16 Female, age 19-36, mean = 23.69, sd = 4.42; 3 subjects were removed due bad signal quality or issues during stimuli presentation and 3 other subjects were removed for not completing the task). Experiments were carried out at the City College of New York with the approval of the Institutional Review Boards of the City University of New York. All subjects provided written informed consent before the experiment.

Stimuli and procedure

The stories consisted of 10 narratives selected from the StoryCorps project aired on National Public Radio (NPR) (“Eyes on the Stars”, “John and Joe”, “Marking the Distance”, “Sundays at Rocco’s” and “To R.P. Salazar with Love”) and the New York Times Modern Love series (“Broken Heart Doctor”, “Don’t Let it Snow”, “Falling in Love at 71”, “Lost and Found”, and “The Matchmaker”). Each story was between 2-5 min and the total duration of the stimuli was 27 min. The stories were played through stereo speakers placed at 60 angles from the subject while facing a gray background in a 27” monitor placed at a distance of 60 cm from the participant. In the attentive condition, participants were asked to attend to the story while looking at the screen. In the unattentive condition participants listened to the stories again but they were asked to count backwards silently in their mind in steps of 7, starting from a random prime number between 800 and 1000.

Recording and preprocessing of EEG

Detailed preprocessing for this data set can be found in ([Madsen et al., 2024](#)). Briefly, EEG was recorded with 64 channels in a 10/10 configuration at a sampling frequency of 2048 Hz using a BioSemi Active Two system. In addition, the electrooculogram (EOG) was recorded with external electrodes placed at the left and right external ocular canti, and under and above the right eye. The signals were referenced online to the common mode sense (CMS; active electrode) and grounded to a passive electrode (Driven Right Leg, DRL). The signals were digitally high-pass filtered (0.01 Hz cutoff) and notch-filtered at 60 Hz to remove line noise. Signals were digitally low-pass filtered (64 Hz cutoff) and downsampled to 128 Hz. Bad electrodes were identified manually and replaced with interpolated channels. The EOG channels were used to remove eye-movement artifacts. Finally, data was epoched into the 10 stories and a 0.1:40 Hz bandpass filter was applied before referencing the data to the average of the 64 channels. For EEG preprocessing MNE 1.0.3 ([Gramfort, 2013](#)) was used.

4.3.3 Intersubject correlation

Correlated component analysis ([Cohen et al., 2016](#); [Dmochowski et al., 2012](#)) is a method to extract projections of the data with maximal correlation across signals, in

our case across the EEG-evoked response of participants when exposed to the same stimulus in a given context. For each trial, the cross-covariance is computed for each pair of electrodes and for each pair of subjects and is aggregated resulting in a between-subject cross-covariance matrix (R_b):

$$R_b = \frac{1}{N_s(N_s - 1)} \sum_{k=1}^{N_s} \sum_{l=1, l \neq k}^{N_s} R_{kl} \quad (4.1)$$

where R_b is a squared matrix with as many columns and rows as the number of channels, and (R_{kl}) is the cross-covariance between all electrodes of subject k and subject l with $N_s =$ number of subjects that heard the stimulus:

$$R_{kl} = \sum_t (x_k(t) - \bar{x}_k)(x_l(t) - \bar{x}_l)^T \quad (4.2)$$

$x_k(t)$ is a vector of voltage values for subject k at time t with $D =$ number of channels, and \bar{x}_k their mean value in time. The within-subject cross-covariance (R_w) is pooled following:

$$R_w = \frac{1}{N_s} \sum_{k=1}^{N_s} R_{kk} \quad (4.3)$$

where R_{kk} is the cross-covariance of all electrodes in subject k :

$$R_{kk} = \sum_t (x_k(t) - \bar{x}_k)(x_k(t) - \bar{x}_k)^T \quad (4.4)$$

The resulting matrices R_w and R_b are averaged over trials (all trials for experiment 1, and all trials including both conditions for experiment 2), and the eigenvectors (V_i) of the matrix $R_w^{-1}R_b$ are calculated as follows:

$$(R_w^{-1}R_b)V_i = \lambda_i V_i \quad (4.5)$$

The eigenvectors V_i with the strongest eigenvalues i define the dimensions that capture the largest correlation between subjects. Before computing the eigenvectors, the

covariance matrix R_w was regularized using a shrinkage parameter ($\gamma = 0.5$) to avoid bias estimation due to outliers (Blankertz et al., 2011).

Pearson correlation of evoked responses for a given participant to the rest of the group experiencing the same stimulus was obtained by projecting the data onto the component vectors V_i :

$$C_{ik} = \frac{V_i^T R_{bk} V_i}{V_i^T R_{wk} V_i} \quad (4.6)$$

where $R_{b,k}$ represents the between-subject covariance and $R_{w,k}$ the within-subject covariance for a given stimulus and condition, averaged across all pairs of subjects involving a given subject:

$$R_{b,k} = \frac{1}{N-1} \sum_{l,l \neq k} (R_{kl} + R_{lk}) \quad (4.7)$$

$$R_{w,k} = \frac{1}{N-1} \sum_{l,l \neq k} (R_{kk} + R_{ll}) \quad (4.8)$$

Finally, the individual intersubject correlation ISC_k for each component and condition was obtained by averaging the correlation values for all trials t during the same experimental condition:

$$ISC_k = \frac{1}{N_t} \sum_t C_{tk} \quad (4.9)$$

Here, we only report the correlation values for the first three components that show values significantly different from zero (indeed, for component three the correlations for most participants are not statistically different from chance) (Figure 4.3). To see the contributions of each electrode to the components we compute a forward model (Haufe et al., 2014; Parra et al., 2005) defined as:

$$A = \frac{R_b V}{V^T R_b V} \quad (4.10)$$

The ISC was computed using Matlab R2021a and modifying custom scripts available at <http://www.parralab.org/isc/>

4.3.4 Speech features extraction

The broadband envelope (E) was obtained for each speech stimulus using the function `mTRFenvelope` of the mTRF-Toolbox (Crosse et al., 2016) that computes the root-mean-square over a window of samples scaling the output logarithmically. The envelope was computed for a 50 Hz sample rate for experiment 1 and 64 Hz for experiment 2. To model human hearing, the signal was compressed by raising the value to 0.3 (Biesmans et al., 2017; Crosse et al., 2021). The spectrogram (S) was obtained by filtering the stimuli into 16 bands between 250 Hz and 8 kHz, and computing the envelope for each band as the absolute value of the complex analytical signal given by the sum of the original signal and its Hilbert transform, resulting in a logarithmically scaled Mel-spectrogram (Schädler et al., 2015). Signals were resampled following the envelope computation. To obtain word onsets, audio files were transcribed using Whisper (<https://openai.com/research/whisper>), manually corrected, and forced aligned to the speech signals using Montreal Forced Aligner 2.0 (McAuliffe et al., 2017). Word onset (WO) was coded as a binary array with value one whenever the onset of a word occurred. The BERT language model pre-trained with RoBERTa base corpus (Liu et al., 2019) was used to obtain predictability values for each word. For experiment 1, the context was determined by the 420 previous words considering the entire 16 minutes of stimulus. For experiment 2, the 350 previous words of each story were used as context. Word unpredictability (WU) was defined as $-\log_2(\rho)$, where ρ is the probability of the word given by the model. (Figure 4.1A). We define this feature as word unpredictability as not only semantic information defines the probability of a given word but also its syntactic surroundings, and any other information captured by the language models. Finally, to test the validity of our WU representations in experiment 2, a randomized WU vector was constructed (WUr) by permuting the unpredictability values across words within stories. Segments of music at the beginning and end of stimulus in experiment 2, and the corresponding EEG data, were not used for the analyses.

4.3.5 Temporal response functions (TRFs)

A linear forward modeling approach was used to predict the EEG response given each speech representation or a combination of multiple representations using the mTRF-Toolbox (Crosse et al., 2016). Each EEG channel response was estimated as a linear convolution of the speech representations over a range of time lags relative to stimulus

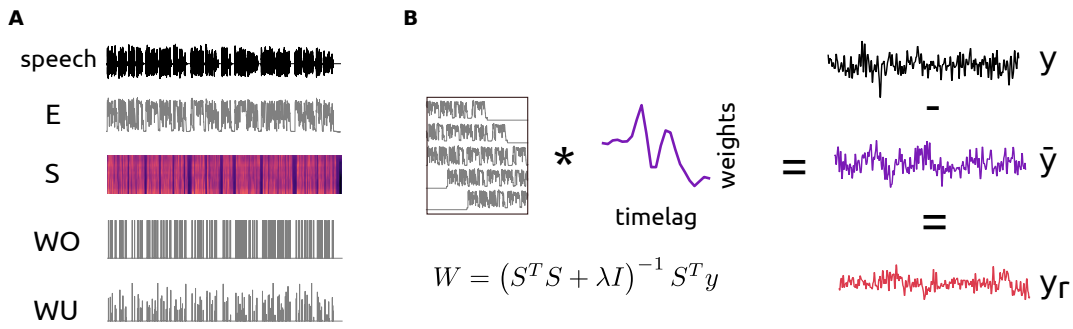


Figure 4.1: Temporal response functions and speech features. **A.** Representation of the features extracted from the speech signal. E - envelope, S - spectrogram, WO - word onset, WU - word unpredictability. **B.** Temporal response functions (TRFs) were estimated using regularized linear regression from time-lagged copies of each feature (S), as represented by the envelope in this example. The TRFs predicted responses (\bar{y}) were obtained for each trial and feature. The predictions were subtracted from the actual EEG response and the residual activity (y_r) was obtained.

onset as follows

$$\bar{y}(t, n) = \sum_{\tau} W(\tau, n) s(t - \tau) + \epsilon(t, n) \quad (4.11)$$

where $\bar{y}(t, n)$ is the neural response in the channel n for time t , $s(t - \tau)$ is the stimulus representation for lag τ , $w(\tau, n)$ is the transformation at that lag, and (t, n) the activity not explained by the model. s can be a single speech feature or multiple speech features, yielding univariate or multivariate models respectively. Fitting the linear models corresponds to finding a set of weights w that minimize the mean squared error between the original response y and the one predicted by the model \bar{y} . The set of weights that relate the stimulus and the response is referred to as temporal response function (TRF) and can be estimated using ridge regression

$$W = (S^T S + \lambda I)^{-1} S^T y \quad (4.12)$$

where λ is the ridge regression parameter used to avoid overfitting, I is the identity matrix, and S is the time-lagged stimulus representation (Figure 4.1B). Subject-level models were estimated following a leave-one-out nested cross-validation approach to select the ridge parameter and to evaluate the prediction accuracy of the models. For

each subject, we iteratively selected one trial to test the TRF, and used the remaining trials to carry a leave-one-out cross-validation to obtain the ridge parameter across channels and folds that maximized the correlation between y and \bar{y} . The $n-1$ trials that took part in the cross-validation were used to train the model with the optimal lambda, and the model was tested on the left-out trial (SFigure 4.7). This iterative process yielded one Pearson correlation coefficient per trial and subject given by the average correlation across channels. The cross-validation was performed across regularization values in the range $10^{-6} : 10^6$. The time lags used to train the model during cross-validation were -100:800 ms and the final lags for model training and testing were restricted to -50:750 ms (Crosse et al., 2021). For experiment 1 the number of trials was 16, for experiment 2 each story was split into two segments to increase the number of folds. The resulting TRF weights are dependent on the λ selected, therefore in order to compare TRF weights across conditions in experiment 2, the mode of the optimal lambdas across channels and subjects was selected, and the subject-level models for the WU, WO, and WUr were recomputed with this ridge value. In addition, multivariate models were constructed with combinations of E, S, WO, and WU, to assess language processing beyond acoustics and word segmentation. The predicted response for each model was subtracted from the EEG and ISC was recomputed on the residual EEG.

4.3.6 Statistical analyses

Chance level ISC values were determined by computing the ISC on 1000 renditions of surrogate data obtained by circularly shifting the data for each subject and trial. ISC significance was corrected for multiple comparisons while controlling the false discovery rate (FDR) (Benjamini et al., 1995). Correlations between ISC and TRF accuracy across subjects were assessed through Pearson correlations. The group analyses of the TRF weights obtained with the common ridge parameter were carried out using a cluster permutation approach. Specifically, we implemented a one-way paired samples t-test using a cluster-level statistical permutation test on the TRFs for time points 0.3:0.7 s as we expected TRFs for WO and WU to show more negative values during the canonical N400 during attention to the stories. The t-test threshold corresponding to an α value of 0.05 was used (number of observations = 26), and samples exceeding this threshold were clustered according to temporal and spatial proximity using the adjacency matrix defined in Fieldtrip for a Biosemi 64 montage. The t-values in each cluster (t_{sum}) are

summed and compared to a distribution of clusters obtained from 2000 repetitions of the analysis with the condition labels randomly swapped. The proportion of clusters from the null distribution with more extreme values than the cluster obtained from the empirical data yielded the p-value for a given cluster. The level of significance was established at $\alpha = 0.05$. To assess the accuracy of the models and the ISC between and within attentional conditions we used two-sided Wilcoxon signed-rank tests. We report the mean values for ISC and model accuracies and the p-values yielded were FDR-corrected. Statistical analyses were conducted in R ([Team RStudio, 2022](#)).

4.4 Results

In the first experiment, we sought to determine which are the features of speech that drive the intersubject correlation observed when participants listen passively to narratives. For this, 16 minutes of an audiobook were presented to participants and encoding models for acoustic properties - envelope and spectrogram -, and linguistic features - word onset and word unpredictability - were obtained for each subject. The intersubject correlation was computed employing correlated components analysis for the original data and after removing the predicted responses for each of the encoding models. In addition, multivariate models were constructed to account for the correlation across features. In a second experiment, we tested the effects of attention on the ISC and whether conscious processing of a set of narratives has a distinctive effect on the acoustic and linguistic contributions by following the same methodological approach as in experiment 1.

4.4.1 Intersubject correlation is elicited during passive listening of narratives

The evoked brain responses of participants during passive listening showed a correlation to the group as indexed by the three strongest correlated components, and the forward model of the components follows the distribution reported in previous studies ([Cohen et al., 2016](#); [Rosenkranz et al., 2021](#)) ([Figure 4.2A](#)). ISC was above chance for all subjects for the first two components, nevertheless for the third component the ISC values were very small, and after FDR correction for half of the participants, it was not different from chance ([Figure 4.3](#)). Considering this, we focused the following analyses

on the first two components.

4.4.2 Acoustic and linguistic information drive the ISC during passive story listening

Univariate models for acoustic features showed better predictions than word onset and word unpredictability (mean r : $E = 4.89e-2$, $S = 4.71e-2$, $WU = 3.44e-2$, $WO = 3.00e-2$. See [Table 4.1](#) for comparisons) ([Figure 4.2B](#)). In addition, the word unpredictability models were more accurate than the word onset models ($W = 31$, $p = 7.04e-5$), and no differences were found in prediction accuracy between the spectrogram and envelope models ($W = 138$, $p = 0.229$). A strong correlation was observed between the ISC values for components 1 and 2 and the prediction accuracies for the univariate models ([Figure 4.3](#)). Moreover, the ISC for component 1 and component 2 were significantly reduced when subtracting the predictions of each univariate model ([Figure 4.4A](#), [Table 4.2](#), [Table 4.3](#)). In addition, the ISC without either acoustic contribution was smaller than the ISC after the removal of WO or WU contributions ([Figure 4.4A](#), [Table 4.2](#), [Table 4.3](#)). All features are correlated, which renders the predictions of our encoding models also very correlated. To account for this and to determine the incremental effect of language features on ISC, we constructed multivariate models combining acoustic features with the WO and WU representations.

4.4.3 Word unpredictability contributes distinctively to the ISC during passive listening

We compared the prediction accuracies for encoding models obtained for the combination of acoustic and linguistic features. Although no mTRF predicted the EEG response significantly better than the rest ([SFigure 4.8](#)), the contributions of each model to the ISC were significantly different. The residual ISC for components 1 and 2, after subtracting the predicted responses of the ESWOWU, ESWO, ESWU, and ES models, were compared to each other and to the original ISC, and components 1 and 2 exhibited similar behaviors. A drop in ISC was produced when accounting for the acoustic information, and incorporating WO to the model yielded a further decrease in ISC. Importantly, models including WU resulted in the greatest decrease in ISC ([Table 4.4](#), [Table 4.5](#), [Figure 4.4B](#)).

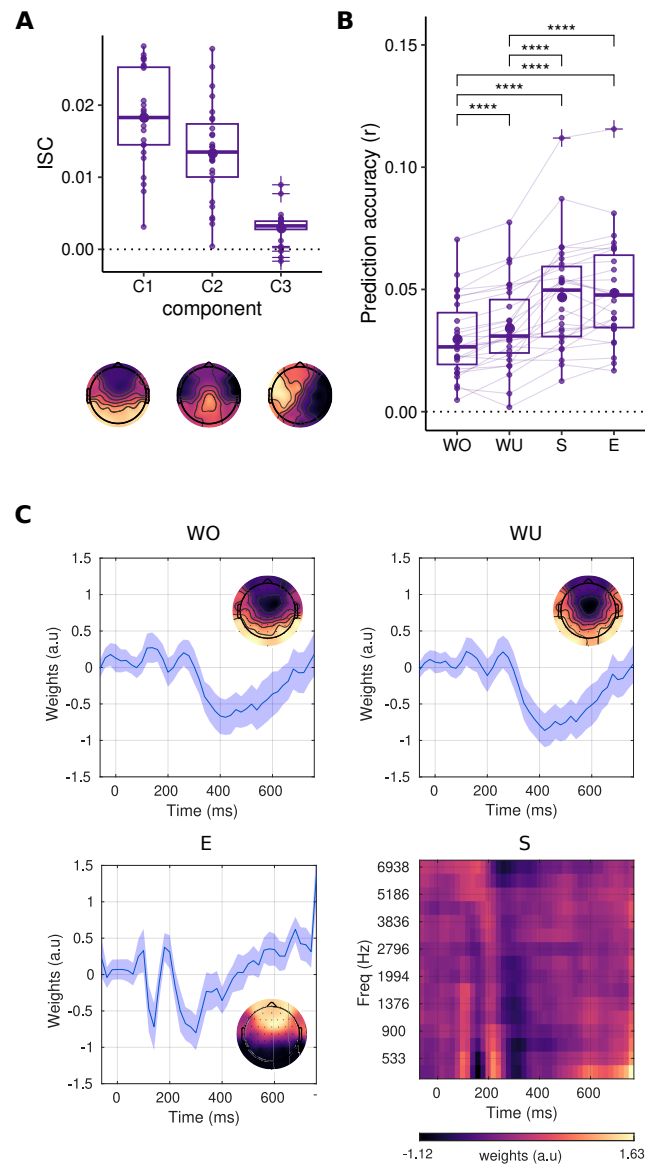


Figure 4.2: Intersubject correlation and encoding models during passive listening. **A.** Top. ISC values for the first three strongest components. Bottom. Forward model for the components capturing its correlation with each electrode. **B.** Prediction accuracy for each univariate model and subject obtained as the correlation between the predictions and the actual EEG response (WO: word onset, WU: word unpredictability, S: spectrogram, E: envelope), Two-tailed Wilcoxon signed-rank test, (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$, and (****) $p < 0.0001$, FDR corrected. **C.** Univariate TRF weights normalized and averaged across subjects for Cz. The inset topographies shown correspond to the 440:480 ms time window for the WO and WU models, and 80:100 for the E model.

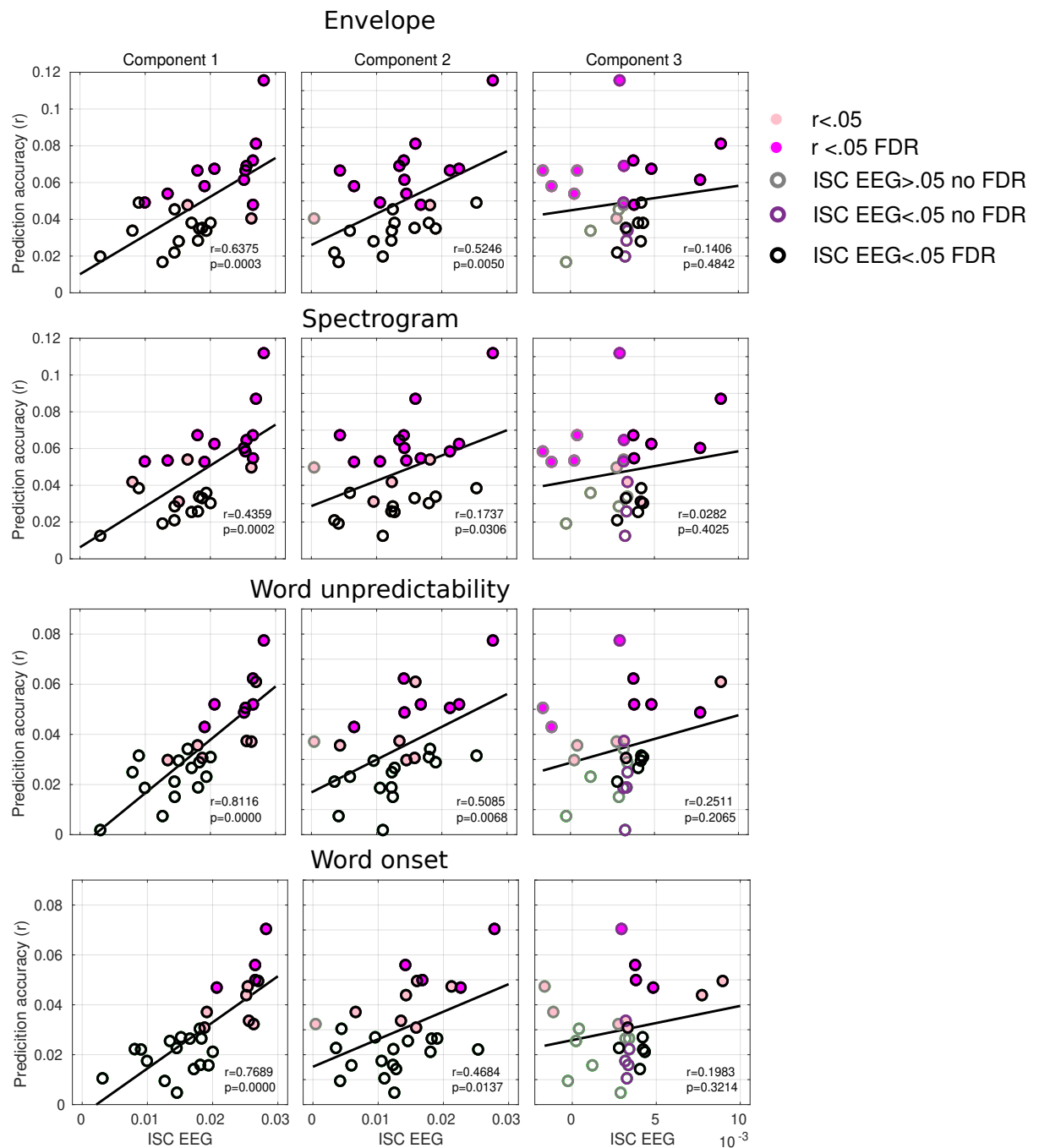


Figure 4.3: Correlation between ISC and univariate TRFs. Correlation between the components that show the highest intersubject correlation (components 1, 2, and 3) and the average prediction accuracy for the univariate TRFs. Each point corresponds to a participant. Color edges indicate statistical significance for ISC: black edge denotes significant ISC EEG ($p < 0.05$, FDR, 0.05 corrected), purple edge indicates significant values before FDR correction ($p < 0.05$, no FDR) and grey edges indicate non-significant values. Color fill indicates TRF statistical significance: dark pink marks a significant correlation between real and predicted EEG signal ($p < 0.05$, FDR corrected), light pink denotes $p < 0.05$ without FDR correction, and no fill denotes $p > 0.05$.

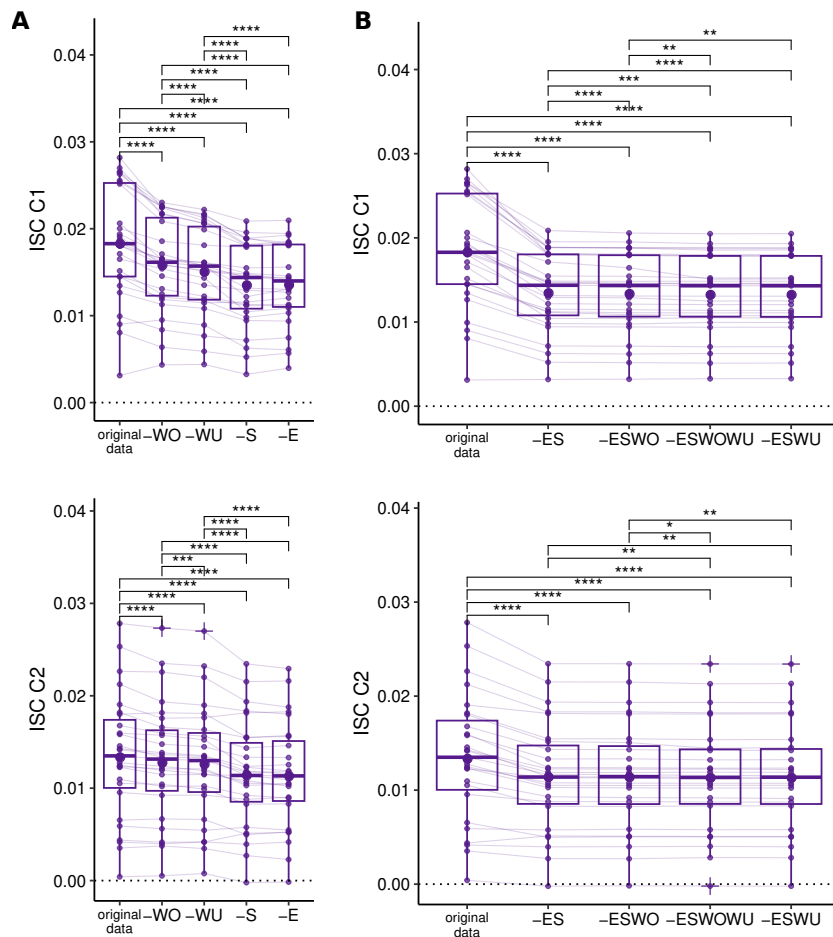


Figure 4.4: Speech features contribute to intersubject correlation. **A.** ISC computed over EEG residuals after subtracting the predicted activity of each univariate model. -E: without envelope TRF prediction, -S: without spectrogram TRF prediction, -WO: without word onset TRF prediction, -WU: without word unpredictability prediction. **B.** Same as A but for multivariate models. -ES: without the envelope and spectrogram mTRF prediction, -ESWO: without the envelope, spectrogram and word onset mTRF prediction, -ESWU: without envelope, spectrogram and word unpredictability mTRF prediction, -ESWOWU: without envelope, spectrogram, word onset and word unpredictability mTRF prediction. Top: ISC for component 1. Bottom: ISC for component 2. Two-tailed Wilcoxon signed-rank test, (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$, and (****) $p < 0.0001$, FDR corrected.

4.4.4 Intersubject correlation and speech tracking are positively modulated by attention

We compared the ISC during attentive listening, and while participants heard the same stories but had to complete a counting task simultaneously. ISC for the first three CorrCA components was reduced during the unattended condition (counting) (Figure 4.5A, Table 4.6). The prediction accuracy for each univariate model was higher during attention to the stories than during the unattended condition (Figure 4.5B, SFigure 4.10, Table 4.7). The models for acoustic features had a better performance than the word onset and word unpredictability encoding models independently of the attentional condition (Figure 4.5B, Table 4.8). Surprisingly, the prediction accuracies for the word unpredictability encoding models were better than for word onset when participants both attended and ignored the stories (Figure 4.5B, Table 4.8).

4.4.5 Acoustic and linguistic information contribute to the ISC for both attended and unattended stimuli

The predicted EEG by each univariate encoding model was individually subtracted from the original brain activity and the ISC was recomputed. The residual correlated components when projected to the 64-channel space had the same topographic distribution as the original data (SFigure 4.9). For the first component, the predicted activity of all univariate models contributed to the ISC independently of the attentional condition (Figure 4.5C). The drop in ISC for each feature subtraction followed the prediction accuracies of the models, such that subtracting the predictions of the acoustic feature models resulted in a lower ISC than for the WO and WU models (Figure 4.5C, Table 4.9). In contrast, the ISC for the second component was not significantly affected by removing the evoked activity predicted by the acoustic models, and a distinct behavior for the WO and WU models was observed according to the attentional condition. For the unattended condition, only the WO predicted activity contributed to the ISC (Figure 4.5C, Table 4.10), whereas when participants were engaged with the stories both features had a contribution to the second component, with a bigger decline in ISC when removing the WU evoked activity compared to the one predicted by the WO (Figure 4.5C, Table 4.10).

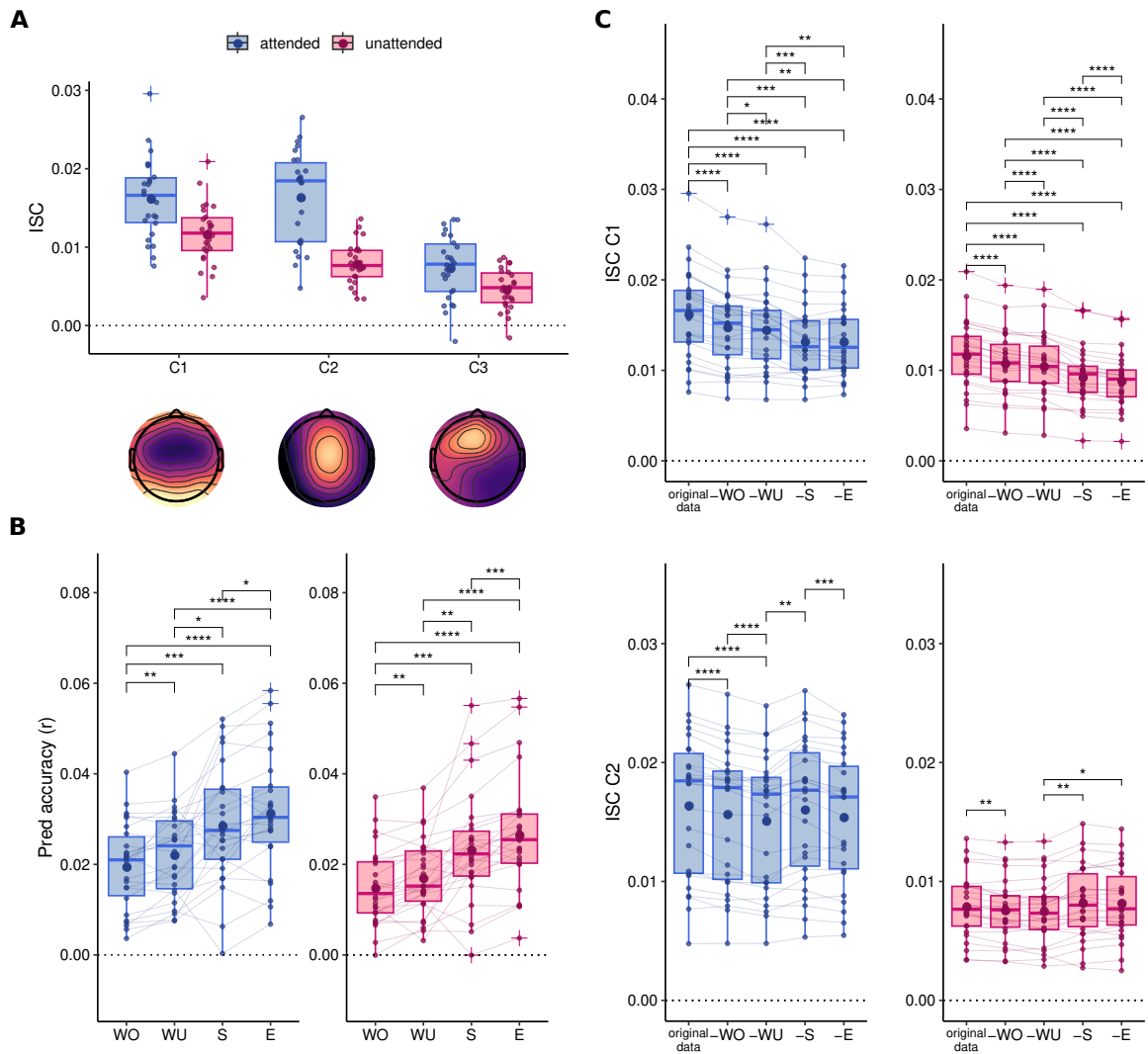


Figure 4.5: Speech features contribute to the intersubject correlation while attending and not attending to the narratives. **A.** ISC for the first three strongest components by attentional condition. Bottom. Forward model for the components. **B.** Prediction accuracies for each univariate model by condition. **C.** ISC computed over EEG residuals after subtracting the predicted activity of each univariate model for component 1 (top) and component 2 (bottom). Two-tailed Wilcoxon signed-rank tests, (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$, and (****) $p < 0.0001$, FDR corrected.

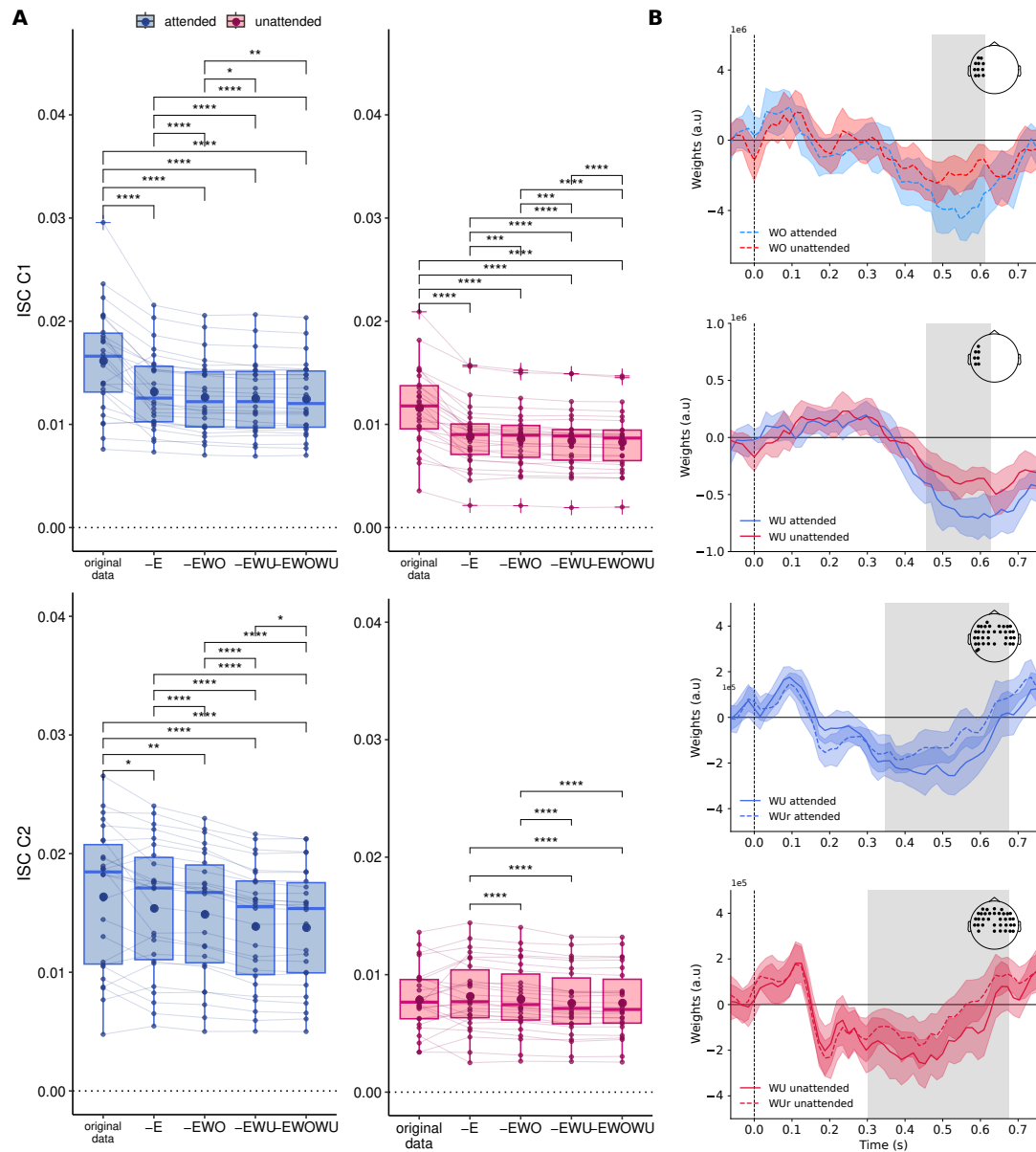


Figure 4.6: ISC during attended speech is elicited by linguistic integration. **A.** ISC for original data during attended and unattended speech, and computed over EEG residuals after subtracting the predicted activity of the multivariate model that showed the best predictions in both conditions (-EWO: without envelope and word onset model prediction, -EWU: without envelope and word unpredictability model prediction). Top: ISC for component 1. Bottom ISC for component 2. Two-tailed Wilcoxon signed-rank test, (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$ and (****) $p < 0.0001$, FDR corrected. **B.** TRF weights obtained with optimal lambda across subjects and conditions. Grey shadings denote time span and inset shows electrodes that take part in significant clusters (WU: word unpredictability, WUr: word unpredictability values randomized within trials).

4.4.6 Linguistic features contribute distinctively to the second correlated component

In order to better assess the relationship between the proposed features, the ISC, and attention, we constructed multivariate models with all the combinations of E, S, WO, and WU features. Pairwise comparison of each multivariate model showed a positive modulation of attention on their prediction accuracy (Table 4.11). The models combining the envelope and word unpredictability, the envelope and word onset, and the envelope and both linguistic features showed the highest accuracies and were selected to further explore their effects on the ISC (SFigure 4.11). Following the univariate models, removing the predicted activity by the EWU and EWO models caused a decrease in ISC for component 1 independently of the attentional condition with a higher contribution observed for the EWU model. During the unattentive condition adding word onset to the EWU model increased the explained ISC for component 1 (Figure 4.6A. Top, Table 4.12). Nevertheless, for the second component only the ISC during the attentive condition was affected by removing the contributions of these models. Crucially, the predicted activity by EWU showed a greater contribution to the ISC than the activity predicted by the EWO model only when participants paid attention to the stories ($W = 350$, $df = 25$, $p < 0.0001$). Moreover, the model combining the envelope with both linguistic features produced the highest decline in the ISC indexed by component 2 (Figure 4.6A. Bottom, Table 4.13). Finally, the drop in ISC is specific to linguistic integration and is not produced by the mere addition of features as the same multivariate model with a randomized version of the WU feature (EWOWUr) explained less of the correlated activity than the EWU and EWOWU models (SFigure 4.12).

4.4.7 Word segmentation and word unpredictability topographies

The TRF weights for the WO and WU obtained with the common ridge regression parameter across participants were assessed with a one-way paired sampled t-test corrected for multiple comparisons using a cluster-level statistical permutation test. Both WO and WU TRFs showed more negative weights in left temporal and parietal electrodes during the attentive than during the unattentive conditions in a time window ~ 500 ms post word onset ($WU_{attended} - WU_{unattended}$: $t_{sum} = -177$, $p = 0.013$, $t = 456:638$ ms, max effect size: $d = -0.92$, T7, $t = 581$ ms; $WO_{attended} - WO_{unattended}$: $t_{sum} = -159$, $p = 0.015$, $t = 472:613$ ms, max effect size: $d = -0.91$, FC5, $t = 503$

ms) (Figure 4.6B). In addition, WU TRFs were significantly more negative than WUr TRFs during attended ($t_{sum} = -1133$, $p = 0.0005$, $t = 347:675$ ms) and unattended conditions ($t_{sum} = -921$, $p = 0.0005$, $t = 300:675$ ms) for central parietal electrodes (Figure 4.6B).

4.5 Discussion

The present study aimed to explore whether the EEG-correlated responses produced when participants listen to the same narratives are elicited by the processing of basic acoustic information of the speech signal or higher linguistic representations related to the content of speech, and how conscious processing of the narratives influences these responses. We built subject-level encoding models from the envelope, the spectrogram, the word onset, and word unpredictability features, and assessed their contributions to the ISC elicited during passive, attended, and unattended speech processing.

4.5.1 Encoding models and attention effects

We show an increase in speech tracking for acoustic and linguistic features as indexed by the higher prediction accuracies of univariate and multivariate models when participants paid attention to the stories. This is consistent with research assessing the effects of attention on neural tracking of the envelope (Rosenkranz et al., 2021; Vanthornhout et al., 2019), the spectrogram (Teoh et al., 2022), semantic information (Broderick et al., 2018) and lexical surprise (Shyanthony R. Synigal et al., 2023). The weights for the envelope encoding model showed similar topographic and temporal unfolding to classical N1/P2 auditory ERPs (Čeponienė et al., 2008) as well as to TRFs obtained in previous research (Di Liberto et al., 2015; Mesik et al., 2023). The word unpredictability model weights were reminiscent of the N400 event-related potential (Kutas et al., 1980), for which amplitude is modulated by, among other properties, word context (Kutas et al., 2014). Indeed, contrasting the word unpredictability encoding models with a shuffled version of this representation yielded more negative weights for central parietal electrodes in a time window consistent with the one described in the N400 literature, further supporting the notion that our model captures context-dependent linguistic information. Interestingly, this effect was obtained independently of the attentional condition, suggesting that some level of lexical access is taking place

even during the unattentive condition. Consistent with this, semantic congruency effects have been observed during sleep ([Ibáñez et al., 2006](#)), and during coma states ([Rämä et al., 2010](#)).

4.5.2 Listening to stories elicits ISC and acoustic features are the main contributors

ISC was elicited during passive, and attended-unattended speech with above chance values for the first and second correlated components, and the topographies obtained were consistent with the ones shown in previous studies ([Cohen et al., 2016](#); [Dmochowski et al., 2012](#); [Ki et al., 2016](#); [Petroni et al., 2018](#); [Rosenkranz et al., 2021](#)). Compared to the word segmentation and the word unpredictability contributions, acoustic information conveyed by the spectrogram and the envelope were more important factors underlying the ISC during the three attentional contexts evaluated. Nevertheless, this result can be at least in part explained by the nature of the feature representations. The acoustic features resulted in dense representations whereas the linguistic properties evaluated correspond to very sparse representations and are therefore expected to yield lower prediction accuracies, underestimating their impact on the ISC. Intriguingly, the explored features explain a small amount of the overall ISC. We hypothesize that the remaining ISC could be produced by levels of information that we did not assess, such as the valency of the stimuli or memory representations, as well as non-linear dynamics not captured by the linear models ([Breakspear, 2017](#)).

4.5.3 Linguistic integration elicits shared evoked activity when attending to the stories

In previous work, the ISC has been postulated as a marker of engagement during film viewing ([Cohen et al., 2016](#); [Dmochowski et al., 2012](#); [Poulsen et al., 2017](#)) and music listening ([Madsen et al., 2019](#)). In agreement, the ISC was positively modulated by attention, with a particularly stronger effect on the correlated activity indexed by the second correlated component. A distinctive pattern emerged from the predictions of the TRFs and the correlated components according to the attentional condition. For the first correlated component, a greater decrease in ISC was observed when removing the EEG predictions by the multivariate models built from acoustic and linguistic features compared to removing the activity predicted by only the acoustic features, and this

was independent of auditory attention. Crucially, the ISC indexed by the second correlated component was sensitive to linguistic contributions exclusively during the attentive condition. Ki and collaborators (Ki et al., 2016) have previously shown an attentional modulation of the ISC reflected by this component for audiovisual narrative stimuli, with a smaller effect for scrambled narratives and no effect of attention when the narrative was in a foreign language. Here we provide evidence of a specific contribution of linguistic information on the ISC beyond word onset as the multivariate models built from the word unpredictability feature explained more of the intersubject correlation than the models accounting for word segmentation. The word unpredictability representations obtained from the language models reflect the probability of that word based on multiple types of linguistic information. As BERT models learn structural properties of language such as syntax, but also semantic roles, and some types of world knowledge (Rogers et al., 2020), we summarize it into the term ‘linguistic integration’. Therefore, our results support the hypothesis that the activity indexed by the second correlated component is probably capturing shared brain dynamics related to linguistic integration while the first correlated component is elicited mainly by the low-level sensory processing of speech, being both sensitive to attention. In fact, these two processes are closely related, as a directional effect in which lexical information influences the encoding of acoustic features has been described (Broderick et al., 2019; Heilbron et al., 2022). In addition, our results show that even in a passive scenario, where participants can have different degrees of engagement with the stories, encoding models can be successfully built, and linguistic information also contributes to the correlated response associated with the second component beyond speech acoustics.

4.5.4 Considerations for studies of unresponsive patients

Unlike experiments where isolated words or short sentences are presented to participants, experiments with narrative stimuli allow probing of the brain in a more naturalistic and engaging way, providing better information on the mechanisms behind the perception of language (Hamilton et al., 2020; Sonkusare et al., 2019). Moreover, participants can be tested with passive paradigms, which allows the comparison of language processing between healthy controls and pathological populations for which following instructions or providing verbal or motor outputs is not possible (Sokoliuk, Degano, Banellis, et al., 2021). In the case of patients with disorders of consciousness, where prognostic

information is fundamental to guide the decisions of caregivers regarding treatment (Russell et al., 2024), residual language capacities are associated with better outcomes (Coleman, Bekinschtein, et al., 2009; Gui et al., 2020; Sokoliuk, Degano, Banellis, et al., 2021). Therefore, developing tools that are easy to implement and that assess with granularity the level of speech processing in these patients is of extreme value. In this line, we believe our work opens a clear avenue for a feasible and informative assessment, and we offer some recommendations for its design based on an unsuccessful attempt to apply our analysis to EEG recordings of DoC patients (see Appendix A).

Firstly, selecting a well-thought-out stimulus is of paramount importance. Stories should be engaging, composed of widespread vocabulary, at least 15 minutes long (Crosse et al., 2021), and preferably conveyed by a unique speaker. Some research has used forward and backward language to compare language processing in DoC patients (Iotzov et al., 2017), we argue that an optimal control would be to use the same story in a foreign language. Although reverse speech can convey information on language-independent auditory processing (Fernández-Espejo et al., 2008), it is questionable whether it has the same statistical properties as actual speech. Brain response in a cohort of healthy controls exposed to the story should be recorded in two attentional conditions counterbalanced across participants. Comprehension questions should be posed at the end of the attentive condition, and the unattended condition should be demanding enough to prevent participants from also engaging with the story. ISC and encoding models for acoustic and linguistic features would be computed, and it should be verified that at least some of the ISC is conveyed by these representations. A patient would be presented with the same stimuli and be asked to actively listen to the story. Regardless of a patient cooperating we have shown that both passive and unattended conditions elicit acoustic and linguistic neural responses. Encoding models for the different features would provide specific information on whether the patient is processing sensory information and also specific language representations. If it is not possible to develop complex linguistic models, models built on acoustic features together with the word onset would by themselves be very informative of speech segmentation. The discreet phenomenology of speech does not occur with an unfamiliar language (Ding et al., 2016) or when exposed to familiar but reverse speech, as it requires knowledge about the transition probabilities between speech sounds and their correspondence to word boundaries, a mapping acquired through statistical learning

(Erickson et al., 2015). Therefore, comparing the encoding models for word onset during native language and foreign language would be of interest. Finally, the patient's brain response to the narratives should be correlated to the healthy cohort response during attended and unattended speech. If the patient shows a greater correlation with the attended than the unattended responses, then we could infer language processing beyond simple acoustics. Moreover, given that most of the ISC is not explained by the features assessed in this work, a patient that correlates highly to the healthy cohort during the attentive condition is probably also responding as healthy participants to other sources of information, or integrating in non-linear ways the stimuli, suggesting highly conserved cognitive capabilities.

4.5.5 Limitations

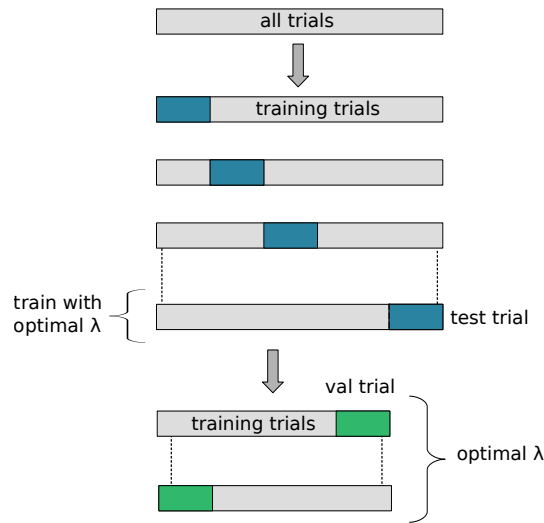
Some aspects of our study should be considered to improve future work. Mainly, the attentional condition was not counterbalanced across participants and could have had effects on the accuracies of the encoding models and the ISC. In addition, the multi-variate models that showed greater prediction accuracies differed between both experiments. One explanation is found in the properties of the stimuli. In the first experiment, participants were exposed to a consistent speaker across trials whereas in the second experiment, the stimuli were composed of multiple stories, and in some of the stories, more than one speaker participated. This variability in the attended-unattended experiment meant that our models had to generalize to more dissimilar stimuli, and is potentially responsible for the lower prediction accuracies obtained for the spectrogram in comparison to the envelope. Therefore, selecting a narrative executed by a consistent speaker instead of multiple short narratives would probably have resulted in better encoding models for the spectrogram in the second experiment.

4.5.6 Conclusions and future directions

We show that a proportion of the intersubject correlation evoked by listening to narrative stimuli is produced by both acoustic and linguistic content present in the speech signal. The increases in ISC produced by engaging with the stimuli are driven by an enhancement in the neural representations of both types of information, with a specific effect of linguistic integration on the second correlated component. Intriguingly, the explored features explain a small amount of the overall ISC and future work should address

which other speech properties are at play. Overall, our results suggest that ISC arises from the integration of multiple levels of information present in speech and propose that ISC, together with encoding models, could provide meaningful information on language processing in unresponsive patients.

4.6 Supplementary material



SFigure 4.7: Cross-validation method. Leave-one-out nested cross-validation to select the ridge parameters. For each subject, we iteratively selected one trial to test the TRF (represented in blue), and used the remaining trials to carry leave-one-out cross-validation to obtain the ridge parameter across channels and folds that maximized the correlation between the actual response and the predicted response. The $n-1$ trials that took part in the cross-validation were used to train the model with the optimal λ , and the model was tested on the left-out trial. This iterative process yielded one Pearson correlation coefficient per trial and subject given by the average correlation across all channels.

Table 4.1: Passive listening: prediction accuracies for univariate TRFs

x	y	W	p	padj ¹
WO	WU	31	3.52e-05	7.04e-05
WO	S	1	2.98e-08	1.79e-07
WO	E	4	1.04e-07	5.20e-07
WU	S	6	2.09e-07	6.27e-07
WU	E	6	2.09e-07	6.27e-07
S	E	138	2.29e-01	2.29e-01

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests. WO: word onset, WU: word unpredictability, S: spectrogram, E: envelope.

Table 4.2: Passive listening: univariate contributions to ISC component 1

x	y	W	p	padj ¹
original data	-WO	374	1.04e-07	3.12e-07
original data	-WU	376	4.47e-08	1.79e-07
original data	-S	377	2.98e-08	1.49e-07
original data	-E	377	2.98e-08	1.49e-07
-WO	-WU	377	2.98e-08	1.49e-07
-WO	-S	378	1.49e-08	1.49e-07
-WO	-E	377	2.98e-08	1.49e-07
-WU	-S	377	2.98e-08	1.49e-07
-WU	-E	371	2.83e-07	5.66e-07
-S	-E	156	4.41e-01	4.41e-01

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests. WO: word onset, WU: word unpredictability, S: spectrogram, E: envelope. The (-) symbol indicates that the predicted activity by the encoding model was subtracted from the EEG response.

Table 4.3: Passive listening: univariate contributions to ISC component 2

x	y	W	p	padj ¹
original data	-WO	359	4.57e-06	1.37e-05
original data	-WU	362	2.52e-06	1.37e-05
original data	-S	374	1.04e-07	1.04e-06
original data	-E	371	2.83e-07	2.55e-06
-WO	-WU	328	4.27e-04	8.54e-04
-WO	-S	362	2.52e-06	1.37e-05
-WO	-E	362	2.52e-06	1.37e-05
-WU	-S	360	3.77e-06	1.37e-05
-WU	-E	360	3.77e-06	1.37e-05
-S	-E	239	2.39e-01	2.39e-01

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests. WO: word onset, WU: word unpredictability, S: spectrogram, E: envelope. The (-) symbol indicates that the predicted activity by the encoding model was subtracted from the EEG response.

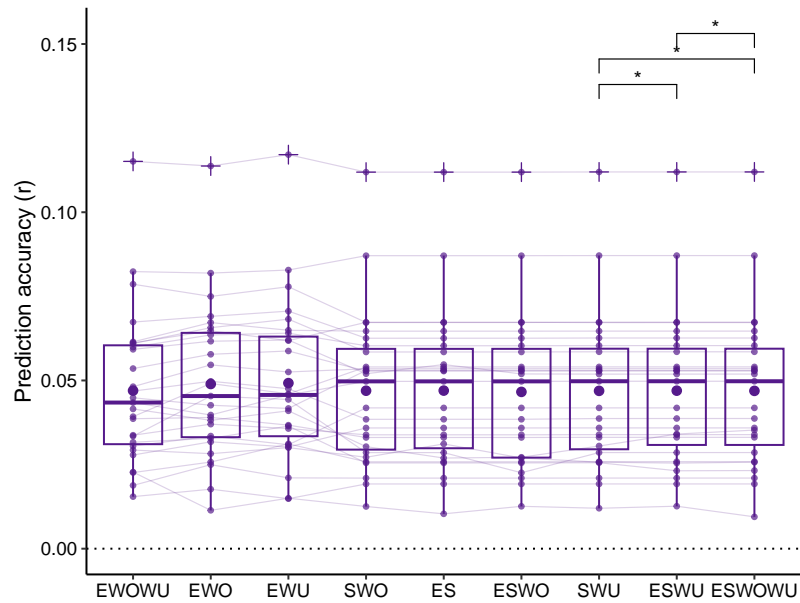


Figure 4.8: Passive listening: prediction accuracies for multivariate models. E: envelope, S: spectrogram, WU: word unpredictability, WO: word onset. Significant differences were only found between ESWU and SWU ($W = 54$, $p = 0.023$), SWU and ESWOWU ($W = 52$, $p = 0.019$), and between ESWU and ESWOWU ($W = 48$, $p = 0.012$). All other paired comparisons resulted in p values ≥ 0.068 .

Table 4.4: Passive listening: multivariate contributions to ISC component 1

x	y	W	p	padj ¹
original data	-ES	377	2.98e-08	2.09e-07
original data	-ESWO	377	2.98e-08	2.09e-07
original data	-ESWOWU	377	2.98e-08	2.09e-07
original data	-ESWU	377	2.98e-08	2.09e-07
-ES	-ESWO	368	6.41e-07	3.85e-06
-ES	-ESWOWU	349	2.59e-05	1.04e-04
-ES	-ESWU	351	1.88e-05	9.40e-05
-ESWO	-ESWOWU	317	1.00e-03	3.00e-03
-ESWO	-ESWU	320	1.00e-03	3.00e-03
-ESWOWU	-ESWU	155	4.27e-01	4.27e-01

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests. ES: envelope and spectrogram model, ESWO: envelope, spectrogram and word onset model, ESWU: envelope, spectrogram and word unpredictability model, ESWOWU: envelope, spectrogram, word onset, and word unpredictability model. The (-) symbol indicates that the predicted activity by the encoding model was subtracted from the EEG response before computing the ISC.

Table 4.5: Passive listening: multivariate contributions to ISC component 2

x	y	W	p	padj ¹
original data	-ES	374	1.04e-07	7.28e-07
original data	-ESWO	374	1.04e-07	7.28e-07
original data	-ESWU	374	1.04e-07	7.28e-07
original data	-ESWOWU	374	1.04e-07	7.28e-07
-ES	-ESWO	270	5.20e-02	1.04e-01
-ES	-ESWU	328	4.27e-04	3.00e-03
-ES	-ESWOWU	316	2.00e-03	6.00e-03
-ESWO	-ESWU	321	9.20e-04	5.00e-03
-ESWO	-ESWOWU	300	6.00e-03	1.90e-02
-ESWU	-ESWOWU	197	8.59e-01	8.59e-01

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests. ES: envelope and spectrogram model, ESWO: envelope, spectrogram and word onset model, ESWU: envelope, spectrogram and word unpredictability model, ESWOWU: envelope, spectrogram, word onset and word unpredictability model. The (-) symbol indicates that the predicted activity by the encoding model was subtracted from the EEG response before computing the ISC.

Table 4.6: Attention effects on ISC

x	y	W	p	padj ¹
attended.C1	unattended.C1	346	2.98e-07	5.96e-07
attended.C2	unattended.C2	351	2.98e-08	8.94e-08
attended.C3	unattended.C3	316	1.26e-04	1.26e-04

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests.

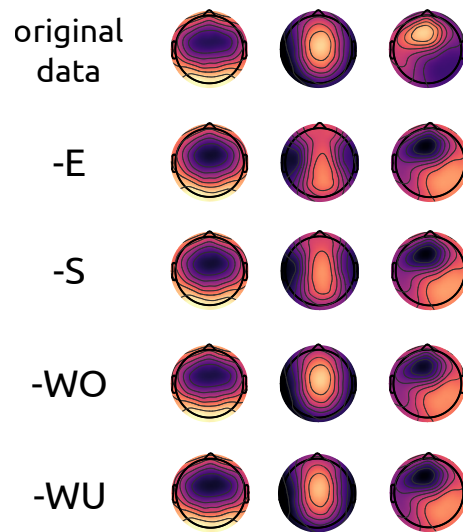


Figure 4.9: Forward model projections of the correlated components into sensor space for the original data, after subtraction of the envelope (-E), the spectrogram (-S), the word onset (-WO), and the word unpredictability (-WU) encoding models predictions.

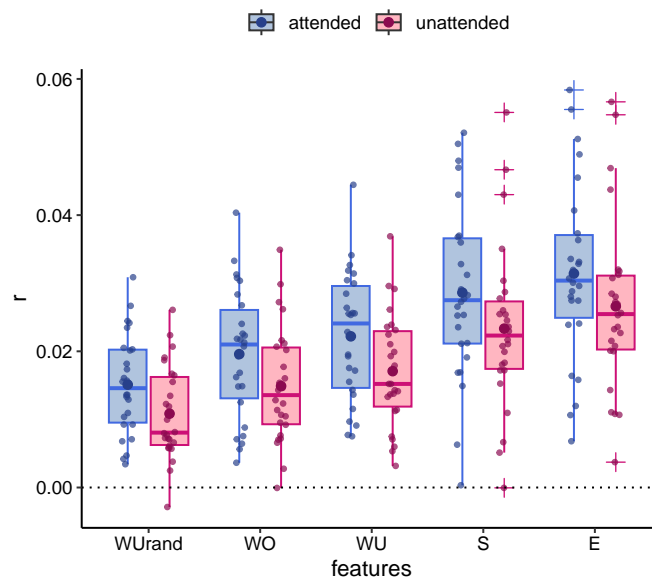


Figure 4.10: Prediction accuracies for univariate models during attended and unattended conditions. Envelope (E), spectrogram (S), word unpredictability (WU), word onset (WO), and randomized word unpredictability (WUrand).

Table 4.7: Attention effects on the prediction accuracies of the univariate TRFs

x	y	W	p	padj ¹
attended.WUrand	unattended.WUrand	301	0.000835	0.00300
attended.WO	unattended.WO	303	0.000664	0.00300
attended.WU	unattended.WU	313	0.000190	0.00095
attended.E	unattended.E	276	0.009000	0.01100
attended.S	unattended.S	274	0.011000	0.01100

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests.

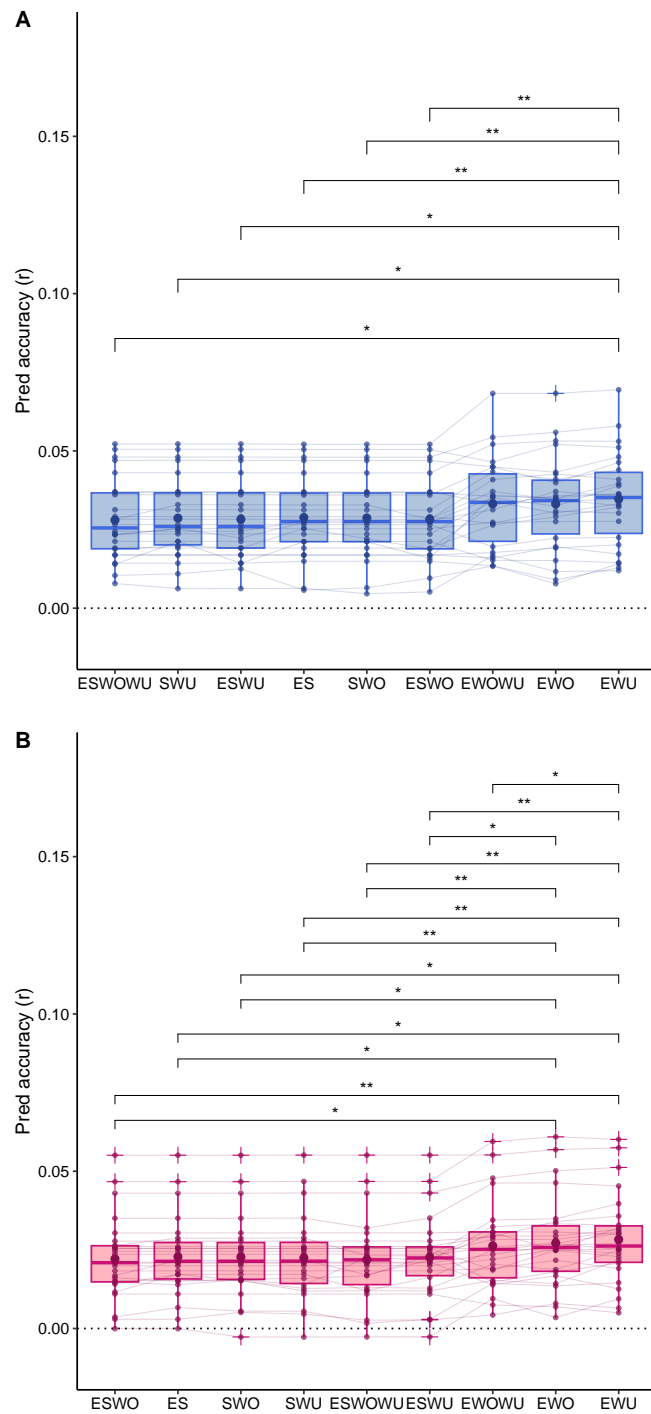


Figure 4.11: Prediction accuracies for mTRFs models during attended (**A**) and unattended conditions (**B**). Multivariate models for combinations of the envelope (E), spectrogram (S), word unpredictability (WU), and word onset (WO). Prediction accuracies are higher for the attended than the unattended condition for all models ($p \leq 0.010$).

Table 4.8: Prediction accuracies for univariate TRFs within attentional conditions

x	y	Attended Condition			Unattended Condition		
		W	p	padj ¹	W	p	padj ¹
WO	WU	57	2.00e-03	5.00e-03	60	2.00e-03	2.00e-03
WO	S	32	8.16e-05	3.26e-04	25	2.69e-05	1.08e-04
WO	E	4	2.09e-07	1.25e-06	2	8.94e-08	5.36e-07
WU	S	69	6.00e-03	1.00e-02	51	9.35e-04	2.00e-03
WU	E	18	7.54e-06	3.77e-05	13	2.62e-06	1.31e-05
S	E	76	1.00e-02	1.00e-02	33	9.45e-05	2.84e-04

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests

Table 4.9: Univariate contributions to ISC C1 within attentional conditions

x	y	Attended Condition			Unattended Condition		
		W	p	padj ¹	W	p	padj ¹
original data	-WO	350	5.96e-08	5.96e-07	351	2.98e-08	1.19e-07
original data	-WU	346	2.98e-07	2.68e-06	350	5.96e-08	1.79e-07
original data	-S	342	9.83e-07	7.86e-06	351	2.98e-08	1.19e-07
original data	-E	333	7.54e-06	5.28e-05	351	2.98e-08	1.19e-07
-WO	-WU	270	1.50e-02	3.00e-02	324	3.76e-05	3.76e-05
-WO	-S	321	6.03e-05	3.02e-04	351	2.98e-08	1.19e-07
-WO	-E	297	1.00e-03	4.00e-03	351	2.98e-08	1.19e-07
-WU	-S	324	3.76e-05	2.26e-04	351	2.98e-08	1.19e-07
-WU	-E	301	8.35e-04	3.00e-03	351	2.98e-08	1.19e-07
-S	-E	176	1.00e+00	1.00e+00	345	4.17e-07	8.34e-07

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank test. WO: word onset, WU: word unpredictability, S: spectrogram, E: envelope. The (-) symbol indicates that the predicted activity by the encoding model was subtracted from the EEG response.

Table 4.10: Univariate contributions to ISC C2 within attentional conditions

x	y	Attended Condition			Unattended Condition		
		W	p	padj ¹	W	p	padj ¹
original data	-WO	345	4.17e-07	3.75e-06	313	0.000190	0.002
original data	-WU	350	5.96e-08	5.96e-07	274	0.011000	0.066
original data	-S	204	4.83e-01	6.71e-01	127	0.227000	0.908
original data	-E	261	2.90e-02	1.46e-01	143	0.423000	0.940
-WO	-WU	332	9.15e-06	7.32e-05	204	0.483000	0.940
-WO	-S	127	2.27e-01	6.71e-01	76	0.010000	0.066
-WO	-E	193	6.71e-01	6.71e-01	89	0.027000	0.136
-WU	-S	39	2.17e-04	1.00e-03	39	0.000217	0.002
-WU	-E	129	2.47e-01	6.71e-01	60	0.002000	0.019
-S	-E	317	1.09e-04	7.63e-04	179	0.940000	0.940

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests. WO: word onset, WU: word unpredictability, S: spectrogram, E: envelope. The (-) symbol indicates that the predicted activity by the encoding model was subtracted from the EEG response.

Table 4.11: Attention effects on the prediction accuracies of the multivariate TRFs

x	y	W	p	padj ¹
attended.ESWOWU	unattended.ESWOWU	277	0.009000	0.010
attended.ESWO	unattended.ESWO	275	0.010000	0.010
attended.ESWU	unattended.ESWU	278	0.008000	0.010
attended.ES	unattended.ES	282	0.006000	0.010
attended.EWU	unattended.EWU	301	0.000835	0.007
attended.EWO	unattended.EWO	283	0.005000	0.010
attended.SWO	unattended.SWO	282	0.006000	0.010
attended.SWU	unattended.SWU	284	0.005000	0.010
attended.EWOWUr	unattended.EWOWUr	301	0.000835	0.007

¹FDR corrected. Bold indicates $p < 0.05$. Wilcoxon two-sided signed-rank tests

Table 4.12: Multivariate contributions to ISC C1 within attentional conditions

x	y	Attended Condition			Unattended Condition		
		W	p	padj ¹	W	p	padj ¹
original data	-E	333	7.54e-06	3.02e-05	351	2.98e-08	1.79e-07
original data	-EWO	345	4.17e-07	2.08e-06	351	2.98e-08	1.79e-07
original data	-EWU	345	4.17e-07	2.08e-06	351	2.98e-08	1.79e-07
original data	-EWOWU	345	4.17e-07	2.08e-06	351	2.98e-08	1.79e-07
-E	-EWO	351	2.98e-08	2.68e-07	308	3.64e-04	3.64e-04
-E	-EWU	351	2.98e-08	2.68e-07	337	3.28e-06	1.31e-05
-E	-EWOWU	350	5.96e-08	4.77e-07	344	5.66e-07	2.83e-06
-EWO	-EWU	277	9.00e-03	1.70e-02	320	7.02e-05	1.40e-04
-EWO	-EWOWU	297	1.00e-03	4.00e-03	351	2.98e-08	1.79e-07
-EWU	-EWOWU	233	1.50e-01	1.50e-01	330	1.33e-05	3.99e-05

¹FDR corrected. Bold indicates p < 0.05

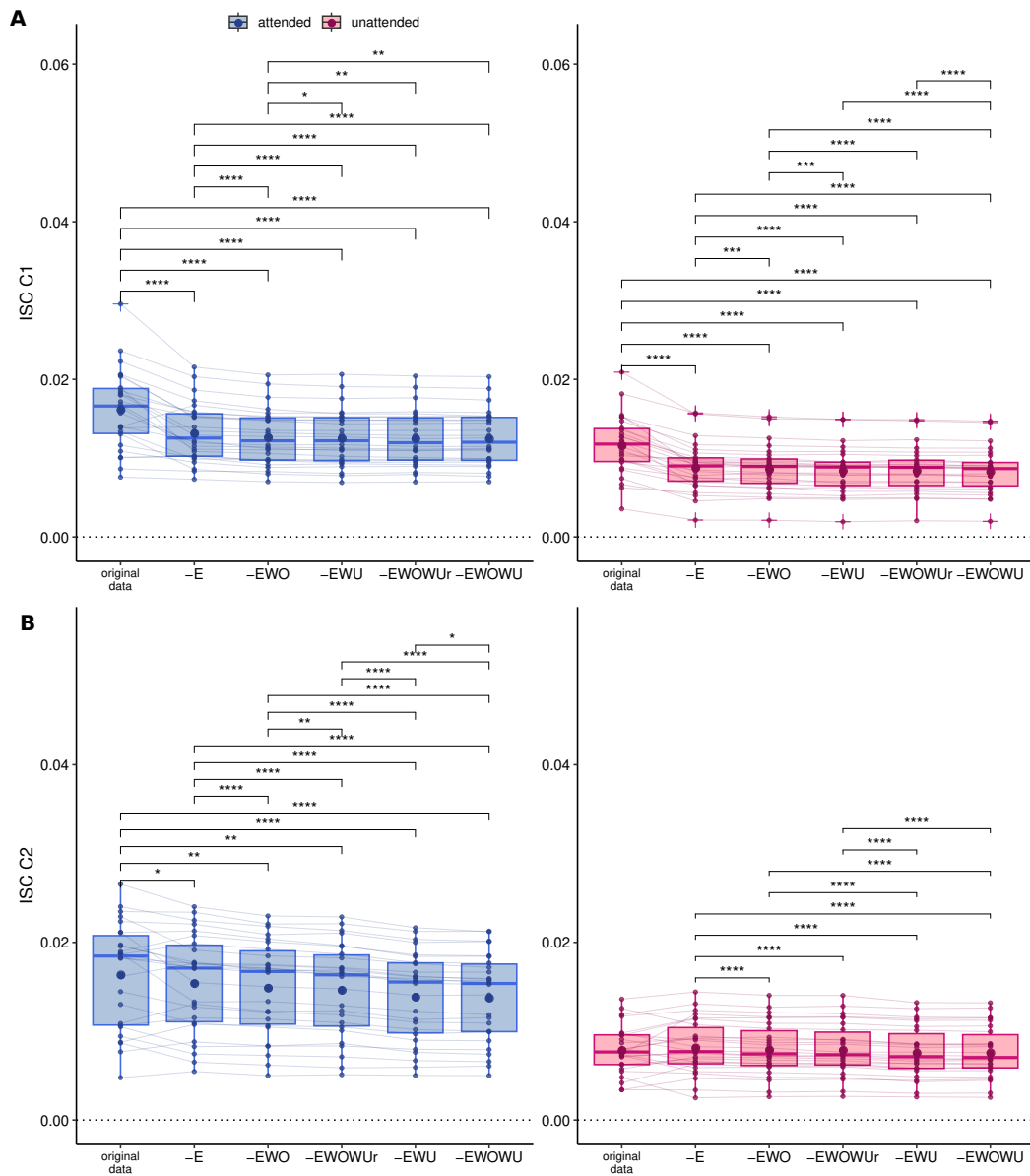
Wilcoxon two-sided signed-rank tests. WO: word onset, WU: word unpredictability, S: spectrogram, E: envelope..

Table 4.13: Multivariate contributions to ISC C2 within attentional conditions

x	y	Attended Condition			Unattended Condition		
		W	p	padj ¹	W	p	padj ¹
original data	-E	261	2.90e-02	2.90e-02	143	4.23e-01	9.04e-01
original data	-EWO	301	8.35e-04	3.00e-03	175	1.00e+00	1.00e+00
original data	-EWU	338	2.62e-06	1.31e-05	217	3.03e-01	9.04e-01
original data	-EWOWU	336	4.08e-06	1.63e-05	216	3.15e-01	9.04e-01
-E	-EWO	345	4.17e-07	2.50e-06	336	4.08e-06	2.45e-05
-E	-EWU	351	2.98e-08	2.38e-07	350	5.96e-08	5.36e-07
-E	-EWOWU	351	2.98e-08	2.38e-07	350	5.96e-08	5.36e-07
-EWO	-EWU	350	5.96e-08	4.17e-07	348	1.49e-07	1.19e-06
-EWO	-EWOWU	351	2.98e-08	2.38e-07	346	2.98e-07	2.09e-06
-EWU	-EWOWU	266	2.00e-02	2.90e-02	145	4.52e-01	9.04e-01

¹FDR corrected. Bold indicates p < 0.05

Wilcoxon two-sided signed-rank tests. WO: word onset, WU: word unpredictability, S: spectrogram, E: envelope.



SFigure 4.12: Contributions of mTRFs predictions on the intersubject correlation. **A.** Component 1. **B.** Component 2. Multivariate models for combinations of the envelope (E), spectrogram (S), word unpredictability (WU), and word onset (WO). EWO, EWU, and EWOWU encoding models show the highest prediction accuracies.

Chapter 5

General discussion

General Discussion

Since Owen's seminal work ([Owen et al., 2006](#)), studies surrounding DoC patients reveal that a significant percentage of patients fulfilling the clinical criteria for a UWS/VS diagnosis are aware and able to modulate their brain activity willfully. In addition, mounting evidence indicates that responses to language predict favorable outcomes in patients with DoC, which is crucial information to guide caregivers and healthcare providers in their treatment approaches. The prospect of cases where patients with covert intentional responses or residual consciousness go unnoticed is unsettling. Such scenarios may be more prevalent in healthcare centers lacking expertise in conducting behavioral neurological evaluations or the costly equipment needed to detect covert responses effectively. Therefore, there is worth in developing affordable bedside tools to promote equity in access to an informed diagnosis for patients with disorders of consciousness. The main objective of our work was to develop new assessments to explore residual consciousness and volitional responses in patients with disorders of consciousness based on electrophysiological measures, brain-body interactions, and language processing. We carried out three studies in healthy participants and tested some of the approaches in unresponsive patients.

Study 1 - Chapter 2: A novel motor imagery task was developed and tested in a healthy group of volunteers to explore the potential enhancement of motor imagery detection by integrating bodily signals with brain activity.

Study 2 - Chapter 3: We focused on brain-heart interactions and whether their modulation by exteroceptive and interoceptive attention could be informative of covert attention in healthy volunteers. The potential of this paradigm to detect command-following

was further tested in 5 brain injured patients.

Study 3 - Chapter 4: We studied the influence of linguistic and acoustic information on the intersubject correlation elicited in EEG when individuals are actively engaged with auditory narratives and during unattended and passive listening. We applied these analyses on EEG recordings of DoC patients while listening to forward and backward speech to detect covert cortical processing.

This final chapter discusses the main hypotheses and results of these studies, addresses their limitations, and explores the perspectives prompted by our work.

Chapter 2 - Brain-muscle networks: a novel protocol to study covert command-following

Behavioral assessments to diagnose patients with disorders of consciousness rely on persevered motor functions and can sometimes fail to detect subtle motor responses (Giacino et al., 2004; Pincherle et al., 2019). Complementary assessments based on neuroimaging typically try to bypass this limitation by demanding motor imagery from DoC patients (Claassen et al., 2024). The first effort of this work was to contribute to the field by developing a new motor imagery task with the potential to detect command-following in DoC patients based on combined information from accessible tools. The paradigm and analyses developed were built on the literature on motor execution and motor imagery (Boonstra et al., 2015; Collet et al., 2013; Guillot et al., 2012; Kerkman et al., 2018). The task design was inspired by an assessment that is currently used in multiple centers to evaluate CMD by asking patients to execute a movement for 10 s while employing spectral power markers to detect whether a patient was following the instructions (Claassen et al., 2019; Claassen et al., 2024; Willacker et al., 2022). As the EEG neural correlates of motor execution and motor imagery are similar (Munzert et al., 2009), and some research using EMG has shown specific muscle activity when participants carry motor imagery (Guillot et al., 2012), we considered that a healthy participant imagining simple movements could be a good model of a DoC patient trying to execute a movement but failing to achieve an overt response. If a patient can produce covert muscular activity in agreement with the instructions, EMG and EEG should be

sensitive to capture their response. In addition, heart activity is affected by the mental content of an individual and was incorporated as a potential physiological marker of motor imagery (Collet et al., 2013). This study was carried out following a registered report-type review process such that all the hypotheses and associated analyses were stated in advance, and data collection started after obtaining in-principle acceptance from a peer-reviewed journal (<https://osf.io/kd7hf>). We adhered to the proposed analyses, tested the hypotheses without biases, and obtained evidence in agreement and disagreement with our initial assumptions. Our main hypothesis was that the mental rehearsal of a movement should elicit modulations of the sensorimotor rhythms, as well as muscular and cardiac responses and that the combination of these markers would improve the detection of motor imagery.

Our task was not as robust to detect motor imagery as typical BCI tasks (Allison et al., 2010; Cho et al., 2017; Dickhaus et al., 2009; Guger et al., 2003), or as in previous work on healthy individuals and DoC patients (Cruse et al., 2011). Although training and feedback affect motor imagery performance (Grimann et al., 2009), the major limitation we attribute to our task is the absence of an external cue signaling to participants when to initiate and terminate each cycle of motor imagery. This, together with the length of the task and the multiple types of motor imagery jointly evaluated probably introduced significant variability affecting the performance of our classifiers. Assessments to detect volitional responses should be highly specific, however, it is paramount that they are sensitive, and in this regard, our proposal falls short.

The network analysis carried out did not reveal changes in intermuscular, corticomuscular, and cortical coherence during motor imagery, however, cortical power, and heart-rate variability provided reliable information to identify motor imagery trials. In the brain-computer interface literature, the potential of hybrid classifiers based on the combination of EEG and ECG information has been proposed (Pfurtscheller, 2010), with some successful implementation for paradigms based on motor imagery (Shahid et al., 2011) and selective attention (Kaufmann et al., 2012). To our knowledge, this approach has not been incorporated in clinical evaluations of motor imagery in patients with DoC. Nonetheless, heart activity has already proven to be useful in improving DoC patient's classification. Research shows that when patients are exposed to auditory regularities, a heart rate acceleration can be elicited by sounds that deviate from the global pattern, and when this information is combined with EEG markers of consciousness (En-

gemann et al., 2018; Sitt et al., 2014), patient classification performance is enhanced (Raimondo et al., 2017). Therefore, cardiac activity can provide valuable insights into self-generated mental content or the conscious processing of external stimuli.

Perspectives

While the limitations highlighted in our study discourage the immediate clinical deployment of our task, we are confident that our findings offer strong evidence supporting the use of bodily signals as a means to detect awareness. We propose that integrating heart activity, measured through ECG recordings, into current clinical assessments could significantly enhance their efficacy. This addition could be particularly straightforward for existing motor imagery evaluations or BCI setups used with patients suffering from disorders of consciousness (Chatelle et al., 2018; Eliseyev et al., 2021), and also holds promise for tasks involving motor execution (Claassen et al., 2019; Horki et al., 2014).

Chapter 3 - Predicting Attentional Focus: Heartbeat-Evoked Responses and Brain Dynamics During Interoceptive and Exteroceptive Processing

The heterogeneity of DoC patients, in terms of etiology (Estraneo et al., 2021) and the associated brain damage, motivates the need for assessments that ask patients different types of responses. For instance, patients with damage in premotor and motor cortical areas may not be suitable for motor imagery tasks (Gibson et al., 2014) but might respond well to tasks involving other cognitive processes. Moreover, tasks that require individuals to imagine movements often prove ineffective in detecting motor imagery in a significant percentage of healthy participants (Allison et al., 2010; Dickhaus et al., 2009; Guger et al., 2003). Sustaining vivid imagery is probably equally difficult for DoC patients, potentially leading to false negatives. Considering these challenges, a novel evaluation based on sustained interoceptive-exteroceptive attention was developed to detect covert attention as a proxy of command following. Our study evaluated the effects of directing attention to the heartbeats or salient auditory targets in healthy participants and assessed the potential of dynamical EEG markers and time-locked responses to the heartbeats to classify trials of heart and sound-directed attention. The main hypothesis of this study was that directing attention to bodily signals or external stimuli should produce increased brain responses to internal and external stimuli, re-

spectively, as well as specific brain dynamics. This was supported by the main findings that we summarize and discuss next.

Time-locked responses to the heartbeats and to the target sounds were inversely modulated by interoceptive and exteroceptive attention, with no changes in respiration or cardiac activity across conditions. The time between heartbeats was unaffected by the target sounds in either attentional condition, and there was an enhancement in cortical response to both salient and hidden auditory stimuli during sound-attended trials. In addition, spectral, connectivity and information theory markers showed distinct responses according to the attentional condition. Importantly, the results were highly consistent across participants, as classifiers based on the HEP and dynamical EEG features showed high accuracies and reliably classified the attentional condition of all participants, suggesting it could be a more robust tool to detect command-following than tasks based on motor imagery.

We were able to assess a small group of brain-injured patients with an adaptation of the paradigm. We demonstrated that the task can be successfully applied in a clinical setting despite using different EEG and ECG equipment than that used for healthy participants. The study was part of a collaboration with researchers from the Department of Biomedical and Clinical Sciences, and the IRCSS Fondazione Don Carlo Gnocchi ONLUS in Milan, in the context of the EU-funded multicentric project Perbrain ([Willacker et al., 2022](#)). The French team developed custom-built stimulation boxes which allowed to remotely upload an Italian version of the paradigm and easily carry the evaluation at the bedside. Out of the five patients that completed the task, the attentional state of a LIS and a UWS/VS patient was significantly classified by a combination of the markers, and both patients showed a HEP modulation consistent with command-following. While the result for the patient in a LIS provides a positive control for our paradigm, the interpretation of the positive responses for the UWS/VS is limited given that an inquiry ~1 month after the assessment revealed that the patient had deceased due to withdrawal of life-sustaining therapies. Nevertheless, the converging evidence of multiple markers suggests that the patient was executing the task and therefore aware at the time of the assessment.

Based on our interoceptive accuracy measure, the modulation of the HEP appears to be unaffected by whether participants could detect their heartbeats. It is possible that awareness of one's heartbeat is not necessary to trigger cortical changes in heartbeat

processing, similar to how hidden noise repetitions were better encoded during sound-attention trials despite going unnoticed by participants. Whether the modulation of the HEP is specific to interoceptive processing of the heartbeats (Coll et al., 2021), an enhancement to somatosensory afferent information from the skin (Khalsa, Rudrauf, & Tranel, 2009), or a general increase to the encoding of visceral signals, can not be determined by our study. Nevertheless, recent research shows that counting heartbeats and counting respiratory cycles both elicited an increase in the HEP amplitude during an early time window (230 ms) for heartbeats elicited during the exhalation phase, with a modulation for later time windows (400 ms) only during cardiac interoception (Zaccaro et al., 2024). This suggests that increases in the cortical response to heartbeats are not specific to heartbeat attention, but can occur whenever attention is directed towards visceral signals and interferences by external stimuli are kept low. Regardless of whether the participant's mental content corresponded with a bodily sensation of their heartbeats or some form of general implicit visceral perception, we show that the HEP constitutes an effective marker of internal and external attention. Crucially, we argue that this modulation can only take place if a sense of self and the surroundings is preserved, among other functions.

Self-referential evaluations in disorders of consciousness have been limited to highly familiar stimuli such as the patients' name (Cheng et al., 2013; Crivelli et al., 2020; Di et al., 2007; Kempny et al., 2018; Laureys et al., 2004; Qin et al., 2010; Qin et al., 2008; Schnakers et al., 2008). It is unclear whether the observed responses are related to self-awareness or a memory effect associated to the relevance of the stimuli (Aubinet et al., 2024). Interestingly, research suggests that this paradigm elicits cortical responses in regions that correlate with the 'self' and overlap with the DMN activation during resting state (Qin et al., 2011). Heartbeat-evoked responses have been traced to multiple structures overlapping with the DMN, and a theoretical and empirical link between the cortical processing of heartbeats and the self has been proposed. According to the self-referential frame theory (Tallon-Baudry et al., 2018), subjective experience is the result of two components: the mental content and a first-person perspective, where the first-person perspective would be stably maintained by the rhythmic visceral information sent afferently from the gut and the heart to the brain (Park & Tallon-Baudry, 2014). Under this theory, increased heartbeat-evoked responses can be considered to index self-awareness. Therefore, the increases in the HEP observed in our experiment

during heartbeat attention, even without conscious perception of the heartbeats, might partly result from heightened self-awareness.

We argue that our interoceptive-exteroceptive paradigm holds many advantages. In the first place, our approach is based on contrasting two conditions instead of the common approach of comparing an active condition to resting state (Claassen et al., 2019; Forgacs et al., 2014). This implies that even if a participant finds it challenging to focus on their heartbeats, focusing on the sound should be much more accessible and may even be enough to obtain an accurate classification. In addition, it has been previously argued that the topographies of the ERPs and their temporal unfolding can be highly variable across DoC patients as a result of cortical and skull damage (King et al., 2013). Even in a case where the HEP would depart from the healthy participants' response, our results show that spectral and information theory markers, which are more robust to noise and have already proven to be useful in classifying states of consciousness (Engemann et al., 2018; Lehembre et al., 2012; Sitt et al., 2014), can identify covert attention. Secondly, if a patient is not able to follow commands cortical responses to the heartbeats and ongoing brain activity can be analyzed as pseudo resting state markers. Previous work has shown that the HEP during resting state (Candia-Rivera et al., 2021) is a useful marker of residual consciousness in DoC patients. Furthermore, power, wSMI and permutation entropy extracted from the regular stimulation portion of the local-global paradigm or during purely resting state are informative for diagnostic (Amiri et al., 2023; Engemann et al., 2018; Lehembre et al., 2012; Sitt et al., 2014) as well as for prognostic (Alkhachroum et al., 2024; Amiri et al., 2023) purposes.

One of our secondary hypotheses in this study was that perceptual learning of hidden repetitions of white noise would be improved by directing attention to the sound. However, we did not find evidence for long-term memory of the noise repetitions. It is possible that more repetitions are required to statistically learn the regularities, or as the memory-evoked potentials elicited by the snippets are small we were not able to detect differences with our analyses. Given these results, we decided to introduce the same repetitions in both conditions in the paradigm adapted for DoC patients. Future work will focus on assessing whether exposition to these snippets elicits memory traces in DoC patients on a subsequent exposure (Ruyant-Belabbas et al., 2023).

Perspectives

The interoceptive-exteroceptive attention paradigm is expected to continue being carried out by the Italian and French teams. A greater cohort of DoC patients assessed with this task will enable us to test the specificity and sensibility of this evaluation. In addition, modifications to this paradigm could be introduced in future studies. In the current assessment, the amplitude-modulated noise targets (AmN) were scarce and this made subject-level analysis of the cortical response to target sounds not possible. An interesting possibility would be to replace the noise repetitions by AmN enhancing the number of events from which to obtain evoked responses. Additionally, the interoceptive-exteroceptive paradigm could be combined with the local-global paradigm by replacing the AmN and noise repetitions with the local-global auditory stimuli. This would allow recording numerous cortical responses to sounds elicited during both attended sound and attended heart trials where the P3b responses to global deviants would index covert attention on a patient level. Furthermore, the same task could be carried out by asking participants to focus on their respiration which is much more salient than the heartbeats, and by limiting the HEP analysis to heartbeats occurring at exhalation ([Zaccaro et al., 2024](#)).

Chapter 4: What drives intersubject correlation of EEG during conscious processing of narrative stimuli?

If a patient with DoC can follow instructions we infer that the patient is aware and that their linguistic capabilities are preserved. Nevertheless, a number of patients with disorders of consciousness who do not show intentional behaviors nor brain activity consistent with command-following do show brain responses to language. Indeed, cortical responses to speech stimuli are more frequent than to motor imagery tasks in DoC patients ([Edlow et al., 2017](#)) as active paradigms are highly specific to detect awareness but have low sensitivity ([Sanz et al., 2021](#)). On the contrary, passive language evaluations do not provide information on the level of awareness but can be informative of residual cortical capabilities beyond low-level sensory processing while having minimum cognitive demands. Crucially, patients with disorders of consciousness who show brain activity during passive language paradigms are associated with better outcomes ([Coleman, Davis, et al., 2009](#); [Di et al., 2007](#); [Fernández-Espejo et al., 2008](#); [Gui et al., 2020](#); [Sokoliuk, Degano, Banellis, et al., 2021](#); [Steppacher et al., 2013](#)). Therefore it

is important to develop patient-level language assessments that can capture the depth of speech processing independently of patients' cooperation or ability to engage with the stimuli. In this line, narrative stimuli can help refine our knowledge of the extent of mental life that is conserved in an individual with impaired consciousness (Naci et al., 2017). This naturalistic approach has been implemented to assess whether a patient produces brain responses correlated to the ones elicited by healthy participants when listening to the same narratives (Iotzov et al., 2017; Laforge et al., 2020). Research showing whether the common responses are due to speech acoustics or to the processing of linguistic information embedded in speech is lacking. The third study of this thesis focused on understanding which are the language properties that elicit EEG intersubject correlation (ISC) when individuals are exposed to common narrative stimuli. This is significant to determine the depth of language processing in unresponsive individuals who exhibit synchronization with healthy individuals' responses. We hypothesized that correlated EEG responses between participants would be elicited during attended and unattended speech and would be mediated by the processing of multiple levels of information that constitute speech. However linguistic information should evoke specific common responses when speech is consciously processed. Next, we summarize the main results and discuss the implications for DoC patients assessments.

We show that ISC is elicited during attended, unattended and passive listening of auditory narratives, and is overall sustained by the acoustic information embedded in speech. Compared to a distracted condition, attending to the stories produced an increase in ISC particularly for the second correlated component. Importantly, we show a distinctive behavior between the first and second ISC components and the evoked activities predicted by our encoding models. The first component was mostly affected by acoustic information with a similar behavior independently of attention. However, during the attentive condition, the activity predicted by models for linguistic features particularly contributed to the ISC indexed by the second component. In addition, word unpredictability explained more of the ISC than word onset. These results show that a proportion of the ISC is elicited by acoustic and linguistic information, and suggest that the second correlated component reflects speech processing beyond speech acoustics and word segmentation when individuals are consciously processing the narratives.

The results obtained while participants passively listened to narratives are highly relevant when considering the suitability of this approach to assess language processing in DoC

patients. During passive listening the distinctive behavior between the ISC components and the acoustic-linguistic speech properties was not observed. However, multivariate models that included word unpredictability accounted for a greater proportion of the ISC, suggesting that during passive listening at least some of the participants were integrating linguistic information beyond word segmentation and speech acoustics. This is supported by the positive correlation between ISC and the accuracy of the encoding models, where models for word unpredictability showed the highest correlation. A participant who strongly encodes the linguistic information of the stimuli is probably also encoding the envelope and the spectrogram, as extracting meaning requires the integration of hierarchical information across time scales (de Heer et al., 2017; Hickok et al., 2007; Lerner et al., 2011). As a result, their brain activity resembles that of participants who are tracking all the speech features or just the acoustic information. Our results show that a passive listening scenario is sufficient to capture acoustic and linguistic speech tracking at the subject level, rendering this approach highly appropriate as a bedside examination to determine not only the presence of covert cortical processing but the depth of speech processing in DoC patients.

Whether the evoked activity associated with linguistic information during passive listening reflects language comprehension or unconscious language processing can not be determined by our analyses. It is well established that low-level sensory information carried by speech can be encoded by the brain without awareness (Beukema et al., 2016; Makov et al., 2017; Portas et al., 2000; Scott et al., 2004). For example, a fMRI study shows that responses to speech in the temporal lobe during wakefulness are preserved during light and deep anesthesia, while semantic processing is reduced in frontal regions (Davis et al., 2007). Consistent with models that postulate that initial syntactic and semantic representations can be automatically activated (a. D. Friederici, 2002; Kumar, 2021), numerous evidence suggest that at least some linguistic processing can occur without conscious awareness. Studies on dichotic listening show that isolated words presented through the unattended channel can influence semantic decisions over attended speech, even when individuals report not hearing the primes (Dupoux et al., 2003; Rivenez et al., 2006). In addition, subliminal syntactic priming has been shown for grammatical category and grammatical number (Berkovitch et al., 2019), and syntactic incongruity effects can be elicited for unconscious stimuli (Hung et al., 2015). Furthermore, ERP studies show that lexical activation can occur at very early stages

of cortical processing during unattended speech (Shtyrov et al., 2010), and syntactic violations can elicit early EEG responses in the absence of awareness (Batterink et al., 2013; Jiménez-Ortega et al., 2014). Moreover, the N400, a classical marker of lexical access and contextual integration (Kutas et al., 1980; Kutas et al., 2014), can be modulated by masked semantic primes during a lexical decision task (Kiefer, 2002). In addition, semantic access indexed by the N400 has shown to occur even when words are not consciously perceived due to the ‘attentional blink’ effect (Luck et al., 1996; Shapiro et al., 1997), and although masked repetition priming is weaker and shorter-lived than unmasked repetition priming, it can still produce N400 lexical activation effects (Nakamura et al., 2018). This suggests that early and late cortical responses evoked by language stimuli can occur without conscious awareness, rendering these markers suboptimal for inferring the state of consciousness of a patient.

Comprehension of complex meaning requires awareness (Rabagliati et al., 2018), and without the patient’s report, it is not possible to conclusively determine whether there is conscious processing of the narratives. However, we argue that a reasoned approximation can be made by integrating evidence from the encoding models and the ISC exhibited by a patient. If a patient exhibits greater ISC with a group actively engaged with the narratives than with an unattentive group, while also showing that the evoked activity predicted by linguistic models affects the ISC indexed by the second correlated component, it would suggest conscious processing of the narratives. Interestingly, most of the ISC elicited by the stories is not explained by the speech features explored. We hypothesize that the remaining ISC is related to the neural integration at different time scales of different linguistic units (phrases and constituents), sub-lexical and lexical features (Gwilliams et al., 2024), and the resulting conceptual abstractions evoked by the stories. In addition, bodily responses to the narratives may also contribute to the ISC captured by the EEG (Madsen et al., 2024; Pérez et al., 2021). In general, a DoC patient showing ISC with subjects listening to the stories would indicate similar mental contents, thus implying overall preservation of language processing and other cognitive abilities like executive functions, attention, and working memory.

The methodological approach carried out in this study has multiple advantages over time-locked analyses of language stimuli. Although, language-related evoked responses are linked to a better prognosis (Ben Salah et al., 2023; Rohaut et al., 2015; Step-pacher et al., 2013), ERPs have several limitations. Numerous trials are required to

obtain a robust stimulus-to-noise ratio especially when aiming for subject-level analysis. Additionally, creating a balanced set of stimuli that do not introduce confounds while avoiding artificial constructions is difficult and time-consuming (Kaan, 2007). Carefully constructed language assessments based on mono-syllabic words and ITPC analysis (Gui et al., 2020; Sokoliuk, Degano, Banellis, et al., 2021) are limited by some of the same constraints. Moreover, it is probable that some languages do not allow natural constructions with the properties required to separate statistical properties from syntax. Conversely, TRFs can be obtained by exposing participants to 15 minutes of engaging narrative stimuli and can be fitted for each participant and feature of interest. Different levels of knowledge are involved in understanding an utterance. In particular, phonological, prosodic, syntactical, semantic, and world knowledge information interact strongly when building the meaning of an expression (A. D. Friederici, 2011; Hagoort, 2019), and language assessments in DoC patients do not exploit the potential of current language models to evaluate language processing in these patients. In this line, in addition to the potential of our approach to assess 'covert cortical processing', it provides a layered approach to study speech processing in DoC patients. For each patient, we could assess whether only the speech acoustics are tracked, if responses to linguistic information are also present, and how language processing changes over time. Notably, it has been suggested that improvements in language capacities parallel increases in the level of awareness (Aubinet et al., 2022). Finally, the task is not invasive, and auditory narratives are likely the most enjoyable stimuli for individuals in these clinical scenarios.

Perspectives

Numerous explorations could be carried out to improve the encoding models proposed here. For example, our word unpredictability models were obtained using long sentential contexts. An interesting possibility would be to test whether different context sizes can provide better models according to the attentional condition. We hypothesize that for unattended speech a few words before each target word result in better predictions as it is unlikely that without attention long contexts would be maintained in memory. Analogously, passive listening would benefit from 'middle size' contexts. In addition, the encoding models could be further adjusted to assess each level of speech with more specificity. Early acoustic features can be explored with shorter TRFs (0-250 ms) to

better capture the early auditory potentials, whereas TRFs adjusted for later times could be used to assess linguistic integration of both semantic and syntactic information (300-700 ms). Although not explored in this study, this approach could be extended to assess the tracking of phrases and sentences by constructing feature representations indexing the terminal nodes of constituents. Presumably, longer stimuli with short linguistic structures should be used in order to obtain a richer representation with which to train the encoding models. In addition, future experiments are needed to disentangle how the level of consciousness affects the speech-related ISC. This could be explored by studying the effects of sleep on the correlated activity and the level of linguistic contributions.

Final considerations

Stating the level of awareness of DoC patients is extremely challenging as it faces practitioners and families with a seemingly impossible situation: faithfully assessing whether an individual is aware of themselves or their surroundings. In the absence of consistent volitional responses observed through direct evaluation of behavior or indirect evidence from neuroimaging techniques and bodily measures, we can not determine beyond doubt whether an individual is aware. DoC patients challenge researchers to integrate knowledge on cognitive processes, behavior and neurobiology to develop tools that can capture the residual consciousness a patient may have.

Much like a biologist with an emergent view of 'life' considers that a set of properties have to be present in order to make a living thing alive ([Miller, 1962](#)), one approach to stating whether a patient is conscious is to have a description of the processes they can sustain, and which are necessary for a being to be aware. Although it is clear that agreeing on a set of properties is not without controversy, describing patients by their preserved functionalities can be clinically relevant to monitor their progress and guide their care. In this line, evaluations probing language capabilities, learning and memory formation, responses to visceral information, and quantitative EEG, can contribute to a description of consciousness in terms of degrees and varieties ([Ropper, 2010](#)). Importantly, evaluating patients using multiple modalities is associated to better accuracy in prognosis ([Rohaut et al., 2024](#)). In addition, multimodal graded assessments have been proposed and articulated into suggested pipelines according to the profile of responses a patient may have ([Comanducci et al., 2020](#)). In this line, we argue for the relevance of quantitative evaluations that have a hierarchically structure, enabling for multiple

processes to be assessed simultaneously. In our work, we tried to develop tools with these characteristics: the interoceptive-exteroceptive task allows to detect volition by assessing the attentional focus of a patient, but also cortical responses to heartbeats and brain dynamics can be measured as pseudo resting state markers. In addition with some modifications this paradigm can be used to detect cortical responses to sound and statistical learning. As for the task to evaluate language processing we can obtain individual measurements of overall engagement with the narratives as well as a finer description of the depth of speech processing.

Overall, this thesis offers novel non-invasive methods that can be used at the bedside to probe cognitive capabilities and awareness in patients with DoC. Importantly, the developed paradigms have varying degrees of complexity and require different levels of engagement, from passive to command-following tasks, allowing the exploration of multiple layers of information processing in patients with disorders of consciousness. Future work should focus on determining the level of specificity and sensitivity of these tools and work on their automatization for an easy clinical implementation.

Appendix A

EEG Intersubject correlation in DoC patients

152 patients with disorders of consciousness admitted for evaluation at the Columbia University campus of New York–Presbyterian Hospital were exposed to 148s of the first chapter of the audiobook ‘Alice in Wonderland’ in the forward (FWD) and backward (BWD) direction. Patients were exposed to the audio at least one time. 9 patients were removed from the study due to issues with the alignment between stimuli and recording.

A.0.1 Main hypothesis

We hypothesized that patients would show higher ISC during forward speech than during backward speech consistent with residual auditory language processing. Moreover, we expected that patients with higher GOSE scores should present higher ISC than patients with bad GOSE scores. Therefore patients were grouped into good (GOSE score > 3) and bad (GOSE score < 4) according to their best GOSE score.

A.0.2 Recording and preprocessing

EEG was recorded with 20 channels in a 10-20 configuration with a sampling frequency of 256 Hz and referenced to Cz. Data was filtered between 1 and 40 Hz with a bandpass filter (one-pass zero-phase FIR filter with a length of 8251 samples). Channels were rejected if their variance was above 3.5 standard deviations from the mean channel variance, this was iteratively performed 4 times. ICA was performed to remove ocular artifacts, bad channels were interpolated, and data was segmented following audio

onset/offset. Sparse artifact removal (De Cheveigné, 2016) was carried out using the meegkit library (<https://github.com/nbara/python-meegkit>) and an average reference was applied.

A.0.3 Analysis

The intersubject correlation was computed following the steps described in Chapter 4 by selecting randomly one assessment in which the patients were exposed to the FWD and BWD stimuli. Linear mixed-effects models were implemented in R (Team RStudio, 2022) to assess the effects of direction on the resulting intersubject correlation for the first three components for all patients and according to good or bad outcomes.

A.0.4 Results

ISC values were very low, and for most of the patients, they were not significant from chance after FDR correction. Only 19 patients showed an ISC above chance at least for the first component in any of the conditions.

We explored the effects of directionality and outcome on the ISC for all patients and for the group showing significant ISCs. No effect of directionality was found for component one ($\beta = 5.6e-4$, $SE = 3.22e-4$, $t = 1.74$, $p = 0.084$), two ($\beta = -1.61$, $SE = 3.21$, $t = -0.051$, $p = 0.96$), or three ($\beta = -4.85$, $SE = 2.78e-4$, $t = -1.74$, $p = 0.084$) and there was no interaction between outcome and directionality on the ISC components (p values ≥ 0.68) when considering all patients (Figure A.1A).

Focusing on the patients that exhibited significant ISC, there was a main effect of directionality for component 1 ($\beta = 5.8e-3$, $SE = 1.9e-3$, $t = 3.11$, $p = 0.01$), with no effect of outcome ($\beta = -1.7e-3$, $SE = 1.9e-3$, $t = -0.91$, $p = 0.37$), nor interaction between both factors ($\beta = -4.3e-3$, $SE = 2.6e-3$, $t = -1.63$, $p = 0.13$) (Figure A.1B). For components 2 and 3 there were no significant effects.

A.0.5 Limitations

The ISCs obtained from this dataset are limited because we are comparing ISC between DoC patients without a gold standard to determine what a normal ISC would be for the stimuli used. Following the analysis described in Chapter 4, we attempted to compute encoding models for the envelope, which showed the best prediction accuracies during

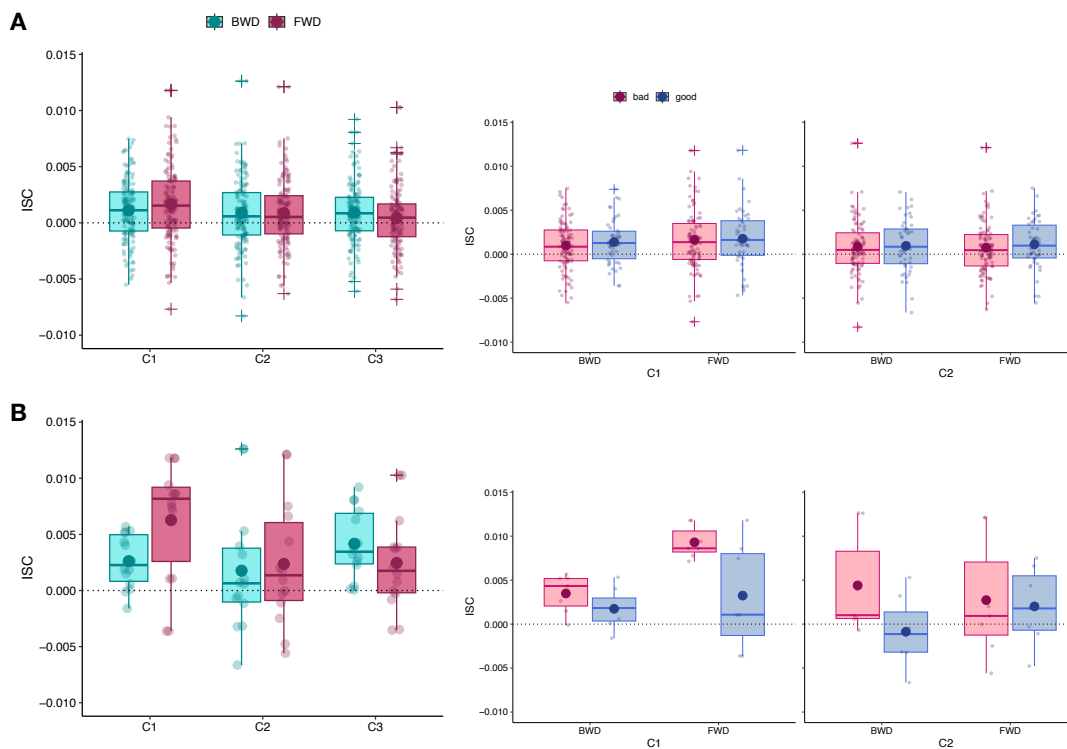


Figure A.1: ISC for DoC patients during narrative stimuli. **A.** Left. ISC for the first three correlated components during backward (BWD) and forward (FWD) speech. Right. ISC for components 1 and 2 for patients with good (GOSE score > 3) and bad outcomes (GOSE score < 4). **B.** Patients with ISC values above chance for component 1 in the forward or backward direction. Right. ISC for the selected patients for components 1 and 2 according to their outcome.

all attentional conditions. Nevertheless, the prediction accuracies for the models were too low to provide meaningful results. Another limitation is related to the behavioral assessment and recording selection. At the moment of these analyses, we only had access to the best GOSE score of each patient but not the behavior evaluations associated with each narrative assessment.

A.0.6 Perspectives

It would be important to obtain healthy participants' responses to the backward and forward speech stimuli during attentive and unattended conditions. This would allow us to evaluate how correlated the patients are to each group and study how these correlation scores relate to a patient's outcome.

In addition, future analyses should focus on selecting the patients' EEG recordings based on proximal behavioral assessments.

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