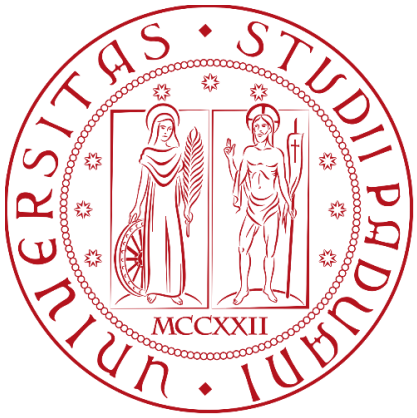

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HOW DO WE SEE THE WORLD? SPONTANEOUS BRAIN DYNAMICS PREDICT INDIVIDUAL VISUAL EXPLORATION PHENOTYPES

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ABSTRACT

Background

Over the last decades, the traditional view of the brain as a stimulus-response machine has been replaced by a new perspective that reconceptualizes *bottom-up* and *top-down* interactions. The brain is no longer considered only as a reflexive sensory-motor analyzer but also as a generator of predictive models, optimized during resting state endogenous activity to anticipate and interact with the environment more effectively. Notably, characteristics of spontaneous brain activity can predict eye movement dynamics during unconstrained viewing, reflecting an integration of *top-down* and *bottom-up* processing with endogenous dynamics, thus emphasizing the role of visual exploration as a window into the cognitive-behavioral functional organization of the brain.

Aim of the study

The aim of the present thesis is to replicate and validate the generalizability of previous findings shedding light on the link between oculomotor dynamics and endogenous brain processes. Specifically, a previous study (Zangrossi et al., 2021) found a low dimensionality of spatiotemporal dynamics of eye movements and identified distinct visual explorative phenotypes guiding spontaneous oculomotor dynamics both in free-viewing and resting state. Another study (Celli et al., 2022) utilized high-density EEG recordings to study the brain correlates of visual exploration phenotypes that were previously highlighted. This study suggested that the viewing styles were related to different patterns of spontaneous brain activity in resting-state. This thesis seeks to replicate and validate all these results on a new sample, exploring the connection between eye movement dynamics, memory recall of visual stimuli, intrinsic brain activity and, moreover, to identify distinct patterns in eye movement and hdEEG data for potential clinical applications.

Materials and methods

A total number of N = 64 healthy participants were simultaneously measured for eye movement dynamics and oscillatory brain activity using a state-of-the-art static

infrared eye tracker and a 256-channel electroencephalograph, respectively, in order to highlight the role of spontaneous brain activity in determining distinct visual exploratory phenotypes. For the purpose of the study, have been considered the data recorded during a resting state phase, in which subjects were asked to gaze quietly at a blank grey screen for 5 minutes, and during a 10 minutes unconstrained free-viewing of 90 real-world scenes.

Results

Analyzing eye tracking data from the free-viewing phase (of 62 out of 64 participants), we found that three principal components (PCs) accounted for 60.2% of the variability in oculomotor movements. Based on the PC1 values, mostly loaded on fixations' features, we identified two distinct clusters of visual exploratory styles: *Static Viewers*, characterized by longer fixation durations and viewing times but fewer fixations and gaze shifts, and *Dynamic Viewers*, with opposite traits. This two-group classification supports the hypothesis that intrinsic factors drive visual exploratory behavior. We then computed eyes-open resting EEG data (of 58 of the 62 participants whose eye movements were computed) employing a nonparametric permutation technique with cluster correction, which showed directions in the correlations between PC1 values and frequency band averaged powers consistent with a previous study (Celli et al., 2022).

Conclusions

Our replication study results confirm the possibility to cluster subjects explorative phenotype according to their oculomotor dynamics features and their intrinsic oscillatory brain activity. This complex spontaneous behavior depend on the interplay between *top-down* and *bottom-up* processing with endogenous activity. We propose that oculomotor dynamics and oscillatory correlates can be employed as a window to enlarge our knowledge concerning the innovative *inside-out* brain perspective and that subject profiling may have potential implications on early-diagnostic methodologies.

SOMMARIO

Background

Nel corso delle scorse decadi, la prospettiva classica che da sempre inquadra l'encefalo in una dimensione di causale meccanicismo stimolo-risposta, ha progressivamente lasciato spazio ad una visione che riconcettualizza le interazioni tra dinamiche *bottom-up* e *top-down*. L'encefalo non è più considerato solo come mero analizzatore sensori-motorio, ma anche come un generatore di modelli predittivi, i quali, ottimizzati durante gli stati di quiete mediante le dinamiche dell'attività neurale spontanea in assenza di input da elaborare, agiscono in modo anticipatorio nei confronti delle condizioni ambientali circostanti interagendovi in maniera più efficace. La caratterizzazione di questa attività neurale endogena può predire le dinamiche dei movimenti oculari durante l'esplorazione visiva non condizionata, riflettendo l'interazione di processi *top-down* e *bottom-up*, interazioni funzionali su cui si basa l'organizzazione cognitivo-comportamentale cerebrale.

Scopo dello studio

Questa tesi si propone di replicare e validare risultati sperimentali pregressi riguardanti una connessione tra dinamiche oculomotorie e processi cerebrali endogeni. Nello specifico, uno studio precedente (Zangrossi et al., 2021) ha riscontrato una bassa dimensionalità dei pattern spaziotemporali dei movimenti oculari e parallelamente ha identificato differenti fenotipi di esplorazione visiva, caratterizzanti i movimenti oculari spontanei sia in condizioni di libera esplorazione visiva che di stato di quiete senza stimoli visivi. Un ulteriore ricerca (Celli et al., 2022), impiegando registrazioni EEG, ha studiato le correlate neurali dei fenotipi esplorativi visivi riscontrati nel lavoro precedente. Ciò suggerisce come gli stili esplorativi siano legati a distinti pattern di attività neurale a riposo. Replicazione e validazione vengono condotte su un diverso campione, esplorando le connessioni funzionali tra le dinamiche oculomotorie, il richiamo mnemonico di stimoli visivi, l'attività cerebrale spontanea, aprendo a potenziali applicazioni cliniche.

Materiali e metodi

Un campione di N=64 soggetti sani si è prestato a concomitante registrazione di movimenti oculari e correlate EEG, tramite un eye tracker statico ad infrarossi e elettroencefalografo a 256 canali, al fine di evidenziare il ruolo dell'attività cerebrale spontanea nel determinare distinti fenotipi esplorativi visivi. Sono stati considerati i dati registrati durante una fase di stato di quiete, in cui ai soggetti è stato chiesto di osservare uno schermo grigio per 5 minuti, e durante una fase di visione libera non vincolata di 10 minuti di 90 immagini di ambienti reali.

Risultati

Procedendo con l'analisi dei dati di eye tracking della fase di visione non vincolata (di 62 dei 64 partecipanti) si è verificata la possibilità di descrivere impiegando tre componenti principali (PCs) il 60,2% della varianza nelle dinamiche oculomotorie. Basandosi sui valori di PC1, ponderata sulle caratteristiche delle fissazioni, abbiamo identificato due distinti cluster di stili esplorativi: *Osservatori Statici*, caratterizzati da tempi di fissazione e di visione maggiori ma un minor numero di fissazioni e spostamenti dello sguardo, ed *Osservatori Dinamici*, con pattern opposti. Questa suddivisione supporta l'ipotesi che fattori intrinseci guidino il comportamento esplorativo visivo. Successivamente, sono stati calcolato i dati EEG a occhi aperti a riposo (di 58 dei 62 partecipanti di cui erano stati calcolati i movimenti oculari) utilizzando una tecnica di permutazione non parametrica con correzione per cluster, che ha mostrato direzioni nelle correlazioni tra i valori del PC1 e le bande di frequenza coerenti con uno studio precedente (Celli et al., 2022).

Conclusioni

I risultati della replicazione confermano la possibilità di classificare i fenotipi esplorativi dei soggetti basandosi sulle caratteristiche della loro dinamica oculomotoria e sull'attività cerebrale oscillatoria spontanea, trattandosi di un complesso comportamento spontaneo risultato dell'interazione tra processi *top-down* e *bottom-up* con l'attività endogena. Proponiamo che la dinamica oculomotoria e i correlati oscillatori possano servire come strumento per ampliare la nostra comprensione della innovativa prospettiva del cervello *inside-out* e che il profiling dei soggetti possa avere potenziali implicazioni in diagnostica precoce.

INTRODUCTION

1. SPONTANEOUS ACTIVITY, TOP-DOWN DYNAMICS AND GENERATIVE MODELS IN THE PREDICTIVE BRAIN

1.1. Historical assessment of the issue

During the late 19th and early 20th centuries, alongside pioneering studies in brain physiology and cytoarchitecture by Cajal, Brodmann, Wernicke, Golgi and many others, yet an issue regarding a dichotomy in brain functionality was brought up by some neuroscientists. William James, already in 1890, stated "*Whilst part of what we perceive comes through our senses from the object before us, another part, and it may be the larger part, always comes out of our own head*"[1,2]. This quote reflected an early debate present at the time, with one perspective, influenced by Sir Charles Sherrington, viewing the brain as primarily reflexive, driven by contingents requests of the enviroment[1,3], while another, promoted by Sherrington's disciple T. Graham Brown, argued for its intrinsic operativity in interpreting, responding and predicting environmental demands[1,4]. This debate laid the groundwork for understanding the brain's complex relationship between external inputs and internal processes.

Traditionally, scientists have explored the brain's function by analyzing its responses to controlled stimuli at the level of single neurons, cortical circuits, or larger systems.[5,6]. Most of the experimental settings were typically based on an action-reaction logic, a causal mechanicism that could explain the majority of physiological and pathophysiological dynamics across various systems in the human or experimental animal body and also gradually expanded the understanding of the brain, with many decades of excellent animal and human neuroscience research that revealed robust and often predictable patterns (of single neuron and neural population) responses to external stimuli[7]. However, although functional in handling a set of initial information, this approach has produced, beyond a decent understanding of basic dynamics, a broad dimensionality concerning higher level brain-wide activity, resulting in a confusion in the overall comprehension of the *file rouge* in cerebral functional dynamics. The notion of causality is, indeed, especially problematic concerning self-organized systems with

enhancing-suppressing feedback loops, like the brain: events don't have a single cause but instead emerge from the interaction of various elements[8].

The urging need for a better understanding of brain organization pairs with the innovative scenarios in neurological disease treatment that this kind of knowledge would inspire, especially in a future prospective of personalized medicine. The uniqueness of human behavior translates, in fact, from the healthy to the pathological brain dynamics. To fully comprehend and treat the latter, we must not remain limited by an incomplete understanding of the former. That's why the brain has often been referred to as one of the final frontiers for science and medicine[7].

1.2. Top-down dynamics and the Brain from Inside-out

Relying solely on the traditional *outside-in* approach[7] (which reflects mostly *bottom-up* processing dynamics), characterized by information processing that moves in a single direction from sensory input through perceptual analysis to motor output, without incorporating feedback information flowing backwards from "higher" to "lower" centers[7,9], may not be enough to clarify how the brain processes information that result in meaningful behaviors. This latter aspect is pivotal considering the brain, a sophisticated evolutionary tool whose ultimate goal is to predict the outcome of any interaction of the body with the surrounding environment, in order to survive and adapt, thus, ultimately, regulating "actions"[1,10]

Over time, increasing significance has been attributed to the alignment of *bottom-up* processing with *top-down* processing. The latter can be defined as a stream of information from "higher" to "lower" centers which conveys knowledge from previous experiences rather than sensory stimulation[9]. This shift ultimately gave rise to a new perspective: the *inside-out view,* which states that the brain functionally engages a preexisting, self-organizing, and self-perpetuating set of neural elements[7]. The interactions among these elements are constrained by the biophysical properties of cells and networks within the brain[7]. According to the *inside-out view*, "actions" should also include the outcomes of neural processing (for instance, providing a "second opinion" in order to validate the meaning and significance of sensory signals[8]). that do not involve *overt* (observable and

measurable behaviors that involve physical movements or verbal responses, which can be directly monitored and analyzed in a research or clinical setting, see 3.1) acts, such as a thought or a recalled memory[7]

György Buzsaki explains this concept in terms of a relationship between a blank state and preconfigured brain models[8]. In the empiricist *outside-in* model, brain starts out as a *tabula rasa* onto which new information is cumulatively written; thus, expanding brain circuits through juxtaposition and superposition, in order to accommodate the amount of newly learned knowledge[8]. The contrasting *inside-out* model views the brain as a dictionary supplied with preexisting internal dynamics and syntactical rules (brain rhythms might provide a framework for neural syntax), which are initially filled with non-sense neuronal words; these have the potential to gain significance through exploratory actions[8]. The brain's distinct components (such as firing rates, synaptic connection strengths, and the magnitude of collective behavior of neurons) lead to a range of distributions, whose two extremes offer complementary advantages: the *"good-enough brain"* can generalize and act quickly, and the *"precision brain*" is slow but meticulous, providing necessary details in many situations[7,8].

Consequently, within preconfigured brain models conceptions, greater significance is assigned to spontaneous brain activity, which has been instead traditionally perceived only as stochastic noise, modeled as random fluctuations able to conditionate thresholds for postsynaptic firing, thus affecting the transmission of information within and/or between cortical circuits[6]. Those fluctuations were firstly recognized and characterized by the early EEG recordings by Berger in 1929[11]. Regarding the issue, he once stated "*mental work, as I explained elsewhere, adds only a small increment to the cortical work which is going on continuously and not only in the waking state*"[12] highlighting the spatiotemporal significance of this intrinsic ongoing cortical activity compared to task-evoked signals. This perspective persisted until early spontaneous fMRI studies, almost sixty years later, changed a bit the perspective: "noise" BOLD signals were proved to exhibit striking patterns of spatiotemporal coherence with sensorimotor regions, revealing organized patterns of activity that occurred in the absence of any *overt* motor activity[12].

It is now evident that intrinsic brain activity plays a central role according to these new theories of brain functioning. Thus, endogenous activity is progressively being viewed as an essential element for understanding *top-down* dynamics, rather than stochastic noise. Resting state activity can be seen as a facilitator of task-related activity modulating *priors* (see 1.5).

In the next paragraphs it will be discussed how cortical activity patterns extend beyond mere sensory-motor analysis and how resting-state activity optimizes subsequent task-engaging interactions with the surrounding environment. This will be explored from the *inside-out* perspective of *top-down* dynamic processing as previously discussed. Next, visual exploration dynamics and their EEG features will serve as a prime example of *top-down* and *bottom-up* interactions, supporting the experimental assessment presented in this work (chapters 3 and 4).

1.3. Spontaneous brain activity: a Restless Brain

When the brain receives no sensory stimuli nor is engaged in task-related activities, still it is constantly active: spontaneous brain activity (also defined as endogenous or intrinsic) consists of sophisticated dynamical patterns of activity that emerge spontaneously across cortical and subcortical structures[12–14]. At the level of large scale systems, these patterns are systematically organized in a series of functional networks that maintain at all times a high level of coherence[15]. This activity, once referred to as "noise", is correlated in space and time; furthermore it can be composed of lower or higher frequency activity, each hypothesized to have a different meaning possibly related to *priors*[13].

Resting-state activity (RSA) consists of a concept, even if physiologically almost defined (see 1.4), difficult to completely frame[16]. First of all, it has to be distinguished from the "*arousal baseline*", the continuously ongoing intero-/exteroceptive input integration from the body and environment[17]. RSA, operatively, reported as a "property of the brain state that exists before a stimulation of interest"[18], anti-correlated with task-engagement (as further explained in paragraph 3.2.3), was initially only thought to be characterizing of the Default

Mode Network (DMN, Figure 1), which is otherwise still considered as the hierarchical apex of the so called Resting State Networks (RSNs, see 1.5).

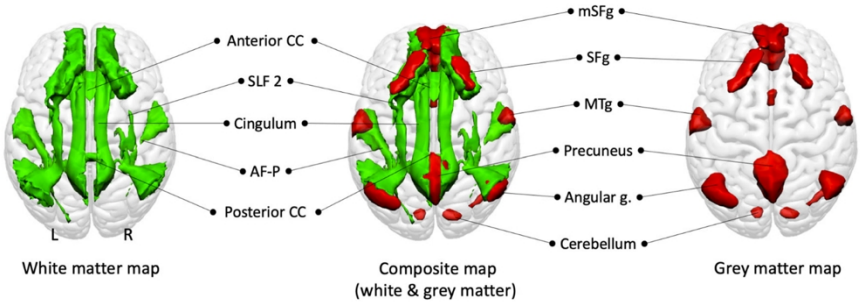


Figure 1: Default Mode Network (RSN18) maps, dorsal view. *In green the white matter map while grey matter map in red, composite map displayed in the middle. Within-related cortical regions: ventromedial prefrontal cortex (VMPFC); dorsomedial prefrontal cortex (DMPFC); sub-/pre-/supra-genual parts of the anterior cingulate cortex (ACC); posterior cingulate cortex (PCC);, medial superior frontal gyrus (mSFg); Middle temporal gyrus (MTg); Superior frontal gyrus (SFg) and precuneus (all anterior and posterior cortical midline areas; some overlap with other networks)). Additionally, certain regions adjacent to the midline, such as the lateral parietal cortex and hippocampus, are also highlighted* [16,19] *The main white matter tracts highlighted: Arcuate fasciculus, posterior segment (AF-P); Second branch of the superior longitudinal fasciculus. The cerebellum is visible through the glass-brain effect*[19].

Imaging and electrophysiological studies, indeed, proved that high RSA may be also observed in sensory cortices, prefrontal cortex, motor cortex, insula, visual cortex; even subcortical regions are characterized by this activity, such as thalamus, hypothalamus (suprachiasmatic nucleus), the ventral tegmental area and hippocampus (see Figures 4 and then paragraph 3.1.2)[16]. Consequently it is evident that a widespread sustained brain activity (brain-wide RSNs) like this must mean something, beyond randomly occurring firing aimed at modulating post-synaptic treshold as traditionally perceived. Finally, these predictive and proactive dynamics occur constantly, during any given disengaged moment, in order to prepare and optimize brain dynamics for future interactions[13]. In the next paragraphs will be exposed some innovative research lines, in order to clarify all the implications of resting state activity.

1.3.1. Infra-slow activity and energy budget

The brain is never truly physiologically at rest, as evidenced by continuous intrinsic activity and consistently high energy consumption, which shows minimal variance between the resting state (behavioral state marked by peaceful relaxation, typically with eyes closed but sometimes with eyes open, with or without visual fixation[1]) and periods of task-engagments[1,13].

A series of experimental assessments over the years showed that the infra-slow activity band activity (ISA, defined as in between 0,01-0,1Hz interval) and infra-slow fluctuations (ISFs) are central in the spontaneous activity dynamics spread brain-wide across resting-state networks (RNSs). These intrinsic dynamics, mediated by ISA and ISFs, have been shown, using different techniques such as resting state BOLD-fMRI, to be independent phenomena and not a mere low-frequency analog of faster neural activity[20]. Whole cortex calcium/hemoglobin imaging in mice, showed stereotypical state-dependent ISA trajectories, different from paths of higher frequency activity; consistently with mice laminar local electrophysiology which showed that ISA crosses distinct cortical layers and exhibits distinctive cross-laminar temporal dynamics, which differ from the higher-frequency local field potential activity[20]. Moreover ISFs observed in electrophysiological recordings, fMRI- BOLD signals, neuronal activity levels and behavioral time series, probably represent a unified phenomenon: overarching network of interacting and transiently oscillatory ISAs. This activity appears to play a dual role in concurrently active neuronal clusters, regulating both their within-integration and the between-dissociation[21].

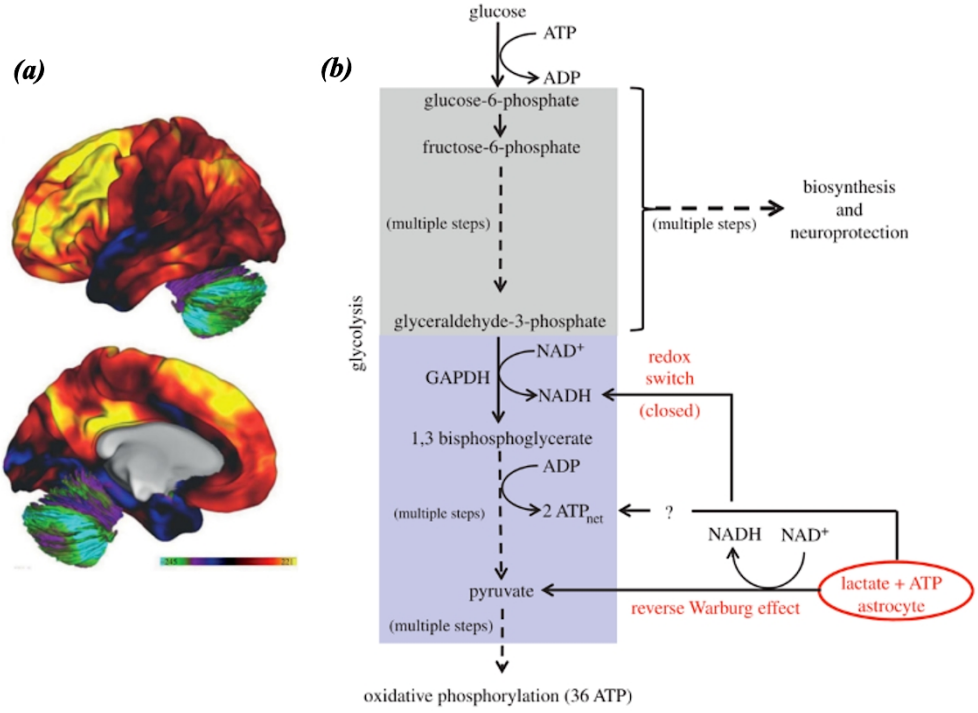


***Figure 2: Brain energy budget**. **(a) Adult human brain lateral and medial surfaces aerobic glycolysis map**, il lustrating the significantly changes in levels of aerobic glycolysis vary significantly throughout the brain[22]. The olor bar represents a glycolytic index, providing a quantitative measure of glycolysis[23]. **(b) Overview of glycolysis in neural tissue**, with biosynthesis/neuroprotection elements (grey) and energy generation components (blue) highlighted in two colored boxes. Astrocyte-derived lactate (generating a reverse Warburg*

effect) serves as a substrate for energy production through oxidative phosphorylation, while, altering neuronal redox potential (defined as redox switch) redirects glycolysis towards biosynthesis and neuroprotection. Finally, astrocytes release ATP alongside lactate, suggesting potential regulation of neuronal activation states via K-ATP channels[22]. Those are the basis of the symbiotic relationship between astrocytes and neurons[22,23].

The brain, although being only 2% of the body weight, consumes up to 50% of the energy during development and then, in an adult, approximately 20% of the organism's energy overall (as seen in Figure 2): this energy budged is partially devolved (25-40%) to housekeeping functions (gene expression and protein synthesis, lipid turnover, microtubule remodeling and so on) but mostly to electrochemical signaling (60-75%) with spikes accounting for 10% of this allocated budget (metabolically expensive, they occur only in subsets of neurons firing simultaneously, from 1 to 10%) and with infra-slow intrinsic activity (ISA and ISF) which is the most energetically demanding dynamic process[12,13]. In summary, most energy is, indeed, spent on resting potentials and sub-treshold activities, not spikes.

So, as just discussed, brain is never truly physiologically at rest and most of its energetical budget is aimed to sustain intrinsic activity, recorded both as ISA and ISFs, which stands as an independent phenomena from spikes and task-engaged activity. These findings support a fundamental (although yet only partially known) functional role of RSA, considering the metabolic relevance that has been highlighted with different techniques and studies. Interestingly, what these research lines proved is consistent with Berger's statement referring to his EEG recordings in 1929 as discussed in the previous chapter, both from a physiological and a metabolic points of view.

1.3.2. Level of similarity between anatomical structure and functional connectivity

Studies of the human brain conducted with fMRI BOLD imaging revealed remarkable patterns of spatial and temporal coherence of intrinsic activity (mostly infra-slow activity as discussed in the previous paragraph) first of all within known networks[12]. The functional connectivity involved, emerges as structured linear fluctuations around a stable low firing activity state close to destabilization,

according to computational modeling of fMRI data, closely linked to (and constrained by) the underlying anatomical connectivity[24].

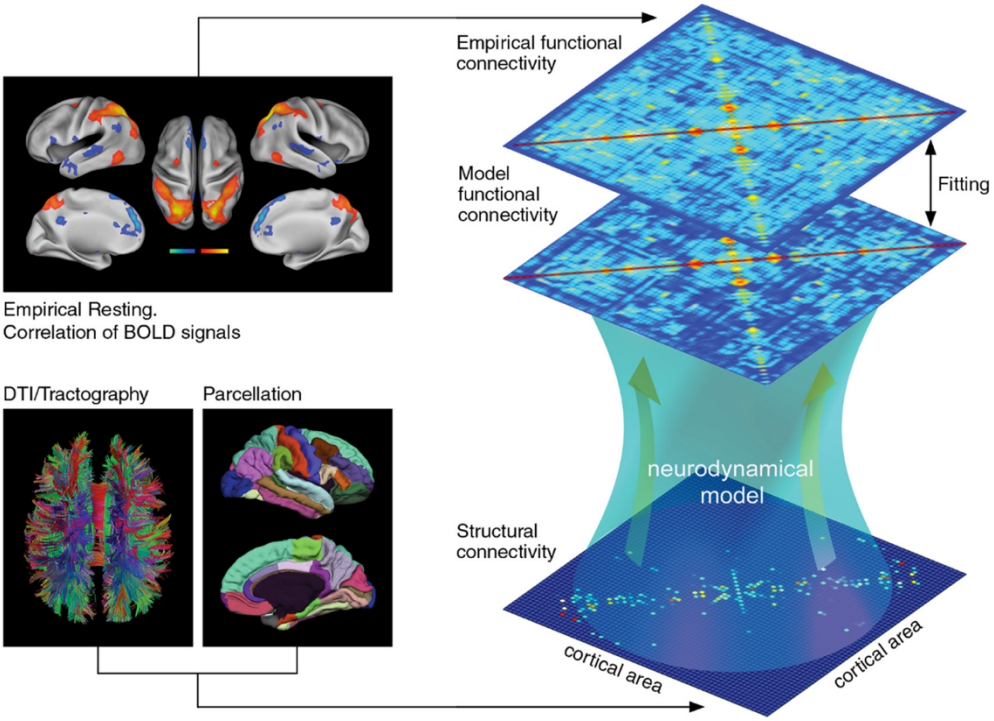


Figure 3: Framework to study the link between neuroanatomical connectivity data *(DSI and tractography after averaging across subjects)* ***and observed functional connectivity*** *(measured employing fMRI BOLD activity). Parcellation provides a connectivity matrix C linking the N cortical areas with clear anatomical landmarks; Using this connectivity matrix C, a neurodynamical model was created based on a set of coupled stochastic differential equations. The model's spatiotemporal patterns were then validated by comparing them with those observed in empirical functional data*[24].

These findings concerning widespread infra-slow activity, no longer characterized as noise, have over the years led to the description of a dual nature within known networks depending on task engagement or disengagement. Furthermore, researchers have defined functional connectivity correlations between different areas regardless of their task engagement activity during disengaged states. These correlations act as a *priors* for future task engagement, differing based on the cognitive state. Networks of spontaneous activity correlation are known as Resting State Networks (RSNs), which are defined as: "*brain regions that activate or deactivate together during spontaneous brain activity at rest and are jointly active during behavioral tasks. The equivalence rest-task is not complete as most tasks involve the recombination of resting state networks*"[13].

They show, indeed, a close relationship with the underlying anatomical connectivity; however, their spatial distribution is also influenced by previous task engagements[13,15]. This functional modulation may facilitate the retention of previous information and may impact future task-dependent networks recruitment, thereby influencing behavioral outputs[15]. Importantly, these networks need to be differentially considered across distinct levels of consciousness[12]: during sleep or anesthesia, their functional connectivity closely reflects the anatomical connectivity, but in the awake state a differential gap between the two connectivities has been observed (although the absence of monosynaptic connections between certain areas, which do not preclude multisynaptic functional connectivity systems[25]) that pairs with the theory of enrichment that arousal and cognition produce to the static anatomical architecture, which furthermore changes due to eventual task-engagment[13].

Regarding spatial architectural distribution of areas recruited within RSNs, the influence of previous task engagements is something consistent both with the notion of RSNs serving as *spatial priors* themselves and with the fact that their topography is shaped by the history of regional coactivation throughout development and experience[6,26]. RSNs activity represent in fact both *spatial* (connections that synchronizing during task performance, maintain a high coherence level even during rest[6,26]) and *temporal* (slow spontaneous fluctuations regulate the excitability of cortical circuitries during task performance, acting as rhythmic streams that shape differential excitability states[6,27]) *priors* for task-evoked activity[6].

RSNs functional connectivity relies on coherently low-frequency oscillating neuronal groups, whose rhythmic excitability fluctuations produce temporal input- and output-windows for communication, which are “accessible” in variable ways across different consciousness levels[28]. Nodes in these networks act as flexible hubs, adapting connectivity patterns to task demands, and also exhibit broadly distributed across-network connectivity, suggesting involvement in large-scale brain activity coordination[29]. Will be then discussed the importance of covariance through learning, development and different conditions, and moreover how all these implications affect strength of coherence between nodes within systems[12] (ensured

by beta band frequency oscillations, see chapter 4) which modulate the effectiveness of spatial and temporal *priors* for brain engaged state.

1.3.3. Intrinsic brain activity and subject phenotypes

RSNs can be evaluated concerning different cognitive states through life stages of the animal (development, age, learning, behavioral state, health and disease; see next paragraph) or between different individuals, employing a between differentiation according to endogenous activity dynamics themselves. For instance, they can be implemented as a feature for subjects' profiling: individual differential coherence within RSNs functional organization has been verified and stated by numerous studies[13]. Utilizing "Human Connectome Project" fMRI dataset, connectivity profiling (e.g. subjects identification within a group) proved successful regardless of the engaged or disengaged state scan session, suggesting the intrinsic nature of the profiles themselves[30].

Interestingly, frontoparietal networks emerged as the most distinguishing between individuals, through positive and negative (e.g. correlation and anti-correlation) feature models analysis[30]. Finally, those same networks, the most distinguishing, were also the most behavioral predictive[30], estimating individual predisposition to new behaviors too[13].

Significantly, Dorsal Attention Network (DAN) belongs within those frontoparietal networks and is part of the RSNs; therefore, it also has a fundamental role both in attention and eye movements dynamics[31] acting, for example, as a preparatory coordinator of oculomotor dynamics toward the salient stimulus, inducing a shift of attention in the same direction (see further, chapter 2). It is closely linked to the aim of this thesis' study, which is to identify visual explorative dynamics phenotypes (consistently with the functional connectivity profiling) and to relate them not only to eye-tracking features but also to spontaneous EEG features. Moreover this profiling was conducted utilizing data both from resting-state and free-viewing (see Experimental settings, chapter 6) recordings, according to the intrinsic nature of the issue, regardless of task-engaging or not.[32,33].

1.3.4. Spontaneous activity patterns and their covariance in clinical conditions or physiological learning and behavioral state

Spontaneous activity patterns covariance changes in relation to development, age, learning and diseases[12,13]. Studying resting state functional connectivity of DMN, for example, was shown deviation in children connectivity compared to adult architecture[34]. Across various ages, default-networks become more integrated via myelin sheath maturation and a process of "*integration trough synchronization*" which occurs because of complex spatiotemporal synchronous activity over time with and without changes in synaptic strengths[34,35] (see also 4.2.6).

These findings are supported also by studies on resting EEG, which indicate that signal coherence within the alpha rhythm between posterior and anterior electrodes rises with age[36]; alpha rhythm is neurophysiologically pivotal studying resting state intrinsic activity and, as in the study of this project, also relates with visual explorative dynamics.

On the other hand DMN has also been extensively studied relatively to its changes in aging people. This is consistent with role of experience (cumulative learning[26] over lifespan) and spontaneous activity itself, which shapes functional activity over years[12]. After sixth decade, considering healthy individuals, regression of the young adult pattern is often evident either in DMN as other networks functional connectivity[37]; this process is quickened and amplified, for example, by amyloid plaque deposition, which early affects DMN and its integration with other networks in the physiopathology of Alzheimer Disease (causing prominent atrophy and metabolic disruption in posterior cortical regions such as posterior cingulate, retrosplenial, and lateral parietal cortex, consistently with those in medial temporal regions[38]). That's in line with the innovative upcoming use of eye-tracking as a tool to be implemented in early diagnostic processes of Alzheimer Disease: DMN and other resting networks interaction drive, as said before many rest and task dynamics, one of them is visual exploration. In particular limbic structures, which are considered the first targets of amyloid deposition and are involved in visual processes besides of memory functioning (see Discussion, chapter 10).

Networks strength and integrity relates to behavioral performance[15]. Apart from the well-studied molecular and functional abnormalities in Alzheimer's Disease, many other conditions have been investigated. The involvement of intrinsic functional

connectivity alterations has been proven[13], particularly concerning motor and attentional impairments (such as in acute conditions like stroke)[39], as well as cognitive and behavioral impairments (such as dementia, schizophrenia, and others). Furthermore, that's deeply related with role of *priors* which is of increasingly interest: excessively strong *priors* could be etiologically related to depression, obsessive-compulsive disorder or schizophrenia reflecting abnormally low sensitivity to low-level stimuli and predictions, while excessively simplification of *priors* may also be an explanation concerning loss of memory or semantic information in neurodegeneration, trauma, and stroke[13].

1.4. Similarity between task-evoked and spontaneous brain activity

The interaction between task-evoked and spontaneous activity is bidirectional: visually evoked responses, for example, reverberate through spontaneous activity[40] , while spontaneous activity itself accounts for the variability in stimulus-evoked responses[13]. Voltage-sensitive dye imaging in rat visual cortex showed reverberation of spatiotemporal activity pattern resembling evoked response, as spontaneous waves, following repetitive presentation of a given visual stimulus[40]. This phenomena goes on for several minutes in absence of any other visual stimulation[40]. Functional connectivity strengthens observed across tasks, closely resembles those observed during rest, representing intrinsic architecture of functional brain organization[41].

A fundamental requirement for perception and cognition is the capacity of neural circuits to maintain the representation of a sensory event for a certain duration following its occurrence[13,40]. Dan et al observed: "*Such wave-mediated reverberation could contribute to short-term memory and help to consolidate the transient effects of recent sensory experience into long-lasting cortical modifications*"[40].

Almost 60 years apart, this concept closely pairs with Hebbian plasticity which postulated that sustained reverberating activity within cells clusters could generate consolidation of short-term memory and, lasting enough (via cell "growth process") enabling long term memory[42]. His innovative concepts were inspired by the

foundational work of Cajal, a pioneer cytoarchitectural scientist, considered one of the fathers of modern neuroscience, who postulated about the necessity of structural changes to maintain memory traces formed during learning[43]. Moreover, at the same time it anticipated the idea of long-term potentiation firstly postulated by Bliss and Lömo in 1973[44]. Defined the influence of task-engaged activity on modulating (not only cytoarchitecturally and anatomically, but in modern era we know that also and foremost that functional connectivity is the one shaped) intrinsic brain activity and their mutual centrality discussing significance of *priors* and generative models.

In 1996 real-time optical imaging was used to study the cat visual cortex, while electrophysiological techniques simultaneously recorded local field potentials and single neuron discharges: evoked activity appeared deterministic and its large variability could be explained by the intrinsic ongoing activity. A linear summation of both could predict single trials evoked response[45]. Interestingly, this is not only a neocortex-related phenomena: both human neuroimaging and single cell rodent recordings showed that following firing activation of place cells along space trajectory, neural activity of sequential replays could be determined (not only summarizing visual experience, but mostly generalizable abstract representations) which occur during non-REM (NREM) sleep and wakeful rest[13]. These replays spontaneously reorganize experience based on learned structure and are factorized, allowing fast structural generalization[46]; these sequences involve high-frequency ripples (up to 120-150Hz) and are temporally coordinated with infra-slow intrinsic activity[13,46]. At rest, hippocampal-entorhinal system and neocortex spontaneously are strongly interconnected (underlying also the evolutional conservational development regarding endogenous brain activity) and their communication is based on real and fictive spatial trajectories, decoupled from current sensory inputs [47].

This is a good example of the wide-brain dynamics of spontaneous neural activity, but the hippocampus also serves as a model of consistent predictability within generative models. Preplays of future firing sequences consists of intrinsic ripple dynamics of the place cells themselves, temporally coherent with the sequences of novel spatial experience, which occur during rest or slow-wave sleep: this arranges

functional cellular clusters in temporal sequences to support the encoding of a novel experience that might occur, or is expected to occur, in the future [48].

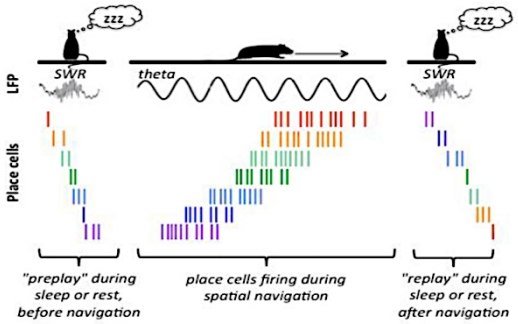


Figure 4: Schematic illustration of internally generated hippocampal sequence, example of spontaneous brain activity. *Each depicted with a different color, seven place cells of the hippocampus spatiotemporal sequence of spikes, any with place field located in different sections of the maze (central part of the figure), visible within the hippocampal theta rhythm during navigation. Same- or reverse-ordered sequential activity, can be decoded during animal sleep or awake rest before ("preplays") and after ("replays") navigation, respectively, often embedded sharp-wave ripple (SWR) complexes.*

According to the evidences exposed in this and the previous paragraphs, stimuli processing accounts only for a part of task-evoked brain activity, while a larger portion can be attributed to intrinsic activity (both in whole-brain networks and single regions) occurring immediately before the onset of stimuli themselves[13]. From that prospective, the dichotomy between task-evoked and spontaneous activity partially loses its meanings and can be misleading: spontaneous activity at rest may reflect the *top-down* dynamics of generative models which can also produce spontaneous dynamics immediately before and during task-engagement: these create the context for stimulus processing[12,13]. Moreover, slightly differences occur relating to the role of generative models during task performance, which prepare to process specific stimuli and upcoming actions, and their role at rest which is to arrange a wider range of responses in future behaviors, in a context independent way[13]. This is consistent with the experimental settings that studied hippocampus and all the previous research lines concerning intrinsic brain activity exposed.

1.5. Generative models, priors and the Predictive Brain

When referring to generative models, we talk about AI generative neural networks (composed of neuron-like units) which can construct sophisticated, distributed

representations of the data by identifying statistical patterns entirely through unsupervised methods[13,49]. These models are essential to move forward from different levels of statistical limitations, from Bayes's theorem (which quantifies the probability of an event, considering prior knowledge of conditions potentially associated to the event itself[50]) driven approaches, to more effective AI neuron-like modelling. They gradually replaced the backpropagation learning procedure, whose layered networks, although able to computationally accommodate and learn multiple layers of representation from sensori stimuli, needed trained labeled data[51] .

Using multilayer neural networks that contain both *bottom-up* "recognition" connections and *top-down* "generative" connections[52] it is possible to overcome those limitations and switch to generative learning, whose aim is "to model the joint distribution of all the variables in the model, thus including also the observed variables"[53]. In other words, the *top-down* connections are able to produce (instead of classifying it, as neural network models are classically trained to) fictive (sensory) data, generating a whole distribution of data-vectors: these will interact with *bottom-up* recognition connection, that can approximate the inference[52], helping to solve uncertainty[13].

These advanced neuron-like network, which contemplate either feedforward and feedback connections, have been implemented in studying both physiologically cognitive-behavior dynamics and pathological conditions etiologically caused by an impairment between *top-down* and *bottom-up* dynamics[53], such as positive visual symptoms in many psychiatric and neurologic conditions such as narcolepsy–cataplexy syndrome, peduncular hallucinosis, treated idiopathic Parkinson's disease, Lewy body dementia without treatment, Charles Bonnet syndrome, schizophrenia, hallucinogen-induced states and epilepsy. Any of these visual hallucination (potentially or strictly) related conditions, is etiologically caused by a perturbation of a wide-brain diffused activity (either involving also brainstem and basal ganglia or only cortical sites), that explains the production of similar, complex mental phenomena[54]. Thus, they can be studied inducing noise and unbalancing *top-down* and *bottom-up* integration mechanisms in these generative neuron-like networks models[53].

Charles Bonnet syndrome, in particular, has been taken as a paradigm to relate with in order to understand the role of generative models in visual cortex regions and their capability to synthetize (in absence of visual stimuli) rich and solid visual representations. This leads, in cortically-blind patients, to produce vivid visual hallucinations of objects, people, and whole scenes[55]. The case of an impressionist painter, described by Oliver Sacks, became famous: he was still able to paint until progressively losing the memory of color, started to produce only black and white canvases[56].

Statistical inference is the key to comprehend perception, action selection, and learning from a generative modeling prospective; that's appliable either to task-engagement and resting state spontaneous dynamics[13], coherently to what has been said in the previous paragraph concerning their fictive conceptual distinction from an *inside-out* prospective. Furthermore, as already approached earlier, *top-down* dynamics are triggered by internal or external inputs, and can be maintained for long periods[13]. They modulate, for example, visual attention and perception, preparing brain to process upcoming stimuli and actions during task engagement maximizing accuracy of explanations (as fitting data in the IA modelling) through preparatory signals which encode context-specific task related information (encoding location, features and decision for expected stimuli in visual cortex for example) sacrificing part of the adaptability to unexpected stimuli. In resting state periods, they modulate instead (consistently with a less important role of accuracy) the formation of *generic priors*, whose role is to maximize the entropy of explanations, amplifying adaptability to unexpected stimuli, but also respecting the imperative of minimizing model complexity (which affects also the microscopical aspects, reflecting to synaptic pruning) in order to do not overfit[13].

During resting periods, offline intervals without *bottom-up* stimulation, *priors* encoded at high hierarchical levels are propagated to lower level coherently with *top-down* dynamics, but cannot be corrected due to the absence of stimuli[13]. They recirculates as *generic priors for representation* and *for spatio-temporal connectivity patterns*[13] which compose a flexible, yet stable functional structure[32].

The former (*generic priors for representation*) consists of information-compressed low dimensional representations of perceptual, cognitive or motor patterns abstracted away from the stimuli or the task that shaped them[52]. They build a representation of the statistical dimensions of the body in the world and can be recycled, after optimizations, during future interactions. They are generic, portraying pattern generally functionally connected during natural behavior, evading from sensory-specific or motor-specific classification. In absence of data, they maximize the entropy of explanations as generative models privilege to remain flexible[13]. The latter (generic priors for connectivity patterns) consist of intrinsic brain network functioning, mediated by predictive generative models, as low dimensional spatiotemporal scaffolds that can be combined to form task-specific activity patterns[13]. These are high-hierarchical level activity follows spatial gradients trough cortex, but its timescale gradients topographically mirrored in striatum, thalamus, and cerebellum[57]. Priors are tuned in to both temporal and spatial statistics of the environment.

Spatial connectivity priors, for example, are evident with fMRI signals during visuospatial attention task where (beside a general within-networks functional connectivity conserved) Dorsal Attention Network induces *a top-down* directed functional connectivity modulation to Visual Occipital Regions, in order to selectively direct visual exploration toward expected relevant stimuli and away from irrelevant ones[6]. While those attention-induced functional connectivity changes occurs within visual regions, DAN functional activity do not change that much, remaining similar to resting state one[6,41]. Similarly, hub regions such as the ones within DAN conserve their functional connectivity; that stability embodies *temporal connectivity priors*, which at rest produce alpha and beta limited power oscillatory frequencies, recorded by MEG, synchronizing with occipital visual regions. In task-engagement alpha activity decreases, and so does beta band fluctuations but only in visual regions, remaining stable within DAN connectivity (see 4.2.3). That's true thought naturalistic visual explorative tasks, according to the predictivity of *priors* which make the brain able to minimally change hub functional connectivity transitioning from rest to task, but changes when visual task provide scrambled visual stimuli: *bottom-up* stimuli overstep *top-down* regulation and

predictive assessments has to change interacting with unexpected new stimuli to processate them, thought variability in frequency and electrical activity[58].

Even without any *bottom-up* component, another activity that occurs in the restless brain, during offline activity is the optimization of generative models for future interactions[13]. This happens trough synaptic pruning within circuits that code for the parameters that are unnecessary to the accuracy, paring with the target of reducing complexity, which is useful also from a metabolic parsimony point of view. Secondly, trough production of fictive data that, as real ones, are compared to generative priors and optimize them. That's just what happens in replays from memory not only in hippocampal-neocortex interactions, but also in other subcortical or cortical structures, such as visual cortex[13]. Computational analysis of fMRI studies showed both presence of memory-mediated replays but also immediately after task disengagements, replays not mediated by memory but spontaneously occurring; the target is to utilize as much disengaged time as possible in order to realize at its best refinements of predictive brain dynamics[59].

This brain dynamics repertoire of functional organization, comprehends spatially coherent rhythmic variations in cortical excitability coordinating ongoing functional activity: low frequency transition to prepare generic *priors* and reduce complexity of brain generative models, with distributed high-frequency ripple to update fictive data.[12,13] Functioning predominantly at a non-conscious level, brain strives to identify predictable patterns from limited information and executes structured responses, all while maintaining the capacity to pause, adapt, and acquire new knowledge[12]. During ongoing spontaneous activity appears the low dimensionality of predictive brain, which always prepares for future interactions; this concept perfectly aligns with a quote of György Buzsáki who stated in 2006 "*Br ains are foretelling devices and their predictive powers emerge from the various rhythms they perpetually generate*"[60].

2. VISUAL EXPLORATION

2.1. Introduction

The evolutionary development of human brain dynamics has been significantly influenced by the fundamental importance of vision and visual perception. Up to 40-50% of neurons are involved in processing visual information.

Our "*visual brain*" fluidly orchestrates visual behavior[61] trough complex dynamics involving, as discussed, both a *bottom-up* visual information guidance (saliency and semantic) and a *top-down* regulation which involves the interactions of multiple cognitive processes[33]. According to a generative models perspective (see paragraph 1.5), several compelling reasons suggest that our visual systems may be conceptualized as a multilayer generative model. In this assessment, *top-down* connections may be employed to generate low-level features of images from high-level representations, while *bottom-up* connections can be utilized to infer the high-level representations which are responsible for generating the observed set of low-level features[52].

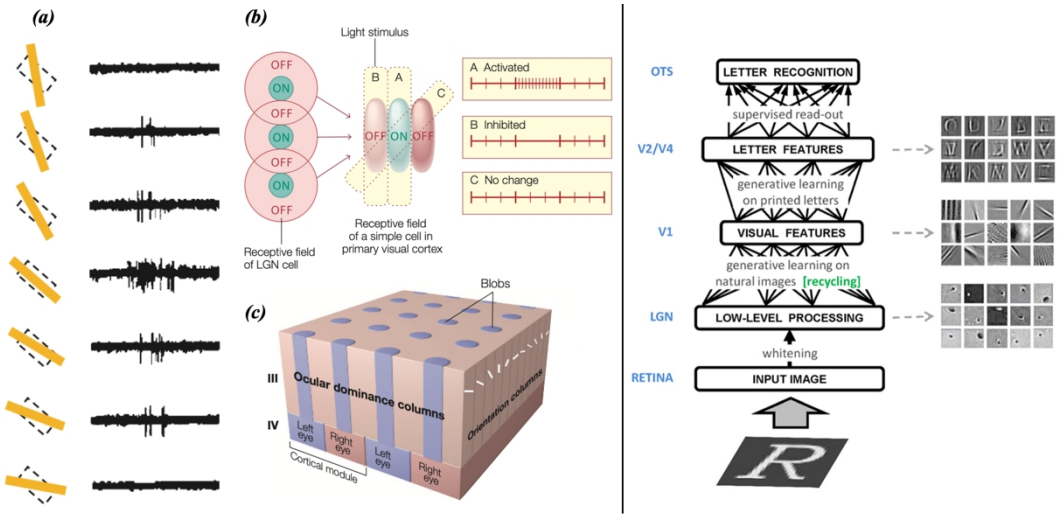


Figure 5 (a),(b),(c) and Figure 6: Comparison between modern adaptations of pioneering studies by Hubel and Wiesel[62,63] on classical neurophysiological visual perception *(brain as a sensory-motor analyzer, with cortical firing occurring proportionally to bottom-up stimuli characterization)* ***and modern visual perception modeling using generative models. (5,a) Orientation selectivity and mechanisms:*** *a primary visual cortex (V1) neuron in response to segment orientation selectively fires when the latter matches the orientation of its receptive field[62,64]* ***(5,b) Characteristic response of LGN and V1 cells****: simple cell in V1 (can be formed by the connections of the outputs of concentric LGN cells with neighboring receptive fields) is either activated or suppressed by an edge aligned with its preferred orientation* ***(5,c) V1 features representation****: simple cells organized in orientation columns, which combine with ocular dominance columns to form a cortical module.*

Within those module, cells have similar receptive fields (location sensitivity), although distinct input sources (right or left eye) and sensitivity to orientation, color, and size of the object (saliency). Then there are feedforward projections to secondary visual cortices. ***(6) DBM for visual perception modeling****. A biologically-inspired algorithm incorporates local spatial correlations in images through contrast normalization, simulating early visual processing in the retina and thalamus. Subsequently, generative learning begins with natural image patches, involving the first hidden layer (V1), which learns basic visual features to form a foundational dictionary describing the statistical distribution of pixel intensities in natural scenes. Training a second hidden layer (V2/V4) introduces specific learning of letters, where neurons combine V1 features to represent fragments and complete shapes of letters. A linear read-out layer (OTS), trained on high-level internal representations, decodes distinct letter categories*[53].

Vivid visual imagery, dreaming, or thinking through visual scene to solve a problem which is not directly in front of us, are all suggestion of the capability of visual system to perform *top-down* generation. In a disengaged introspective state, moreover, it is like as "*all the neural machinery for sensory processing is available for thought […] which often involves writing in a purely top-down mode on the active blackboards of low level areas*" as argues Mumford explaining the process of creating mental images[52,65].

Consequently oculomotor system, considering both topographical aspects and spatiotemporal dynamics of visual exploration, mirrors the interaction between all of these intrinsic dynamics so that naturalistic eye movements are partially independent from the visual content[33]. Moreover, differences in eye movement dynamics signify distinct individual exploratory styles when freely observing naturalistic visual stimuli; that variability also relates to stable individual differences at the EEG oscillatory activity recording at rest, intrinsic predictive signature of the explorative style itself [32].

To fully grasp the complexity discussed in previous and current chapters, which lays the foundation for the experimental assessment of this work, it's crucial to begin by examining oculomotor dynamics and thoroughly analyzing the anatomical and functional structures involved. Eye movements are essentially the brain interface to actively explore the surrounding world trough sight; they are directed by a relatively simple motor system that coordinates the movements of 12 evolutionarily preserved muscles[64] whose "*ancient and original function was not really to move the eye, but rather to hold it still with respect to the environment*" as Walls stated in 1962[66,67].

Control of the gaze, in fact, primarily, aims to precisely regulate the position of the fovea (although less than 1% of the visual field and less than 1 mm in diameter, it's the region of the retina of most vision acuity, in which rod receptors are absent and cones are most densely packed) so that objects images persists stabilized onto it[64]. Furthermore, to avoid vision blurring, the *"strategy of saccades and fixation"* (utilizing information acquired during stable fixations, and employing saccades to rapidly shift the direction of gaze) has to be coherent with receptor acceptance angle response time, which in humans is about one degree per second (the smaller the receptor acceptance angle, the better the eye resolution, the greater the need for precise stabilization)[67]. That's why, even looking to a stationary target, eyes never stop moving, in a continuous pursuit of the perfect foveal fixation, because of the small receptors' acceptance angle.

2.2. Types of eye movements

After Raymond Dodge in 1902, who established the first classification of eye movements[68] capable of centering and reasonably stabilizing object images onto the fovea, many others have been presenting over time new classifications, and still some more are being introduced. The most widely adopted is the one proposed by D. A. Robinson in 1981, which distinguishes: Vestibule-ocular reflex (VOR), Optokinetic reflex (OKR), Smooth pursuit, Saccades, and Vergence[69].

These are the primary, but not exclusive, eye movements. Considering the issue from a wider prospective and referring it to the "*strategy of saccades and fixation*" many movements, some within the previous classification (VOR, OKR) but also some others (fixational visual movements), as it will be exposed, can be included into the fixational movements class (see 2.2.2).[67] Foremost, both saccades and fixational movements are definable as *conjugate gaze movements* (also called *version* movements) , although opposite because the first one function is of *gaze-shifting* and the second ones of *gaze-holding* movements[70]. Smooth pursuit is partially a class on its own within *conjugate gaze movement*, because it is a *gaze-shifting* movement so strictly related to saccades (positional errors that occur during pursuit are mainly corrected by saccades, which rapidly realign the object's image on the fovea but also allow future changes to be taken into account) that some author

consider them as an effective component of smooth pursuit movement[71]. On the other hand, smooth pursuit can be considered itself as a component of some fixational movements such as OKR and VOR, comparable to their slow phase[67]. Finally, *vergence* movements (convergence and divergence) are, on the other hand, *dysconjugate gaze movements*; they also have both *gaze-holding* and *gaze-shifting* properties[70].

2.2.1. Saccades

Looking at a human face image and superimposing eye movements recordings, it became clear since early Yarbus[72] experiments, how fixations spend time focusing on important features (eyes and mouth looking at a face, for instance; see Figure 7 below)[72], while less time is spent over intermediate positions. Gaze rapidly shifts toward expected relevant stimuli locations pointing there the fovea and allowing through fixations time to gather useful visual information concerning regions of interest and contours[13,64,67].

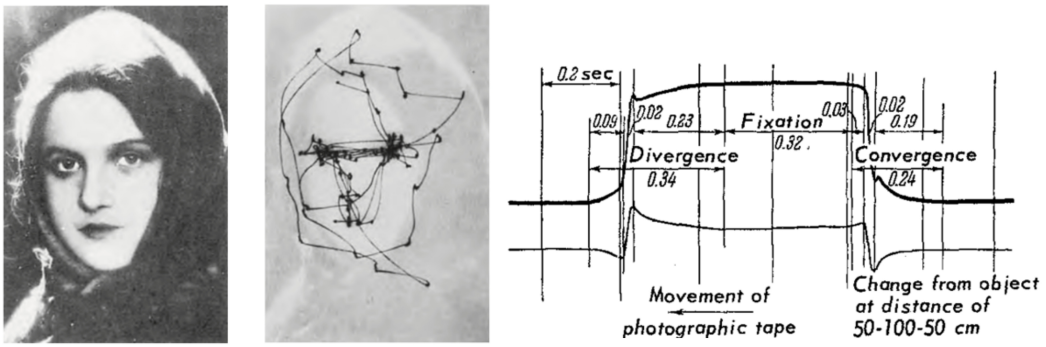


Figure 7 and 8: Static and dynamic schematic eye movements patterns. (7) Eye movements track the outline of a static object of attention*. Recorded eye positions are superimposed on the picture of a woman observed for one minute by a viewer, who spent most of the time on certain features of the face, concentrating fixations, for instance, on the woman's eyes and mouth. Less time was spent over intermediate positions through which the gaze passed performing rapid saccadic movements*[72]*.* ***(8) Record of movements of both eyes on a dynamic photokymograph*** *during a change of points of fixation in space; evidence of integration between fixations and vergence movements.*

These gaze shifting quick movements are stereotyped (a single smooth increase and decrease of eye velocity, standard waveform[64]), and ballistic due to high velocity. They have brief duration and a predetermined landing target, so they cannot be changed once motion begins: duration of most saccades is <70 msec (although variable between the range 50-200 ms at highest amplitude), so visual information

does not have time to influence these movements once they begin[70]. Peak velocity is determined only by the amplitude (linear relationship[67]) of the saccades and can reach 900°/s [64], while amplitude, mostly < 15° [73], can reach 20° as maximal range[64] . The relationship between duration, peak velocity, and magnitude of human saccades is defined as *"main sequence"* (an astronomical term referred to the bond between brightness and temperature of a star) which illustrates the nonlinear nature of the saccadic system[74]. All those properties, allow to scan the environment (a sequence of saccades is the *"scanpath"*) or read (task that, until E.Landott studies in 1890, was considered to be a smooth movement); they differentially articulate depending on whether saccades are *voluntary* (*top-down* goal directed), where amplitude and direction can be modified differentially from speed (which can be reduced by fatigue, drugs, or pathological states), or *reflexive*, induced by *bottom-up* visual stimuli that attract the eyes regardless of their significance for the subject [64,67]. A *voluntary saccade* is characterized by longer latency than *reflexive* ones, as they involve the activation of complex cognitive functions such as attention, working memory and decisional making. Latency is defined either as the intersaccadic interval in a *scanpath* or the time of the exposition of stimuli and the reaction, an inter-trial time. On average, saccade latency ranges from 200 to 250 ms [67]. Latency is additionally impacted by environmental variables such as brightness and object distance, as well as the presence of distractors that impede movement planning[67].

When the position of a distractor is near the target, it doesn't influence latency but does so with saccade's landing position, so the saccade lands at intermediate position between the two objects: that's called *"global effect"* and occurs in a wide range of stimuli, such as when a distractor has an opposite contrast polarity to the object, or when two similar targets are presented side by side[75].

In a disengaged state, saccades also represent intrinsic predictive brain activity of generative models' *priors* during offline periods. For instance, saccades are the main rapid eye movement that occurs during REM sleep, strongly relating to memory consolidation and to low-amplitude brain waves cortex activity[76].

Moreover, in more naturalistic dynamical settings where both the observer and the environment are in motion, and other objects within the surrounding environment

are also moving, saccades do not occur in isolation. Instead, they must coordinate with other ocular movements to maintain visual stability and direct the fovea towards regions of interest[67]. To land to the position of a target further than 5°, a slight head rotation and a VOR coordinated interaction is necessary; referring both to VOR and OKR, saccades occur determining their fast phase. Furthermore, also during smooth pursuit eye movements, often saccadic intrusions happen. All eye movements are integrated in order to achieve visually qualitative inputs to optimize processing by the visual system.

2.2.2. Vestibulo-ocular reflex (VOR) and Optokinetic reflex (OKR)

The Vestibulo-ocular reflex (VOR) stabilizes gaze and maintains clear vision while the head is in motion, particularly during locomotive dynamics[70]. It consists of two components. Rotational VOR compensates for head rotation and receives its input predominantly from the semicircular canals, whose endolymph moves within due to inertia, generating stimuli via vestibular hair cells projections. Translational VOR compensates for linear head movement; vertical and horizontal linear acceleration are encoded respectively by utricle and saccule maculae due to depolarization of hairy cells within of otolith organs[64].

These eye movements occur toward the opposite direction of the head movements, arising from connections between vestibular nuclei neurons and the abducens, oculomotor, and trochlear nuclei neurons: this maintains ocular orientation and gaze stability in time and space[64,67]. The fixational stabilization of the image onto the retina consists of a *slow phase*, proportional to head velocity, which constitutes the actual reflex, and an integrated *corrective saccade* aimed at repositioning gaze due to the smaller range of eye movement compared to the head's[67].

Optokinetic movements, on the other hand, hold images stationary during sustained or slow head movements: VORs are although imperfect, poorly able to compensate sustained motion at constant speed during translation or constant angular velocity during rotation, and insensible to very slow rotations or low-amplitude linear accelerations[64]. As the labyrinthine signal declines or fails to activate, while watching as stationary viewer to a moving object, visually mediated eye movements supplement or take over thought the optokinetic reflex (OKR) also known as optokinetic nystagmus (OKN). Consistently with the VOR, the OKR is composed

of a *slow phase* represented by smooth pursuit movements and a *fast phase* consisting of saccades[64,70].

2.2.3. Microscopic fixational movements

During fixations or periods of rest, eyes are never completely still; they continuously generate microscopic fixational eye movements that are highly integrated and include microsaccades, drifts and tremors. Those are essential in order to prevent image from fading: due to energy parsimony, sensitive neuronal adaptation causes perceptual vanishing. Primate oculomotor system found this evolutionary system to be advantaged in in the wild compared to other animals, like frogs, whose neuron also adapt and are blind to static objects[67].Other than this, they participate in gathering object contours information and contribute to enhance visual perception converting spatial information into spatiotemporal ones[67].

- Microsaccades (or fixational saccades): once considered as a nervous tic, nowadays they have a well established importance, and perceived to share a large amount of properties with saccades[67]. They are binocular, conjugate movements that follow the *"main sequence"* just as saccades (with a linear relation between peak velocity and amplitude), and can be reduced intentionally or during specific tasks reflecting shifts in *covert* attention[67]. Interestingly, innovative results strengthen even more the relationship with saccades: rates and amplitudes of microsaccades decrease prior to the onset of a saccade[77] and both during fixation and free-viewing/visual search tasks, the intersaccadic intervals remain consistent across all combinations in pairs of saccades and microsaccades[78]. Finally, microsaccades in the horizontal components are more dominant, at short time scales, than in the vertical direction in fixational eye movements; at long time scale (see further 4.1.3) both horizontal and vertical components are less affected by the microsaccades[79].

- Drifts: slow, wandering movements that occur surrounded by the rapid, linear microsaccades[67].

- Tremors: smallest type of fixational movements, so that its tiny but really fast oscillatory motion (about 90 Hz) is as broad as the width of one photoreceptor. They are superimposed to drift[67].

2.2.4. Smooth pursuit

Smooth pursuit may be the ocular movement where balance between *top-down* and *bottom-up* component is most impaired: often coordinated with saccades (with which composes the *ocular pursuit*) it is driven by the selection of an object image in the scene or in the environment, which it tracked and held onto the fovea. Because of the strong influence of *top-down* dynamics, there's also anticipation on predictable movements of the object[67]. In particular, in first place it's the visual feedback of the object that mostly guide the pursuit, but central mechanisms quickly take over: the aim is to calibrate eye speed to the one of the object and maintaining, through this smooth motion, visual acuity by holding image to the fovea. Saccadic movements allow realignment of the image in case of drop out that part of the retina of the selected visual stimulus[64,67].

2.2.5. Vergence movements

Deconjugated gaze movements which occur in order to maintain the image of the object focalized onto the fovea bilaterally, regardless of the target movements toward to (convergence, rotation of the eyes each in the direction of the other one) or away from the observer, avoiding diplopia and enhancing depth and tridimensional sight[64].

This type of movement occurs transversal to the plane of the eyeball either in medial or temporal direction; consistently vergence movements are a function of the level of tonic contraction of the two pairs horizontal rectus (see next paragraph)[64]. Convergence is also coordinated with ciliary reflex (accommodation): at any given time, when we focus to close objects, rear environment appears blurred. Coherently when we focus on far objects, closer ones appear blurred. Accommodation, by mediating changes through radius of the lens due to ciliary muscle contractions, aligns with convergence to maintain, especially acting when the objects gets closer (and the range of medial movements toward one another of the eyes is at its plateau) focus of its image on both retinas[64].

2.3. Oculomotor plant, extraocular muscles and cranial nerves

Binocular vison allows stereopsis as well as depth perception, each contribute to three-dimensional perception of a scene. Thus, coordinating extraocular muscle

system, the acuity of that scene can be preserved focalizing regions of interests onto the fovea[64,67].

Eye movements are, indeed, simply rotations of the eyeball in the orbit, through *version* or *vergence* movements, that can be following a horizontal axis to generate vertical movements (*elevation* or upward rotation; *depression* or downward rotation) and following a vertical axis to generate horizontal movements (*abduction* and *adduction*) changing line of sight redirecting the fovea[64]. Or they can be torsional movements (*intorsion* or rotation of the top of the cornea toward the nose; *extorsion* or rotation away from the nose) which rotate the eye around the line of sight while preserving where it's looking. These are also the three degree of freedom of eye rotation[64,80].

The *Listing's Law* and *Donders' Law* govern the three-dimensional orientation of the eye and its axes of rotation, indicating that for any gaze direction, the eye assumes only one unique orientation[70,80]. The former states that, given a fixed head position called primary position (a reference eye position that differs from the clinical primary position, which indicates a straight gaze position that approximately aligns with the center of the range of ocular movement) from which all other eye positions can be can be achieved through a single rotation around an axis within *Listing's plane*, a plane orthogonal to the line of sight when in primary position (see further, Figure 10)[80]. Although *Listing's law* quantitatively defines a specific torsional angle for each gaze direction, it's broaden up by *Donder's law* which states that regardless of how the eye moves to that particular gaze direction, the torsional position remains constant[70,80]. This is because each combination of horizontal and vertical eye positions corresponds uniquely to a single torsional position[70,80]. Another expansion of the *Listing's law* is the *Listing half-angle rule*, that widens the same occurrences to the eye movements from any position. Finally, *Listing's law* applies during fixation, saccades, smooth pursuit, and vergence, but not during sleep and the vestibulo-ocular reflex. This suggests that it is actively enforced by a neural mechanism[67,80].

These intricate movements are accomplished through the coordinated action of six extraocular muscles per eye. Their geometric arrangement, combined with the

various orbital positions of the eyeball, governs motor control, which is regulated by three cranial nerves[64]. Each eye is equipped with:

- Four rectus muscles: medial and lateral for *adduction* and *abduction*, inferior and superior for *depression*, *elevation, intorsion* and *extorsion*. All of them share a common origin at the annulus of Zinn, at the apex of the orbit, and they have different insertion at the cardinal points of the eyeball, each contacting surface of the sclera anterior to the center of the eye[81]. Inferior and superior recti are also addressed to as cyclovertical muscles, because they produce both vertical and torsional eye rotation[64];
- Two oblique muscles: both insert to the sclera posterior to the center, so that superior oblique muscle can *depress* the eye and the inferior oblique muscle can *elevate* the eye. The inferior oblique muscle originates from the medial wall of the orbit, while the tendon of the superior oblique muscle passes through a trochlea before inserting to the globe (this arrangement effectively positions its origin on the anteromedial wall of the orbit)[81]. In primary gaze position the acute angle between eyeball orientation and the orbit axis, so that the eyes are in a basal mild adduced position, makes the oblique muscles the ones charged with vertical movements duty. When the eyeball is in a more abducted position, cyclovertical muscles are the ones involved in those movements; all intermediate positions need to be regulated by effective coordination between superior and inferior recti and obliques[64,70].

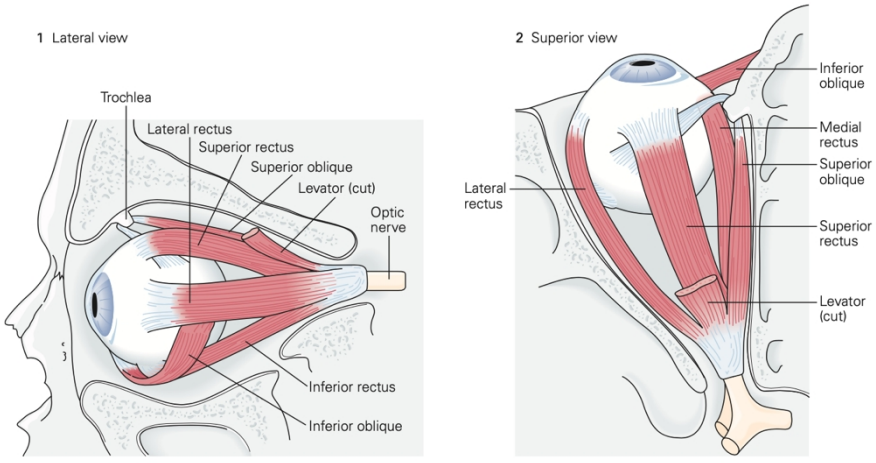


Figure 9: Extraocular muscles. *lateral view of the left eve with the orbital wall cut away (1) and superior view of the left eye with the root of the orbit and the levator muscle cut away(2)*[64].

These muscles are directed by three cranial nerves, which functionally concert each muscle with its antagonist in the same orbit and pair them with the contralateral muscles that move the opposite eye in the same direction[64]. Those nerves are:

- The oculomotor nerve (cranial nerve III) innervates medial, inferior, and superior recti other than the inferior oblique. Also some autonomic parasympathetic fibers compose this nerve, which regulate pupilar sphincteric muscle and ciliary muscle; moreover motor fiber are also dedicated to the elevator of upper eyelid. Its nucleus lies in the midbrain at the level of both the mesencephalic reticular formation and superior colliculus[64,81];
- The trochlear nerve (cranial nerve IV) innervates superior oblique muscle, and its nucleus lies in the contralateral midbrain, caudal to the third nucleus, at the level of the inferior colliculus[64,81];
- The abducens nerve (cranial nerve VI) innervates lateral rectus. Its nucleus lies in the pons, in the floor of fourth ventriculus, at the level of the paramedian pontine reticular formation (PPRF)[64,81].

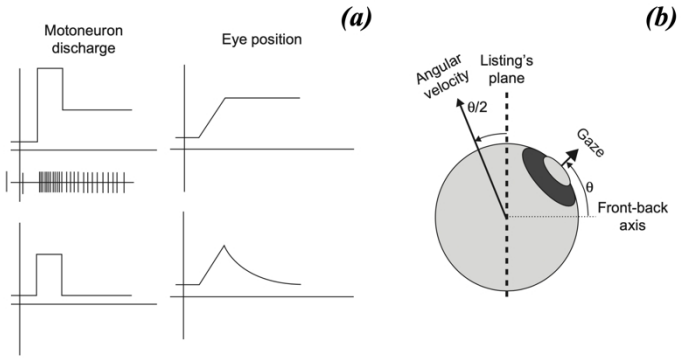


Figure 10: Phase-tonic motoneuron activity and eye rotational axis. (a) Schematic illustrating the phasic-tonic motoneuron discharge*: the phasic component facilitates quick eye movements, meanwhile the tonic component stabilizes the eye position just reached against elastic restoring forces. Thus motoneurons must generate a burst-tonic signal to adjust and maintain eye position at a new steady-state level (top traces); on the contrary, if a motoneuron discharge only include a burst without a tonic signal, eye positioning won't be stabilized (bottom traces)*[67,82]*. **(b) The axis of rotation of the eye according to Listing's law.** Those are (as defined by the angular velocity) neither head-fixed nor eye-fixed, but rotate in the same direction of gaze through the half of the gaze angle (**θ/2**; **half-angle rule**)* [67,82].

Considering single oculomotor neuron recording (as just exposed in figure 10) to enhance a saccade and so to move the eye to a target and to keep it there, the motor

signal must include both a position component (to counter the elastic force of orbital tissue which tends to restore a central position of the eyeball) and a velocity component (to overcome orbital viscosity that opposes to quick movements)[64]. When a saccades is launched, neuron firing rate rises quickly (*"saccadic pulse"*) with a frequency (firing rate bursts can reach frequencies as high as 500 spikes/s[67]) that determines the speed of the gaze-shifting movement and an amplitude that codes for the amplitude of the motion. Then activity returns to tonic, but the difference between tonic activity before and after the saccades is defined as *"saccadic step"*[64].

Moreover, extrinsic ocular muscles fibers, both in global and orbital layer which insert respectively to the sclera and to fibrotic pulleys around recti, are anatomically differentiated in *twitch* (single-nerved fibers that respond quickly to burst of firing with jerk contraction) and *non-twitch* (multiply-innervated, fatigue-resistant muscle fibers that respond to tonic stimuli). Actually, two sets of motoneurons are subclustered in all three brainstem nuclei of oculomotor, trochlear and abducens nerves: the subset for twitch fibers which is central and more peripheral subset for non-twitch fibres[67].

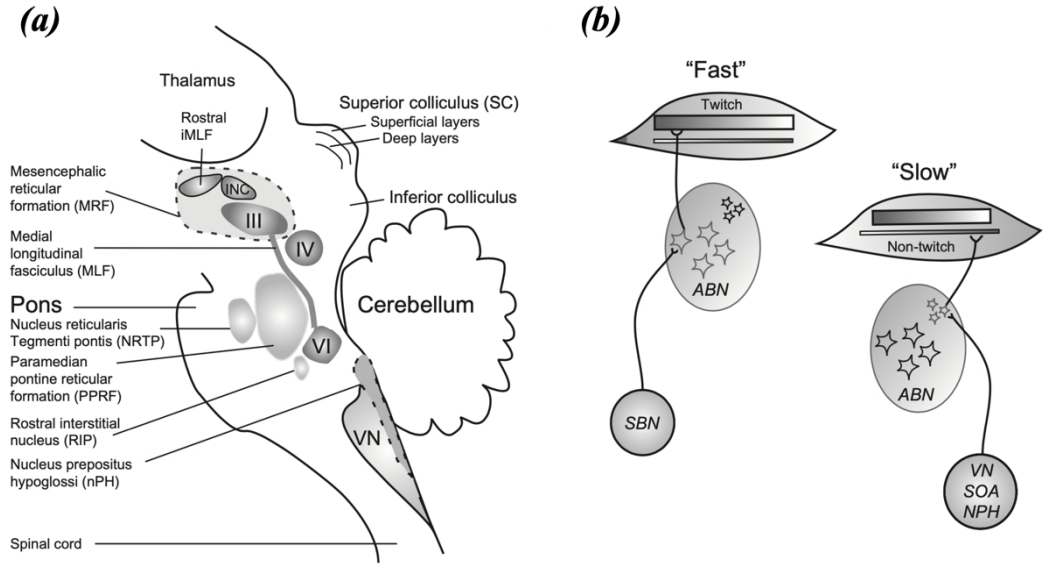


Figure 11: Brainstem and extraocular muscle fibers innervation. (a) Schematic illustration of the brainstem *. Excitatory burst neurons (EBNs) for horizontal saccades lie in the paramedian pontine reticular formation (PPRF); for vertical and torsional saccadic movements lie in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Oculor motoneurons lie in the abducens nucleus (ABN: VI). the oculomotor nucleus (OMN; Ill) and the trochlear nucleus (IV). INC: interstitial nucleus of Cajal; (NRTP): nucleus reticularis tegmentis pontis; nucleus prepositus hypoglossi (nPH); vestibular nucleus(VN)*[67]*.* ***(b) Schematic illustration of muscle fibers innervations****. Twitch fibers receive innervations from large motoneurons while small motoneurons 8tendo to lie peripheral) project to non-twitch fibers. Large motoneurons receive premotor*

signals from the saccadic burst generator (SBN) whereas small motoneurons receive innervations from premotor sources involved in executing slow eye movements (e.g. VN, NPH and supraoculomotor nucleus (SOA)) [67].

According to *"dual motor control hypothesis"* subsets of large motoneurons that regulate twitch fibers should be the only one involved in saccades and VOR pathways, and more in general highly implicated in eye movements where saccadic shift are very often part of, or coordinated to, other type of movements. On the other hand, subsets of small motoneurons that regulates non-twitch fibers should be more involved in a proprioceptive system (where sensory afferences are transmitted by via trigeminal nerve and spinal trigeminal nucleus) therefore stabilizing fixational movements and alignment of the eyes[67,83].

2.4. Brainstem, superior colliculus, cerebellum, basal ganglia and cortical regions. Many actors orchestrate oculomotor networks

Brainstem is the frontier where coordinated broken up instructions to oculomotor muscles are generated, in order to execute the inputs resulting from the integration between superior colliculus, basal ganglia, thalamus and cortical areas[70]. Superior colliculus is a major visuomotor and multimodal integration site, the last hub where instructions for movements are represented on a spatial retinotopic map[84], and acts regulating saccades and fixations, integrating cortical with basal ganglia's and retinoic inputs. Several cerebellum regions (vestibular cerebellum, oculomotor regions of vermis, flocculus and paraflocculus, hemispheric parts of the cerebellum, involving parts of Crus I, II, and the simple lobule) are highly integrated in any type of ocular movement. Finally, numerous cortical areas, interact constantly in order to integrate and coordinate all the subsets of eye movements: VOR, OKR, saccades, smooth pursuit, fixational movements and vergence movements can not be considered as segregated worlds but as an integrated continuum that constantly reflects internal environment dynamics and allows visual perceptive congnitve-behavioural interaction with the surrounding environment.

In the next paragraph peculiar functional relationships and integration between these different anatomical structures will be highlighted in order to lie the

groundwork for the visual explorative dynamics features considered in the two experimental settings of studies behind the replication (see chapters 3 and 4).

2.4.1. Saccades and fixations strategy

To generate a saccade, a *"pulse signal"* rises from high frequency firing excitatory burst neurons (EBNs) located in the rostral portion of the paramedian pontine reticular formation (PPRF) and within rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) that lies in the mesencephalic reticular formation (MRF). PPRF burst neurons drive horizontal saccades regulating ipsilateral abducens nucleus and contralateral oculomotor nucleus via medial longitudinal fasciculus (MLF); MRF burst neurons drive vertical saccades regulating oculomotor and trochlear nuclei, bilaterally coordinated via posterior commissure after vertical and torsional neural integration are performed in the nearby interstitial nucleus of Cajal (INC)[64,67,70]. Moreover, both system contemplate the role of inhibitory burst neurons (IBNs), whose firing is essential in order to coordinate motoneurons within the system silencing antagonist motoneurons. EBNs and IBNs, are commonly referred to as saccadic burst neurons (SBNs), which burst 10-20ms prior to a saccade onset with a duration of firing that relates to the amplitude of the saccade itself; on the other hand they are silent during steady gaze, smooth pursuit, slow vergence, and during the slow phases of vestibular nystagmus. SBNs are regulated directly and indirectly (via long-lead burst neurons; LLBNs) by superior colliculus and caudal fastigial nucleus of cerebellum (the oculomotor vermis, through fastigial nucleus, calibrates the bursts to keep saccades accurate). Finally, both systems act together in the generation of oblique saccades, which have both horizontal and vertical components[67].

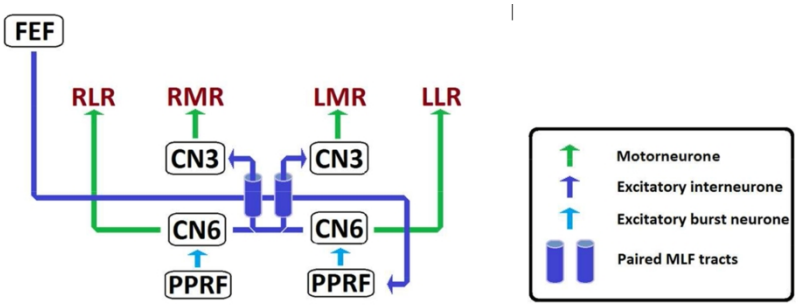


Figure 12: Schematic diagram of anatomy and physiology of horizontal eye-movements. *Frontal eye field (FEF); cranial nerve III, oculomotor (CN3); cranial nerve VI, abducens (CN6); left lateral rectus (LLR); left medial rectus (LMR); medial longitudinal fasciculus (MLF); paramedian pontine reticular formation (PPRF); right lateral rectus (RLR); right medial rectus (RMR)*[85].

Receiving only a *"pulse signal"* eyes would drift back to starting position due to elastic restorative forces as analyzed in the previous paragraph; GABAergic omnipause neurons (OPNs), which lie in the nucleus of the dorsal raphe at midline, are responsible for *"steps"* enhancing a tonic firing activity which stabilizes gaze to the new position (where fixational visual input collection can realize). These neurons fires continuously in a tonic way, except when a saccade occurs; they are regulated by SBNs themselves (which realize this way an inhibitory feedback) and by superior colliculus. Finally, nucleus prepositus hypoglossi (nPH) and in INC also participates encoding robust positional signals (lesions of either the nPH or INC would result in an inability to hold the eyes at a new position after a saccade)[64,67].

Superior colliculus (SC) is a fundamental structure of interest concerning *"saccades and fixation strategy"*: visual stimuli responding builds up neurons activity, gradually increasing until being strong enough to induce burst neurons activity, which lie in the intermediate and deep layer; they fire high-frequency efferent signals to PPRF and riMLF to launch saccades[84]. While superficial layers receive inputs directly from retina and from striate cortex, representing the opposite visual hemifield, so neurons organize in a retinotopic map, intermediate and deep layers are the ones where multimodal integration occurs (employing somatotopic, tonotopic, and retinotopic maps) but above all where push-pull integration between inhibitory inputs via nigrotectal projections from the substantia nigra pars reticulata (SNr) and the excitatory inputs from frontal eye field (FEF) and lateral intra-parietal area (LIP) occurs[64,84]. FEFs in addition, excite caudate nucleus, which inhibits substantia nigra: cumulatively they enhance in both ways positive regulation to saccade generator neurons in the superior colliculus[64].

Moreover, also supplementary eye fields (SEFs), dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) project to intermediate superior colliculus layer[67]; interestingly, the majority of connections within the networks, that see SC as multimodal behavioral hub, are directly or indirectly derived from cortical regions, which is consistent with the *inside-out* brain view. Finally, SC superior layer's projections to intermediate layers are a crucial hub for the interaction between sensory (*bottom-up*) and goal-related (*top-down*) processes: neurons within this layer show correlate firing both with exogenous and

endogenous shifts of visuospatial attention, where visuomotor neurons in the SCi show enhanced activity during an endogenous shift of attention into their response fields, even in the absence of a visual stimulus[67,86]. Additionally, apart from visuospatial attention, the superior and intermediate layers are intricately linked through target selection, exemplifying a combined representation of *bottom-up* salience and *top-down* relevance. This discrimination process integrates projections from V4, IPS, and FEF/SEFs[67].

On the other hand, eye movements can occur independently of visual stimulation; despite this integration, the majority of projections from the superficial layer do not connect directly with the intermediate layer. Instead, they are directed towards the pulvinar and lateral posterior nuclei of the thalamus, which then project to cortical regions that send projections back to the SC, at the intermediate layer. So SC is part of cortical-thalamic oculomotor loops, to which basal ganglia also participates as seen before, where higher elaboration occur instead of immediate sensory-motor integration[64].

Thalamus serves as the gateway to the cerebral cortex. Pathways passing through the central and posterior thalamus are implicated in directing visuospatial attention, which in turn guides eye movements. It receives input from various brain regions such as the brainstem, basal ganglia, and cerebellum, and sends output to cortical areas involved in eye movement, including the FEF, SEF, and DLPFC [67].

Rostral (retrolateral) SC neurons, have been defined as fixational neurons because of their tonic firing during periods of active fixation that persists without a visual stimulus and before small saccades to contralateral visual field; moreover they are also implicated in generating microsaccades coherently with fixational dynamics exposed before. They receive inputs from the fovea and the foveal representation in primary visual cortex (V1); they also inhibit movements-related neurons of the caudal part and also project to nucleus of dorsal raphe, where they inhibits saccadic shifts exiting OPNs[64,67].

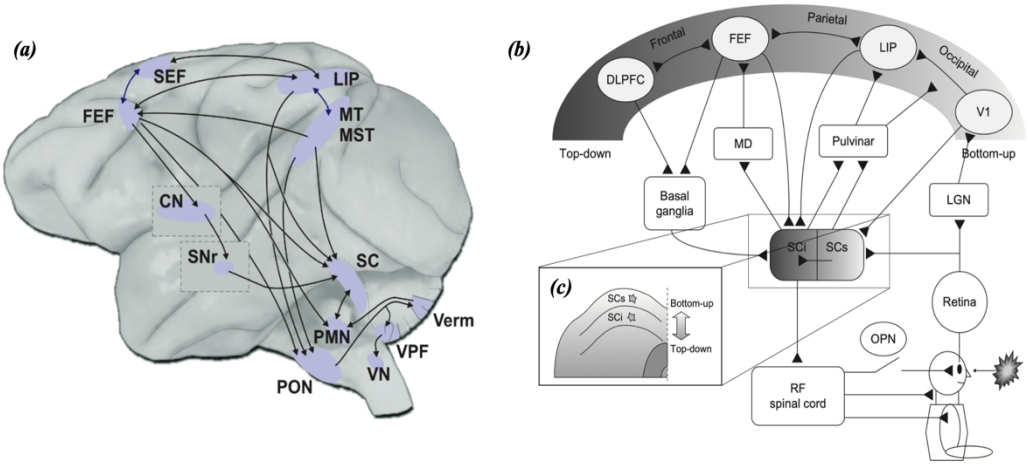


Figure 13: Brain cortical areas, thalamic and superior colliculus top-down and bottom-up integration. (a) Schematic outline of the pathways for pursuit and saccadic eye movements on a lateral view of the monkey brain. *Not all relevant areas are depicted (e.g., ascending pathways are omitted), and arrows do not always correspond to direct anatomical connections. Caudate nucleus (CN); Frontal eye field (FEF); Lateral intraparietal area (LIP) ; Middle temporal area (MT); Medial superior temporal area (MST); Brain stem premotor nuclei (PMN: PPRF, riMLF, cMRF); Precerebellar pontine nuclei (PON); Superior colliculus (SC: intermediate and deep layers); supplementary eye field (SEF); Substantia nigra pars reticulate (SNr); Oculomotor vermis (Verm: cerebellum, lobules VI and VII); Vestibular nuclei (VN); Ventral paraflocculus (VPF: cerebellum)*[87]. ***(b) Dominant extrinsic and intrinsic circuitry of the primate SC.*** *Shading from light to dark represents the gradual shift from bottom-up to top-down processes respectively. Other than the areas previously highlighted: Dorsal lateral prefrontal cortex (DLPFC); Primary visual cortex (V1); Medial dorsal nucleus of the thalamus (MD); Lateral geniculate nucleus (LGN); Brainstem omnipause neuron region (OPN); Superior colliculus superficial layers (SCs); Superior colliculus intermediate layers (SCi)*[67]. ***(c) Transverse view of the SC.*** *The progression from top to bottom represents a shift from mostly bottom-up towards increasing top-down processes*[67].

Partial segregation between SC superficial (which receives most of the global luminance inputs from retina) and intermediate layers is also proven with single cell recordings, that show how variances in luminance conditionate pupil diameter, but not saccadic dynamics[88]. On the other hand, non-luminance-mediated changes in pupil diameter correlate with cortical (especially with ACC and PCC) and subcortical neuronal activity: effects that can be described in terms of activation of norepinephrine-containing neurons in the brainstem nucleus locus coeruleus (LC) which interacts mostly with SC intermediate layer and Edinger-Westphal nucleus relating parasympathetic-sympathetic balanced tone (reflected trough pupil diameter) with eye movements and fixations[89].

Moreover, LC norepinephrine-mediated projections are widely diffused to the brainstem, cerebellum, diencephalon, and neocortex[90]. LC-NE tonic activity

enables transitions between behavioral states (increasing from low levels at sleep, to moderate levels in focused task, filtering out irrelevant stimuli, to high levels when exploring surrounding environment with uncertainty) . Brief phasic firing it's, instead, related to target selection. A decrease in tonic activity from exploratory to task-focusing, participates in inducing a reflected deactivation in right-hemisphere temporal parietal junction (rTPJ) and so ventral attention network (VAN), which is on the contrary activated and timed also from LC/NE system phasic activity other than high tonic firing in redirecting attention (which has so also an autonomic integration, and interacts with modulation of pupil diameter) to unattended behaviorally relevant stimuli (see also 3.2.3).

Pupil diameter tone fluctuations occur during fixations not only consequently luminance changes, but also reflecting arousal, attention[92], cognitive effort, during explore-exploit trade-off, surprise, salience, decision biases; coherently they do not only occur concerning contrast-based saliency during eye movements[89–91]. So, changes in pupil diameter are just another reporter of the integration between cortical and subcortical areas (mediated especially with reciprocal cortex - LC connections) which reflects endogenous implications on ocular dynamics, mirroring integrations between *top-down* dynamics, and the *bottom-up* processing that, with different magnitudes, always occurs when talking about oculomotor and visuospatial related dynamics[89].

In the upcoming chapter, we will delve into the intricacies of these highly integrated dynamics, which manifest through saccades, fixational movements, pupil diameter variations, and other features. Specifically, we will focus on cortical-subcortical *top-down* integrations and its blending with *bottom-up* stimuli processing, consolidating and organizing the information already presented in Chapter 1. We will explore how the low-dimensionality of visual exploration spatiotemporal dynamics, driven by intrinsic factors that correlates with various EEG features (also discussed in Chapter 4).

3. LOW DIMENSIONALITY OF VISUAL EXPLORATION DYNAMICS AND THE PREDICTIVE BRAIN

3.1. Predictive brain as a theory to fill gap of unexplained variance in eye movements dynamics

Collecting information from chapters 1 and 2, it becomes clear how complex and structured is our *Restless and Predictive Visual Brain*. An open issue in neuroscience is what can explain variance within eye movements dynamics, explored as a gateway to infer about visuospatial attention dynamics.

Generally speaking, an attention mechanism refers to a neural system capable of dynamically select or modulate information processing, typically in response to task demands or guided by learned cues and instructions. Essentially, it enables flexible control over the flow of information, guiding it from the environment through various stage of neural processing[67]. The organism is capable of selectively engaging (or disengaging) these mechanisms for specific stimuli by adjusting motor-control signals for the sensory organs, a process known as *overt attention*[67]. This ability allows for dynamic selection of where to focus the high-resolution circuits of the visual system via oculomotor dynamics and head movements, to highlight stimuli recognized trough mechanisms that do not involve explicit involvement of sensory organs: *covert attention*[67].

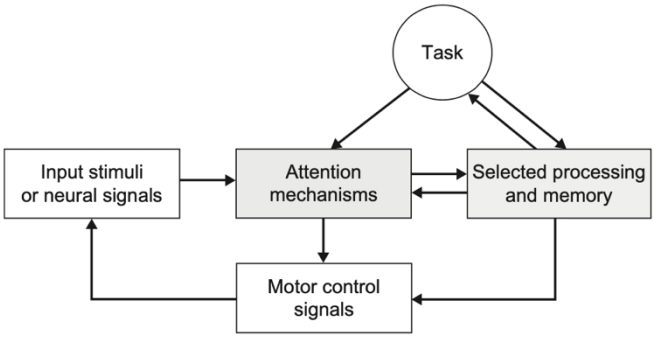


Figure 14: General schematic framework for models of covert and over attention*. Grey-colored parts refer to the covert attentional ground, around which the white parts representing overt attentional dynamics are integrated* [67].

Many explanations over the years tried to address the relationship between *overt* (eye movements) and *covert* attention. Models attempted to depict feature maps in a purely *bottom-up* saliency-mediated manner (basing on the hypothesis that

attention, and hence gaze, is drawn to image features that perceptually stand out in some way from the other image features[67]) leading to the creation of a "s*aliency map*" that systematically encoded the local prominence across the entire visual field and had no need for any type of *top-down* integration, so that only low-level features of objects organized in multiscale structured the map drove eye movements[93]. Moreover this topographical approach, led to infer conceptions concerning how fast stimulus-driven saliency should have a much prevalent role in driving *overt* attentional selection than *top-down* directed mechanism under natural viewing conditions[94]. Many other models have been raised, basing on the core concept that revolves around the brain using the present image (or a broader set of images) to formulate a statistical model of local image attributes, with saliency depending on how different these local image features are compared to the statistical model[67,95].

Saliency refers to the "*sensory distinctiveness and behavioral relevance of an object relative to other objects*"[96] and it is still fundamental, along with semantic (defined as the "*intrinsic value dimensions within the objects comprising the scene", which are weighted differently in the image in term of saliency relating to those semantic categories, that predict gaze steps"*[97,98]), in constituting *bottom-up* processing driven component. But, as extensively discussed in Chapter 1, *top-down* driven component is of increasingly interest: recent theories and computational models focus on the importance of both sensory stimuli and cognitive processes in guiding *overt* attention and so naturalistic eye movements behavior[33]. Moreover, *overt* visual attention probably has its origins in *covert* attention: these two processes operate closely interconnected and, indeed, the same cortical areas are consistently implicated in those processes, both at cellular and network level[31] (see also paragraph 3.2.3)

Finally, another concept brought up by those new perspectives is the fact that individuals' eye-movement behavior profiles can be studied using some metrics (up to six: fixation rate, duration, and size; saccade amplitude; micro-saccade rate and amplitude) which highlight stable idiosyncrasies trough different task in oculomotor dynamics[99]. Individual profiling, as already discussed in paragraph 1.3.3 is closely related also to spontaneous brain activity, and coherently to that, during free viewing and resting state, EEG recordings (see chapter 4) are able to show characterizations of subjects relating intrinsic brain activity and ocular

movements dynamics[32]. Considering the relationship between endogenous activity and predictive brain modeling, that's a reason why brain predictiveness may be a theory supposed to fill the gap of unexplained variance in eye movements dynamics, and so to relate to the intertwined relationship between *covert* and *over* at tention dynamics as their interaction occurs within resting state-task dynamics.

Before delving into these speculations, it is necessary, however, to explore the anatomical and functional cortical areas and their highly integrated networks that correlate with eye movements, attentional and cognitive dynamics, memory recall of visual stimuli and how these act synergistically in determining oculomotor dynamics behavior.

3.2. Cortical networks for eye movements and visuospatial attention

Many cortical areas participate to pre-saccadic, saccadic and post-saccadic activity; their networks are highly overlapped with the attentional systems, thus underling a dynamic interaction between oculomotor-attentional and visual areas.

3.2.1. Posterior parietal cortex

The intraparietal sulcus, IPS (whose middle third is the human homologue of the monkey lateral intraparietal area or LIP[100]) of the posterior parietal cortex (PPC), which is part of Brodmann's area 7, plays a role in saccade target representation regarding contralateral visual field and provides guidance signals related to saliency, target value and timing, interacting also with sensory working memory[64,67] . IPS, although not being as directly involved in the production of saccades as compared to the FEFs and SC, forms representations of potential saccade targets. Referring to studies in monkeys connectivity, the antero-dorsal region of LIP (dLIP) is primarily recruited during visual fixation and visually-guided saccades, exhibiting connections mostly to temporal cortex visual areas, with a role in visual processing[62]. The posterior-ventral region of LIP (LIPv) is more involved in regulating saccadic eye movements and has strong reciprocal connections with FEF and SC (both with SC intermediate and superficial layers, as directed connections or via pulvinar; see also back to paragraph 2.4.1) being active during both visually- and memory-guided saccades[62]. In addition, magnitude of pre-saccade activity in IPS shows visual dependence and is significantly reduced when saccades are made

in the absence of a visual stimulus, although it does not contain neurons directly controlling saccade enhancing[67,101].

Finally, IPS participates alongside with FEF, to guarantee working memory trough delay periods until next saccade, where persistent activity (vawe-mediated reverberation that contribute to shot-memory and contributes in consolidating transition to long-term memory[40]) also when object has vanished, is fundamental in providing memory-mediated saccade orienteering[67,101,102].

Lesions of a monkey PPC, and consequentially LIP, increase the latency and reduce accuracy of saccades; moreover it produces selective neglect of the contralateral hemifield[64,70].

3.2.2. Frontal cortex

Regarding eye movements, there seems to be a continuum ranging from the frontal eye fields (FEFs), which directly initiate saccades concerning contralateral hemifield, to other regions such as the supplementary eye field (SEFs), prefrontal cortex (PFC), anterior cingulate cortex (ACC), and pre-supplementary motor area (pre-SMA), that facilitate flexible and adaptable control of eye movements by modulating activity in the oculomotor system, based also on cognitive processes[67].

FEF is considerate the main cortical eye field, whose firing is related to both saccades (contralaterally) and smooth pursuit (ipsilaterally)[67]. It counts three different types of neurons: *visual neurons* that fire responding to visual stimuli (almost half of them even more vigorously to the saccades target stimuli), *movement-related neurons* which fire before and during saccades to their movement fields (exhibiting firing only before behaviorally relevant saccades, deferring from SC ones which fire prior to any saccade) and *visuomovement neurons* which discharge most strongly before visually guided saccades[64,70].

FEF exhibits reciprocal connections with the occipital, temporal, and parietal cortex, as well as neighboring and contralateral regions of the prefrontal cortex. Other fundamental reciprocal projections are stipulated with intermediate and superficial layers of SC, manly ipsilaterally but also contralaterally (and also

indirectly mediated by basal ganglia pathways). Additional inputs come from substantia nigra pars compacta and posterior portion of the dentate nucleus through the mediodorsal nucleus of the thalamus; it sends projections to caudate and putamen, other than PPRF and MRF (although not to SBNs but only to premotor and intermediate neurons)[67].

Both FEF and IPS, in particular, contain areas with retinotopically organized maps of contralateral space, making them candidate for the maintenance of spatial priority maps for *covert* spatial attention, saccade planning, and visual working memory[103,104]. A multitude of studies showed highly integrated functional-anatomical organization within frontal cortex, sustaining the fact that other than direct control on saccades generation (trough SC regulation) that coordinate them also to other eye and head movements producing complex *overt* attention orienting responses, it participates alongside with the other frontal cortical areas, to a multitude of cognitive functions, including target selection, spatial working memory, arbitrary stimulus-response mapping, response suppression, and reward[67].

First of all, within these regions, the SEF (dorsomedial to FEF, within Brodmann's area 6) has the property of evoking fixed-vectors saccades trough firing of its neurons[105] such as the FEF, but its activity is more related to the encode of visual space in *"head centered"* coordinates: continuedly microstimulating FEF neuron produces a series of saccades meanwhile doing the same to SEF, the eye persist in the gaze position reached at the beginning of the stimulation[67,106]. There are neurons sending saccade-related signals (underlying gaze-shifting) and some other carrying fixational signals (underlying gaze-holding)[105]. Moreover, if a neuronal in left SEF normally fires before a saccadic movement rightward, firing will be also observed before a leftward eye movement if it has been coded to occur in the right side of the target[64]. Integrated with all the other frontal cortex structures activity, SEF is engaged in executive control, especially in control of eye movements based on cognitive dynamics[67].

PFC is a highly interconnected hub which shares reciprocal projections with higher order visual, auditory, somatosensory, and polysensory areas; it also projects to all motor areas, to SC and to pontine nuclei. Its role is to modulate saccadic movements

and to perform cognitive control of *overt* attention mainly through visuospatial working memory, response suppression and flexible control[67]. ACC, which lies at the medial wall of the cerebral hemispheres surrounding the corpus callosum (Brodmann's areas 24 and 32), is highly interconnected with PFC and its purpose regarding eye movements could be to signal the mismatch between intended and executed eye movements, or to monitor for conflicts arising from incompatible oculomotor commands solving conflicts by engaging other cortical regions[67]. PFC (in particular its dorsolateral component) and ACC *top-down* regulations have been studied with fMRI while subjects were performing Stroop color-word task, which is a complex of task where interference and conflict are the foundation and also has been used in the study exposed by this thesis (see Methods, chapter 7). PFC (DLPFC) showed enhanced activation during the cognitive-controlled preparatory periods, not relating to behavioral responses, while ACC showed more activation during responding phase analyzing eventual behavioral conflicts[67,107]. Single cell-recording showed that ACC have higher task selectivity after task switch and that this decreases during task block, compared to PFC selectivity that stayed stable; ACC cells get recruited also in task maintenance when cognitive effort required increases, participating at the *top-down* integration with PFC[108].

3.2.3. Attention and saccades: shared networks for overt and covert attention

Already in 1876 David Ferrier stated: "*Among the reactions excited by electrisation of the anterior of motor part of the hemispheres, is one of a special character, which results from stimulation of in the monkey […] The head and eyes are directed to the opposite side and at the same time pupils dilate widely […] the attitude is also one of excited attention or surprise*" underling the multiple nature of some areas related to eye movements in the frontal cortex, although just discovered, also concerning cognitive domains.

In everyday life in order to coordinate visual, oculomotor and attentional signals *covert* attentional shift and *overt* saccadic movements are highly integrated[31]. In many studies, using single-cell recordings in cortical (FEF, SEF, DLPC, PPC) and subcortical areas (caudate, pulvinar and superior colliculus) during guided saccadic eye movements, responses to visual stimuli have been shown to be modulated also

from the behavioral relevance of the stimuli[79]. So those cells showed to be recruited both in oculomotor and attentional processing[31,86]. Moreover, consistent results have been showed in neuroimaging studies during *covert* attention shift to peripheral stimuli, discrimination tasks or looking at (*overt*) peripheral stimuli during oculomotor localization task[31].

Considering the analysis of a peripheral visual location, this can be driven in two ways: either by orienting gaze (by making a foveating saccade) or by covertly shifting attention to that peripheral location without making an eye movement[86]. Studying fMRI and surface-based representations of brain activity while subjects were involved in two task design to accomplish the two ways of analyzing a peripheral visual location: all the areas considered by the single cell recording showed to be overlapped trough both oculomotor task and attentional task[31,86]. Functional anatomy appears to be shared also when the two processes are not conducted at the same time (two different task showed overlapping in frontal, parietal and temporal areas)[31]. Moreover, single-cell recordings in SC showed that in the intermediate layer, the *visuomotor neurons* (as said before, employed in saccades preparation) showed to be active also in *covert* shift of attention other than *covert*[86], consistently with the *top-down* regulation of this common dorsal network which coordinates also sub-cortical structures that functionally belong to it[31].

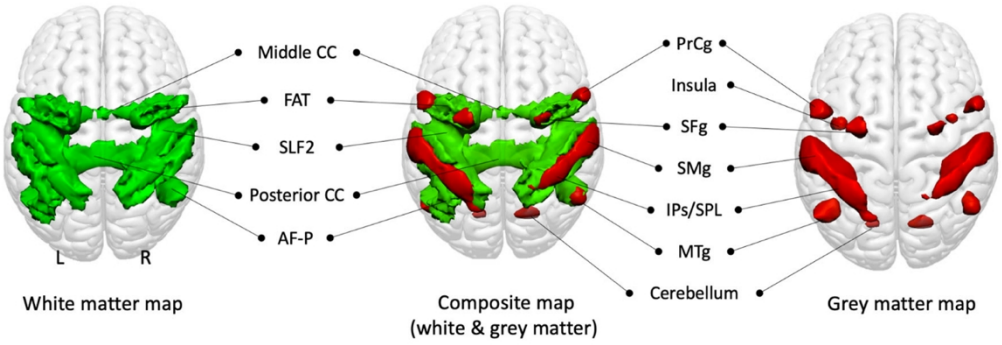


Figure 15: Dorsal Attention Network (RSN13) maps, dorsal view*. White matter map in green, grey matter map in red. Union of the two maps in the middle. Arcuate fasciculus, posterior segment (AF-P), Frontal Aslant Tract (FAT), Intraparietal sulcus and superior parietal lobule (IPs/SPL), Middle part of the corpus callosum (Middle CC), Middle temporal gyrus (MTg), Posterior part of the corpus callosum (Posterior CC), PrCg Precentral gyrus (PrCg), Precentral sulcus (Precentral s), Superior frontal gyrus (SFg), Second branch of the Superior Longitudinal Fasciculus (SLF2); Supramarginal gyrus (SMs). Frontal eye field is at the intersection of the middle frontal gyrus with the precentral gyrus. The insula and cerebellum are visible through the glass-brain effect*[19].

This common network, the dorsal attention network (DAN), is a widely distributed system dynamically anticorrelated to DMN[109] (see Figure 16) in fMRI recordings during performance of novel, attention-demanding, non-self-referential tasks in which the DMN areas (MPF, medial pre-frontal cortex; PCC; LP, lateral parietal cortex; cerebellar tonsils) decreases its activity while the DAN related areas (mIPS; precuneus; superior parietal lobule, SPL; FEF; SEF; DLPFC; MT, middle temporal region. In addition to those grey matter areas, recent studies allowed also to define for the first time its white matter projections, as in the Figure 15[19]) showed it increased[101,109]. Other areas activated by demanding cognitive tasks are dorsal-lateral and ventral-prefrontal regions, insula, and SMA[22,109]. Moreover, neither of those networks appeared to be highly-related with primary sensory and motor cortical areas, which are the direct interfaces to the surrounding world: data have been found trough different resting states (such as fixation, eyes closed, and eyes open) demonstrating that results could not be attributed to the demand of a low-level task (such as a fixation), eye movements, or the presence or absence of visual input [22,109]. This is consistent in showing how infra-slow intrinsic activity of those high-hierarchical networks through all brain states, in which they have high within-correlation, low between-correlation and the absence of preferential mild dynamic correlation with sensory-motor areas[109].

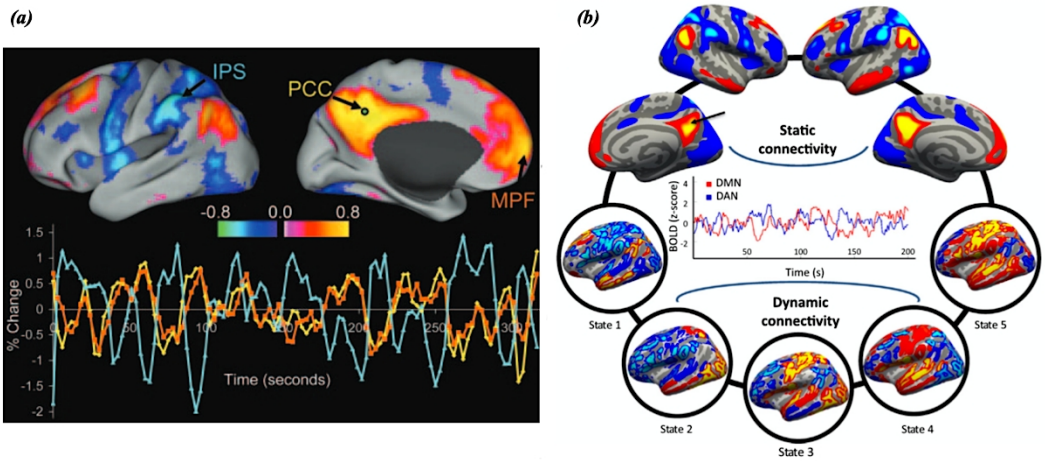


Figure 16: Anticorrelation between DAN and DMN, measured with fMRI. (a) Intrinsic correlations between a seed region (ROI) in the PCC and all other voxels (positively or negatively correlated to the seed region)*; single subject, resting fixation. The time course shows relative fluctuations of a seed region (PCC, yellow), of a region positively correlated in the MPF (orange), and of a region negatively correlated in the IPS (blue)*[109]*.* ***(b)*** ***A map of the static (time-averaged) temporal correlation of the BOLD*** *signal between ROI in medial parietal cortex (black arrowhead), and the rest of the cortex over many minutes. Central in the composite image the* ***BOLD-fMRI signal time curse fluctuations*** *of the DMN and DAN. The surrounding maps represent the main patterns of* ***dynamic connectivity*** *across brain areas, identified by a sliding window analysis, and the projection*

*on the cortical surface of the first eigenvector**, across different cognitive resting states**. Time-course fluctuation (frequency 0.1 Hz)*[13].

DAN regions are engaged in governing visually- and memory-guided saccades, with an almost complete overlap of visuospatial attention and eye movement related activations[31,96]; this involvement facilitates the voluntary allocation of attention to specific locations or features, based on task relevance or sensory value, through *top-down* guidance[104]. These cortical regions exhibit predominantly symmetrical organization, with each hemisphere primarily representing the contralateral side of space[9,96].

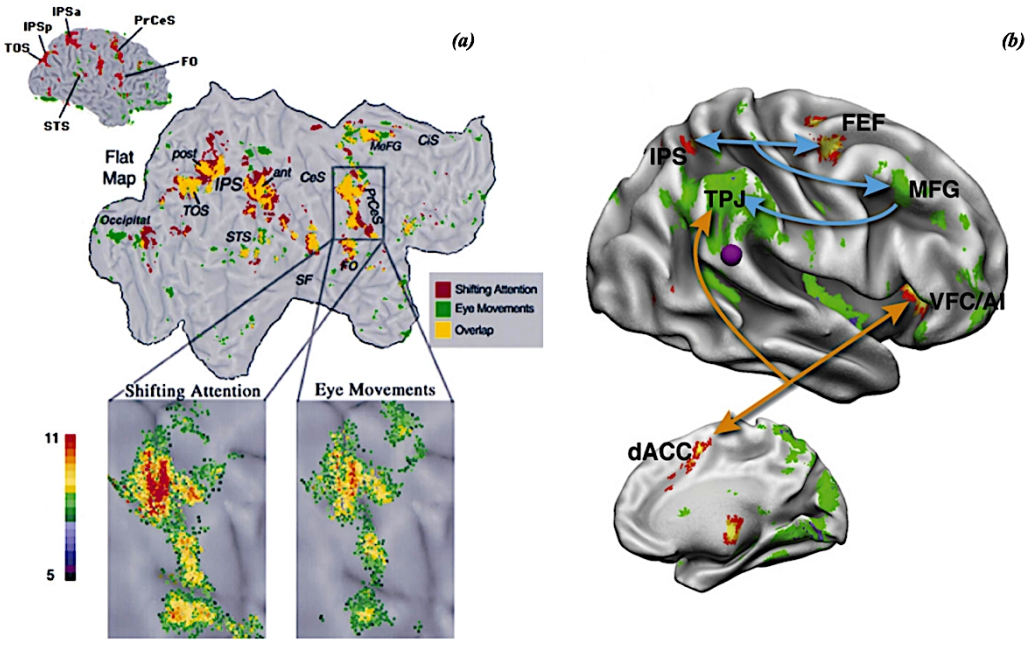


Figure 17: DAN, a common network for attention and eye movements, integrated via rTPJ regulation with VAN. (a) 3D single subject surface reconstruction and flattened cortical map of the Right Hemisphere. *Showed in red the areas recruited in a shifting attention task, in green the ones recruited in the eye movments task and in yellow the overlaps between the two. The inset highlights the precentral region that includes the frontal eye field (FEF)*[31]. ***(b) Regions exhibiting sustained activity in visual-search task**, including DAN regions such as IPS and FEF (depicted in red/orange in the surface-rendered brain); additionally, areas in the anterior insula and anterior cingulate, which are part of a proposed task-control network, also show activity. These regions send top-down signals (arrows) to the VAN areas, determinning sustained deactivations during search (blue/green in surface-rendered brain), restricting its input to task-relevant objects*[90].

This network, or at least its grey matter areas, although containing all these physiological signals is not the one often damaged when suffering of neglect (which causes egocentric spatial bias other than arousal and vigilance affections)[96]. Perhaps a right-lateralized ventral frontoparietal system (ventral attention network, VAN) is the one frequently affected (or the fibers affected are the white matter ones which

connect DAN to VAN[19,96]). VAN comprehends right temporoparietal junction (rTPJ), right inferior parietal lobule/superior temporal gyrus (IPL/STG), right ventral frontal cortex (VFC) which are involved in detecting unattended or unexpected stimuli and triggering shifts of attention, in particular briefly interrupting rTPJ-IPS projections (VAN-DAN white matter interactions[19])[9,96,104]. Dynamically, these systems interact during different brain states: at rest, each one is relatively distinct and exhibits high within-network correlation, while during attentional focus, VAN is suppressed (rTPJ activity in particular is reduced or suppressed during focused attention) to prevent reorienting to distracting events (VAN is more engaged in stimuli-driven attentional dynamics, detecting salient and behaviorally relevant stimuli in the environment, especially when unexpected, only when informative even if they are not much distinctive)[90].

Finally, relating to visuospatial attentional and eye movements systems and to what has been exposed in chapter 1 relatively to RSNs, it is important to evaluate temporal dynamic whitin- and between-correlation of DAN and VIS. The latter is identified as a functional network where activity occurs bilaterally in intermediate visual hierarchy regions such as ventral (V4-V8), dorsal (V3a-V7) and lateral occipital cortex or MT (the latter, as seen before, recruited also among task-positive networks overlapping with DAN[109]) but also trough primary visual occipital cortex (V1–V3)[6].

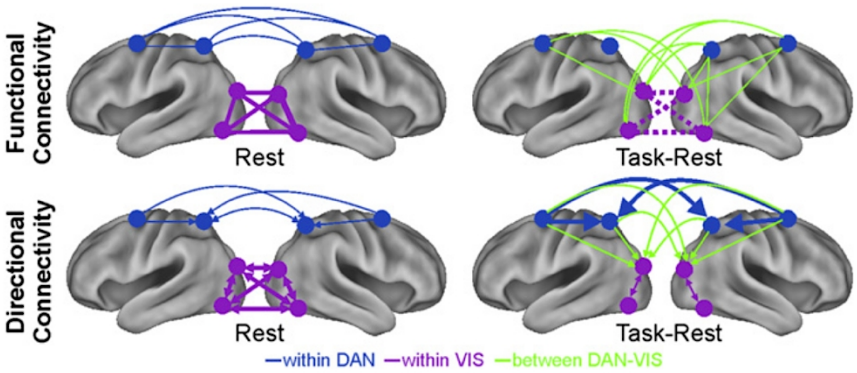


***Figure 18: Spatial priors seen as of functional connectivity summary analyses**. Main resting-state (upper and lower left) and significant state (upper and lower right) task-induced modulations[6]. The functional and directional functional connections within the dorsal attention network (blue) are not significantly different during fixation or a demanding visuospatial attention task. In contrast, connections within the visual system (pink), or between visual and dorsal attention networks (green) are modified[110].*

During the transition from a wakefulness rest to a visuospatial attentional task (either focusing on a stream of visual stimuli or shifting attention to competing) it occurs a decrease in correlation within the visual network, while higher-order resting connectivity in the DAN remains relatively stable during attention[6], suggesting the role of intrinsic activity as a preparatory spatiotemporal *prior*[13]. Moreover, an increase in temporal correlation occurs, between frontoparietal regions of the DAN and visual regions bilaterally, indicating a strong *top-down* influence, especially from prefrontal (FEF) to posterior parietal (IPS/SPL) areas and both prefrontal–parietal areas to visual regions bilaterally, especially V3a–V7[6]. These functional interactions were accompanied by a decoupling of temporal correlation of previous resting state, particularly between hemispheres, and an increase in directed interactions within hemispheres between visual areas, which appeared to be more segregated[6]. Moreover, these modulations in functional connectivity were proved to be behaviorally significant, correlating with enhanced task accuracy[6].

Activity in DAN regions IPS and FEF, produce a disruptive effect on bilateral synchronization of α-rhythms in visual occipital regions, with a stronger *top-down* coupling with DAN influence[6,110]. Accordingly, decrements of temporal correlation within visual cortex during visuospatial attention match the desynchronization of α-rhythms observed during spatial attention, anticipation, or visual processing; desynchronization and formation of cluster of visual processing in the VIS areas, consistently with *top-down* influence of DAN[6,110] (see chapter 4). These phenomena have been interpreted differently: DAN within-functional connections relative stability underlies pre-engagement (even during rest) schemes, which act in order to anticipate an attentional state, potentially serving as a *prior* for incoming information[6,13]. All those features posit for the centrality of this network, far away from the influence of sensory stimuli. In contrast, the ongoing resting activity in the visual cortex is seen as a state of idleness that needs to be interrupted for active vision to occur[6].

Defined deeply all those complex interactions that occurs during different brain states such as trough visuospatial attention and eye movements dynamics, it’s time

to delve into experimental assessment that explore even further their relationship with intrinsic activity.

3.3. Subjects clustering, explorative styles, phenotypes of human visual exploration

In order to understand naturalistic eye movements behavior, it is important to consider its spatiotemporal dynamics, whose feature may be employed to explore, according to what has been presented in the previous paragraph, interaction between RSNs, priors and individual characterization concerning cognitive style, genetics and personality traits[33,112–114].

Previous studies employing recordings of multiple features of saccades, anti-saccades and smooth pursuit eye movements over 1000 healthy young adults ocular movement recordings proved the reliability over time in individual differences in 10% of the subjects (stableness across second session 18,8 days later). All measures displayed variability among individuals: most of them exhibited 2 or 3 fold differences between participants, while some showed a variance greater than 10-fold differences[114]. Although characterization trough different sets of eye movements, sex, personality and cognitive traits outline an *oculomotor signature*, it is not possible yet to completely categorize an individual by his/her loadings on a small number of factors[114]. At the same time, it is evident how across time and different tasks, features as precision/duration of fixations or their *scanpath* dynamics are pretty much defining the individuals as a fingerprint[114].

Another study found reliable associations trough 42 participants between eye movements dynamics and prediction of characterization of personality traits[112]: in particular reliable relations with four of the Big Five personality traits (neuroticism, extraversion, agreeableness, conscientiousness). Personality traits characterize an individual's patterns of behavior, thinking, and feeling; people with similar traits tend to move their eyes in similar ways[112].

Genetic factors play a significant role in shaping eye movement features, impacting both the overall inclination towards visual exploration of scene contents and the

specific spatiotemporal sequences of fixations when observing complex social and non-social scenes[113]. Above all, genetics highly influence both complex social visual engagement (fixations toward eyes and mouth of the face in the images) in healthy and autistic infants[115], such as complex non-social visual scenes content.
Collecting these information and all the others exposed trough chapters until now, Zangrossi et. al designed an experiment in order to analyze spatiotemporal characteristics of eye movements dynamics in a cohort of 114 healthy individuals satisfying inclusion criteria, while they were asked to observe various real-world scenes, and to compare the recordings to the ones of blank screen viewing (lacking of any visual stimuli)[33]. This was aimed at quantifying the role of endogenous and stimulus-driven parameters, indagating first of all, the amount of dimensionality in visual explorative features recorded across many subject and many scenes (see 3.3.1 and 3.3.2). Secondly, whether saliency and semantic (*bottom-up*) or power law distribution of gaze steps (measure of intrinsic *top-down* dynamics) drive visual exploration spatiotemporal dynamics (see 3.3.4). Lastly, to compare measurements of spatiotemporal eye movement parameters in the absence of visual stimuli and during visual exploration (see 3.3.5)[33].

3.3.1. Low dimensionality in eye movements dynamics

As already exposed, a few studies focused on the idiosyncratic nature of eye movements behavioral profiles and the low dimensionality of eye movements, studying them from a spatiotemporal perspective[116–118]. Some of them concentrated on the consistent individual differences in fixation duration and saccade amplitude across tasks[116–118]; in addition Andrews and Coppola in 1999 suggested also that visual behavior consistency is in some degree linked to the attentional and cognitive demands of the tasks, showing that saccade amplitude and fixation duration were consistent across active–active and passive–passive task pairs, but not across passive–active pairs[116]. Some others, pushed the issue forward, such as Poynter et. al in 2013 who enlarged with their findings the range of features showing reliability across tasks, not only in fixational duration and saccade amplitude but also in fixations rate and several measures of micro-saccadic movements[99]. Furthermore, they observed that correlations between different metrics were associated to a single factor, therefore underling strongly a low dimensionality of visual exploration dynamics[99]. They speculated that the link between macro and micro eye movement

behavior may in some way be tied to individual differences (evidenced by clustering subjects in two groups with opposite visual exploration dynamics, but within-group correlations brought together proportionally to scores related to attention) in visual attentional strategy and that the operational effectiveness of the attentional apparatus (comparing eye-tracking recordings to questionnaires related to attention, AD and ADHD features)[99].

Consistently, Zangrossi et al. observed that eye movement spatiotemporal parameters across subjects and participant were strongly correlated and that 60% of their variance could be explained by three components[33]. Moreover they clustered two types of observers, characterized by different eye movements dynamics and whose assignment to one cluster or the other, had more than 90% of accuracy, being stable across different sets of images[33]. To do that, in first place, a principal component analysis (PCA) was run on the scaled and mean-centered complete set of features derived from the gaze data collected with an eye-tracker, during participants real-world scenes unconstrained exploration[33]. A PCA is an exploratory statistical technique that enables to reduce the dimensionality of a large dataset (as in this case), by creating new uncorrelated variables that increase interpretability; at the same time it minimizes information loss preserving as much statistical information (variability) as possible[119].

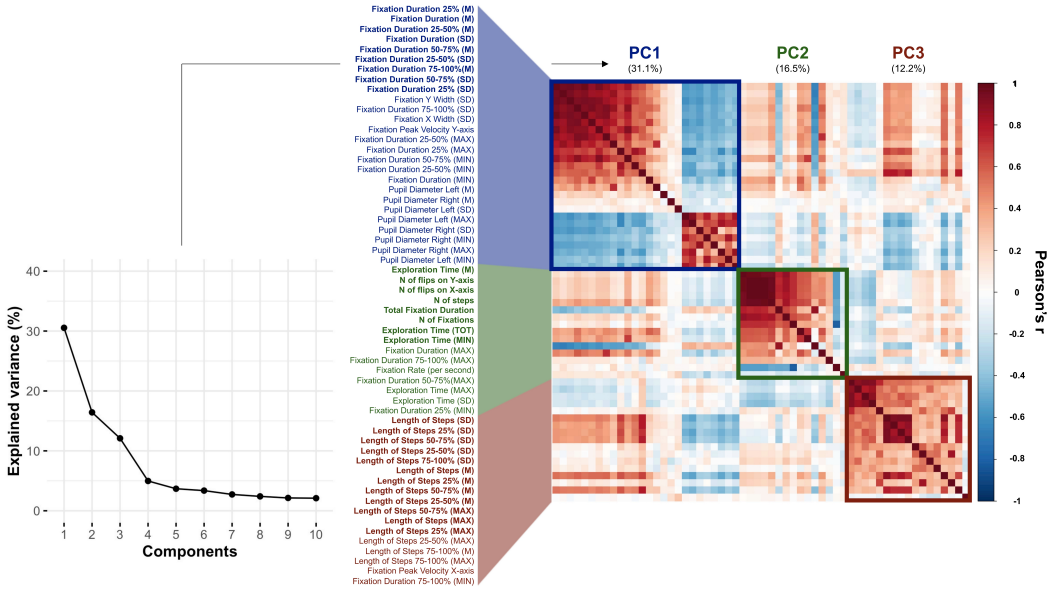


Figure 19: Correlation matrix of spatiotemporal features and principal components (PCs). *The Scree Plot shows the amount of variance each one of the PCs explains. The correlation (Pearson's r) between features, ordered according to their loadings in the first three PCs, is shown in the matrix on the right. The Y-axis labels*

color indicates the PCs with the highest loading for the corresponding feature; the ones written in bold are those with loadings major than 0,2 [33].

The novel variables (components) created were named PC*n*: three components accounted for roughly 60% of the total variance within the dataset[33]. The first component (PC1), which accounted for 30.5% of variance, was mainly loaded on features directly describing fixation duration[33]. Time spent during fixation was anticorrelated with pupil diameter[33], accordingly to the interactions between ACC, VAN, SC and LC modulating NE tone trough fluctuate releasing that increases during fixation in non-luminance constrictions, detected by pupillometer recordings of monkeys and human beings[88,90,91,120] (as exposed in 2.4.1). The second component (PC2), which accounted for 16.4% of variance, was loaded on gaze steps (see 2.3 for *saccadic step*) direction and exploration time; the third one (PC3), which accounted for 12.1% of variance, was charged on gaze step length[33].

3.3.2. Subjects visual explorative phenotypes clustering

Considering distribution of observers across those three components, was applied preliminarily a *Silhouette method*, a robust tool for assessing the quality of clustering solutions[121]: computing for each data point the average distance to all other points in the same cluster and then the average distance to all points in the nearest neighboring cluster[121,122]. Through this computational dynamic, each cluster happen to be represented by a so-called *silhouette*, based on the comparison between its tightness (average intra-cluster distance) and separation (average inter-cluster distance)[121,122]. Those operations, enable to evaluate clustering validity by analyzing the average silhouette width and so they might be also employed to select an "appropriate" number of clusters in a pure data-driven manner[121,122]. Then, considering the distribution of observers across those three components (PC1, PC2 and PC3), a k-means cluster analysis, (the principal clustering analysis used among multimodal biomedical data[123]) splitting the sample into two groups (*k=2*), was performed and best separation was obtained along PC1 loadings[33].

Subjects with high PC1 values, referred to as *"Static Viewers",* showed longer fixation time, longer spontaneous viewing time, smaller mean pupil diameter and a lower fixation rate (less frequent but longer fixations)[33]. Moreover, they're characterized by an average of higher amplitude and more numerous gaze steps, as

long as more gaze flips (a *gaze flip* is a double saccadic step with in between a shift of direction) and a distribution of gaze steps more similar to a power law (see 3.3.3) [33]. On the other hand, subjects with low PC1 values, referred to as *"Dynamic Viewers*", showed opposite features such as more fixations and at an higher rate, wider mean pupil diameter and a distribution of gaze steps less similar to a power law[33].

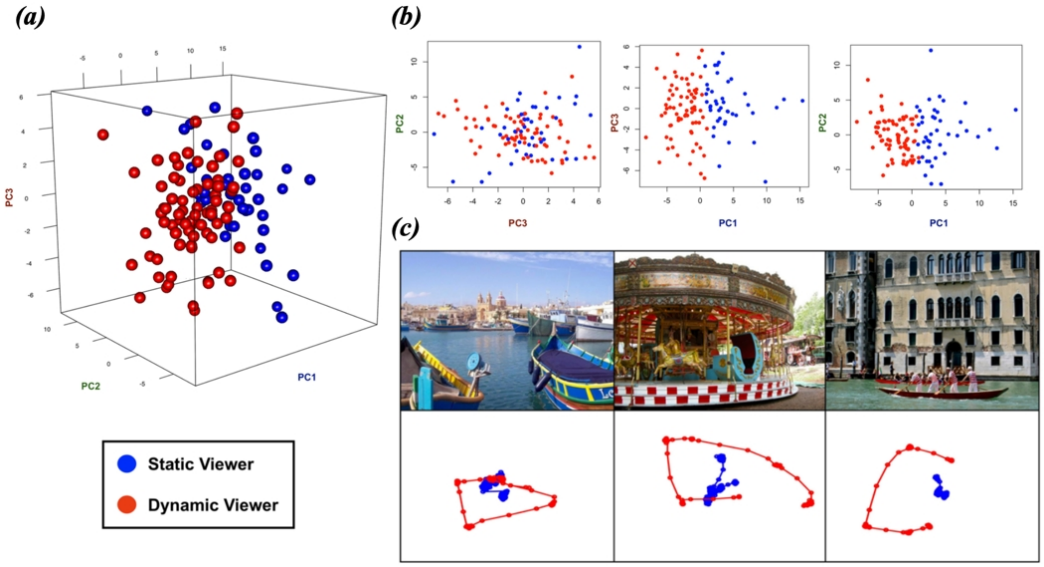


Figure 20: Subjects' clustering and PCs. ***(a)*** *Three-dimensional space, defined by the first three PCs, clusters' projection.* ***(b)*** *Two-dimensional PC scores relationships: PC1 values are those best describing the two clusters.* ***(c)*** *Examples of Static (blue dots) and Dynamic (red dots) Viewers oculomotor dynamics patterns (each dot represents gaze position sampled at a timepoint)* [33].

Trough chapters 2 and 3, has been widely exposed how "*saccades and fixation strategy*" at neural level is related to a complex interconnection between cortical and subcortical functional networks[33,67]. In particular, DAN and VAN control the interactions between focal processing (focused attention) and attentional shifts/reorienting to other locations[9,33,90]. Moreover, considering that fixations is the time when foveation of the image (in a dynamical stability, as seen relatively to fixational movements) allows visual processing, the engagement of *Static Viewers* in longer fixations suggests deeper single processing of each one of the quantitatively fewer stimuli[33]. Conversely, *Dynamic Viewers* tend to scan more rapidly and superficially, shifting across multiple visual scene items[33]. Finally, as neuro-behavioral tests proved (e.g. Stroop color-world, see paragraph 4.3), regarding the ability to inhibit automatic responses, *Dynamic Viewers* tend to be more impulsive than *Static Viewers*[33].

To confirm this assumptions a PCA was ran concerning any subject recording after splitting images (*odd vs even*), and both image-category computation showed a high degree of similarity with PC1[33]. The latter's scores, alongside with PC2 and PC3 values (which explained of course a lower similarity amount), again in order to test the robustness of the assumptions, was used to reconstruct the original features of the matrix and then pattern of the two explorative styles: again, the degree of similarity was very high[33]. Finally, comparing PC1 scores from category-specific images (indoor, outdoor natural, outdoor manmade, scenes with humans, scenes without humans) by applying PC1 loadings calculated on all images, showed a regularity in high or low correlations independently from the type of images analyzed, trough any subject[26].

So intrinsic brain activity drives visual exploration, which can be explained by a low dimensionality of feature in its dynamics; consistently, any subject expresses a idiosyncratic visual explorative style[116], whose dynamics are relatively independent of image content[33].

3.3.3. Power law in neuroscience

A power law is a functional relationship between two quantities, where one quantity changes as a power of another. Mathematically, it can be expressed as:

$$P(s) \propto s^{\alpha}$$

It states that probability P of an event size s is proportional to s to the power of a constant α, the power law exponent[124]. In a power law distribution, the frequency of an event (or the occurrence of a value) is inversely proportional to its size or magnitude, raised to a power. This means that small events or values are much more common than large ones, following a scale-free pattern. It is also characterized by a heavy tail, meaning that there are a few extreme events or values that occur much more frequently than would be expected in a normal distribution (concept used to describe multiple natural and social phenomena: size of earthquakes, distribution of wealth and also neural dynamics)[124].

Neural systems' adherence to power laws is believed to mirror intrinsic neurobiological limitations imposed by anatomical connectivity and neural

dynamics. These constraints, influenced by the slowest temporal factors, then permeate through subsequent neurocognitive and motor processes at increasingly faster rates[114]. Each constraint level influences and shapes the following one, setting up the system so that only relevant information needs to be further processed, in a "cascading" manner[33,125]. Cascades refers to the hierarchical organization where progressive clustering occurs nested at any time into each other; importantly these properties are indicative of non-linear correlations across space or time[125].

Power laws describe the foundation of brain function at any level, shaping a fractal system: they have been found ubiquitously in the temporal organization of channel openings, single spikes and complex firing rates, as well as in the local amplitude signals of fMRI, EEG and MEG recordings[124]. These observations reflect a functional linking of cortical areas, sustained by neuronal avalanches (cascades of activity across many spatiotemporal scales[126]) produced by transient functional cell assemblies[124].

Moreover, behavioral performance fluctuations, such as eye movements, also may follow a power law and tend to correlate with slow and fast neuronal activity (correlated across individuals during both task-engagement and rest; see also chapter 4). *Static Viewers* exhibited small extent and a relatively small amount of long-range gaze movements; conversely, *Dynamic Viewers* achieved a more even distribution of both short and long gaze steps[33].

3.3.4. Relative influence of sensory variables on saccades and fixations distribution

To determine the relative importance of stimuli-driven components in predicting eye movement dynamics, four nested linear regression models where built and compared by means of likelihood ratio in order to weight any component added. PC1 scores were constantly used as a dependent variable, alongside to a different combination of other factors: SAL, SEM, ShEN, and KSD [33].

SAL represented the mean of local sensory saliency values across fixations, while SEM was based on semantic maps obtained by a convolutional neural network[93]. ShEN reflected the interaction between gaze transition entropy (GTE) and

stationary gaze entropy (SGE); these two measures of entropy are fundamental considered its role in influencing gaze spatiotemporal dynamics concerning the optimal integration between *top-down* and *bottom-up* dynamics[127]. Finally, KSD or Kolmogorov−Smirnov distance, measures the discrepancy between the individual distribution of gaze steps and a power-law distribution (two cumulative distribution functions)[33]. KSD proved to be the most significant factor in explaining variance, and was proved to be reliable and robust across different range of values and excluding potential biases related to eye-tracker spatial resolution; on the other hand SAL and SEM were not significant in explaining spatiotemporal patterns during free viewing[33]. Running linear regression also with PC2 and PC3 as dependent variables, was showed again a non-significant contribution of SAL and SEM factors [33].

In conclusion, the analysis of free-viewing eye movements spatiotemporal dynamics revealed a low dimensionality with three components (PC1, PC2, PC3) explaining 60% of the variance[33]. These components, in particular PC1, enabled the clustering of subjects into *Static* and *Dynamic Viewers* groups with over 90% accuracy, independently of saliency and semantic values, highlighting the role of intrinsic factors in visual exploration[33]. These factors (KSD primary), explained around 20% of the variance in spatiotemporal oculomotor dynamics, capturing the levels of similarity between eye gaze step length distribution and a power law[33]. Conversely, for the topography of fixational patterns, mixed effects models showed that saliency and semantics maps accurately predicted eye movement behavior during free viewing, with a smaller role for intrinsic factors (KSD maps). *Bottom-up* components thus play a pivotal role in shaping the topography of oculomotor behavior in absence of any visual task engagement, with gaze directed to salient and semantic areas of the visual stimulation[33]

3.3.5. Blank screen vs unconstrained free-viewing

According to the pivotal role of intrinsic brain activity in behavioral dynamics exposed thus far and demonstrated through this experiment concerning eye-movements dynamics, the hypothesis was that these intrinsic features, so influential that they could delineate visual exploratory phenotypes, would have been impactful even more during observation of a blank screen[33]. This would strengthen the

assumption of relative independence from visual stimuli in spatiotemporal dynamics of visual exploration, especially in an “extreme” scenario such as this one, intrinsically lacking in visual stimulation[33].

To test the hypothesis, the same PCA pipeline was applied to the analysis of eye movements recordings during the first phase of the session (so that subjects saw the images for the first time only later), when participants were asked to look at a grey screen with a cross in the middle (14 subjects maintained a steady fixation, so were excluded due to lack of variability, thus the subsequent analysis included only n=100 subjects vs n=114 analyzed in free-viewing recordings computation)[33]. Again, three components (confirming low dimensionality) described a consistent amount of the variability, almost 50%, but they were loaded on different features order than the components on free viewing. Intuitively, aside from the conceptualization concerning different influences of *bottom-up* and *top-down* dynamics, visual exploration occurs differently when an individual is freely looking at images or is viewing a grey blank screen; consistently feature analysis lie on different perspectives[33]. PC1 accounted for the 23.4% of variance and was mostly loaded on the number of steps, number of flips, and steps’ length variability (features related to PC2 and PC3 during free-viewing); PC2 explained the 19% of variance and was mainly loaded on pupil diameter and steps’ length; PC3 accounted for the 8.4% of variance and was mainly loaded on fixations duration (feature manly included in PC1 during free-viewings recordings)[33]. Running a linear regression model between PCn of the blank screen viewing as dependent variables and the ones of the free-viewing as predictors, was shown how, for example, PC3 during image viewing significantly predicted PC1 during blank screen viewing *($t = 2.98$, $p = 0.004$)*[33].

Then was performed a statistical analysis technique that combines a Random Forest Algorithm (a machine learning algorithm used for classification and regression of multivariate analysis, based on a set of decision trees composing the forest, each of which trained on a random subset of the training data and provides a prediction; combination of all predictions able to obtain an accurate and robust result[128]) and cross-validation (used to evaluate the model's performance, by using subsets of dataset both as trainer and tester) in order to evaluate the accuracy, which was

showed to be 79%, of the blank screen viewing features in predicting explorative phenotype of the subject accuracy[33]. This suggests that oculomotor properties shown during resting-state were consistent with those highlighted during image viewing.

Moreover, the stability of clustering derived by both free-viewing and blank screen viewing was compared showing 68% of coherence in classifying individual explorative styles as part of the same group[33]. Analysis of the between-subjects correlation matrix, during both image exploration and blank screen viewing, reveal that individuals tend to exhibit significantly higher correlation with members of their own cluster (within) compared to members of the other cluster (between)[33]. In addition, both in free-viewing and blank screen-viewing, mean correlations within *Static viewers* cluster were stronger than the ones in *Dynamic viewers*; the similarity between groups had a well conserved structure from one recording phase to another [33].

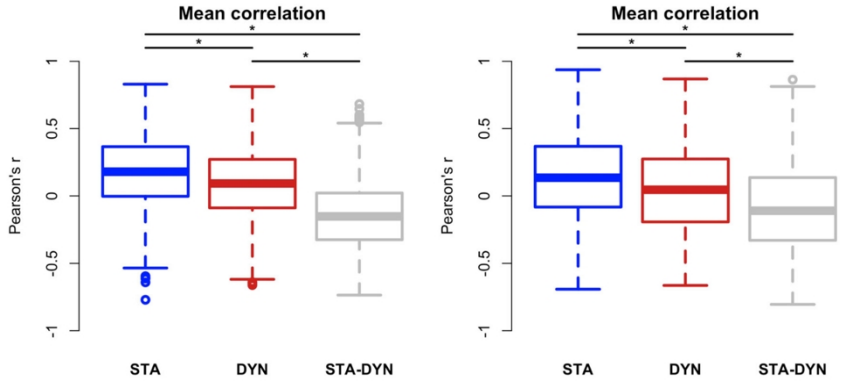


Figure 21: Subjects similarity in image-viewing and blank screen viewing. *Boxplots showing the comparison between the mean correlation within each group and between groups. STA: within-group correlation in Static Viewers (n = 42); DYN: within-group correlation in Dynamic Viewers; STA-DYN: between-groups correlation.*

This study marks the inaugural large-scale investigation in which spontaneous eye movement dynamics are compared with those observed during the exploration of numerous real-world visual scenes. Additionally, it stands as a pioneering effort to demonstrate that features of resting eye movements can be utilized to categorize distinct styles of visual exploration (whose stronger predictor is the level of similarity between the spatiotemporal distribution of gaze step and a power-law). This suggests the existence of constrains within neuroanatomical configurations, cell-level and network connectivity functional dynamics, which shape behavioral features such as visual exploration. Moreover, many studies showed that,

consequently, visual exploration recordings may represent a early marker of neurodegenerative processes (see Discussion, chapter 10).

4. BRAIN ACTIVITY SIGNATURE OF EXPLORATIVE STATES

4.1. Electroencephalography

Examining the temporal dynamics of the brain's ongoing rhythmic activities offers a significant opportunity to delve into how prediction could be implemented. As pointed out in chapter 1, since the introduction of electroencephalography in humans in 1929 by Berger, endogenous activity was noted[11].

EEG is widely used to address issues concerning RSA, mostly because of its high temporal resolution, which is much higher than fMRI's one. EEG can record brain activity with a millisecond precision, allowing the study of rapidly occurring brain processes such as sensory stimuli responses or fluctuations in brain activity during cognitive processing. Moreover, compared to MRI machines, it is more cost-effective in terms of initial cost and maintenance, and its devices are more compact and portable. On the other hand, EEG also has limitations such as lower spatial resolution compared to fMRI and susceptibility to conductivity and movement-related artifacts from body or facial muscles (electromyogenic influences)[129].

Neighboring frequency bands within a given neuronal network typically correlate with distinct brain states and engage in competitive dynamics. Conversely, multiple rhythms can concurrently manifest within the same or disparate neural structures, enabling interplay and mutual modulation[130]. The human EEG detects a multitude of simultaneous frequencies, exhibiting a distinctive power law spectral distribution: as the logarithm of frequency increases, the logarithmic power of the EEG decreases approximately linearly[131]. The power density of the local field potential inversely correlates with frequency (1/f), indicating that disturbances at lower frequencies can initiate a chain reaction of energy dissipation at higher frequencies. Furthermore, slow oscillations across a broad spectrum govern faster local activities [130].

4.2. EEG features predicting visual exploratory phenotypes

Zangrossi et. al showed how eye movements spatiotemporal dynamics are low dimensional (three components accounted for roughly 60% of variability during unconstrained natural-images viewing and for almost 50% during resting-state

blank screen viewing) and driven mostly by intrinsic factors according to the *inside-out* brain perspective ("where" subjects look, determined by saliency and semantics, was strongly less predictive than the level of concordance to a power-law of the distribution of gaze step that refers to "when" and "how" subjects look[32])[33]. Moreover, it proved how intrinsic features of resting eye movements can be utilized to categorize distinct styles of visual exploration[33].

Celli et al., one year later, recruited *n=40* subjects from the previous sample, who showed extreme positive (*Static*) or negative (*Dynamic*) loadings on the PC1 score; they were asked to undergo high-density electroencephalographic recording during eyes-open and eyes-closed resting state settings, in the absence of any task[32]. *Static Viewers,* showed longer fixation time and spontaneous viewing time, smaller mean pupil diameter, a lower fixation rate (less frequent but longer fixations), an average of higher amplitude and more numerous gaze steps, as long as more gaze flips, and a distribution of gaze steps more similar to a power law[33]. On the other hand, *Dynamic Viewers* showed opposite features such as more fixations, at an higher rate, wider mean pupil diameter and a distribution of gaze steps less similar to a power law[33]. In order to highlight the hypothesized link between intrinsic brain activity (representative of cognitive providing of spatiotemporal patterns of activity during behavioral tasks) and oculomotor behavior, speculating that differences in visual explorative styles might be implied by stable individual variations of intrinsic EEG oscillatory activity, three EEG metrics were employed being well representative of behavior and being thought to be able to describe a trait-like constraints of exploratory eye movement dynamic features[32]: resting-state frequency power (see 4.2.1), individual alpha-frequency (IAF, see 4.2.3) and long-range temporal correlations (LRTCs, see 4.2.5).

4.2.1. Resting state frequency power

This metric is believed to indicate the baseline level of cortical activation. Trough EEG recordings of parieto-occipital electrodes (VIS), some researches showed that greater resting alpha-to-beta power might mirror wider attention during a subsequent attentional task; consistently, greater attentiveness at rest would predict subsequent narrowed attentional breadth[132]. Therefore, higher alpha power at rest, would forecast broader attentional breadth, while increased beta power would

indicate narrowed attentional breadth[132]. Furthermore, resting alpha and beta powers, but also the predominance of alpha relative to beta, have been shown to be predictive of performance on temporal attentional tasks[133].

Two resting-state EEG sessions were conducted by Celli et al., lasting ten minutes each: one with eyes open (participants were asked to look at a fixation cross for the whole duration) and one with their eyes closed (participants were asked to keep the eyes shut for the whole duration)[32]. In the eyes-open condition, significant differences between groups were observed in the alpha, beta, and gamma bands ($p<0,05$), while in the eyes closed condition, only the beta band showed significant differences[32]. Overall, *Static Viewers* oscillation profile exhibited higher alpha power and lower gamma power in occipital electrodes, while revealing lower beta power in frontal electrodes; on the other hand, *Dynamic Viewers* profiling showed lower overall alpha power but higher beta and gamma power[32].

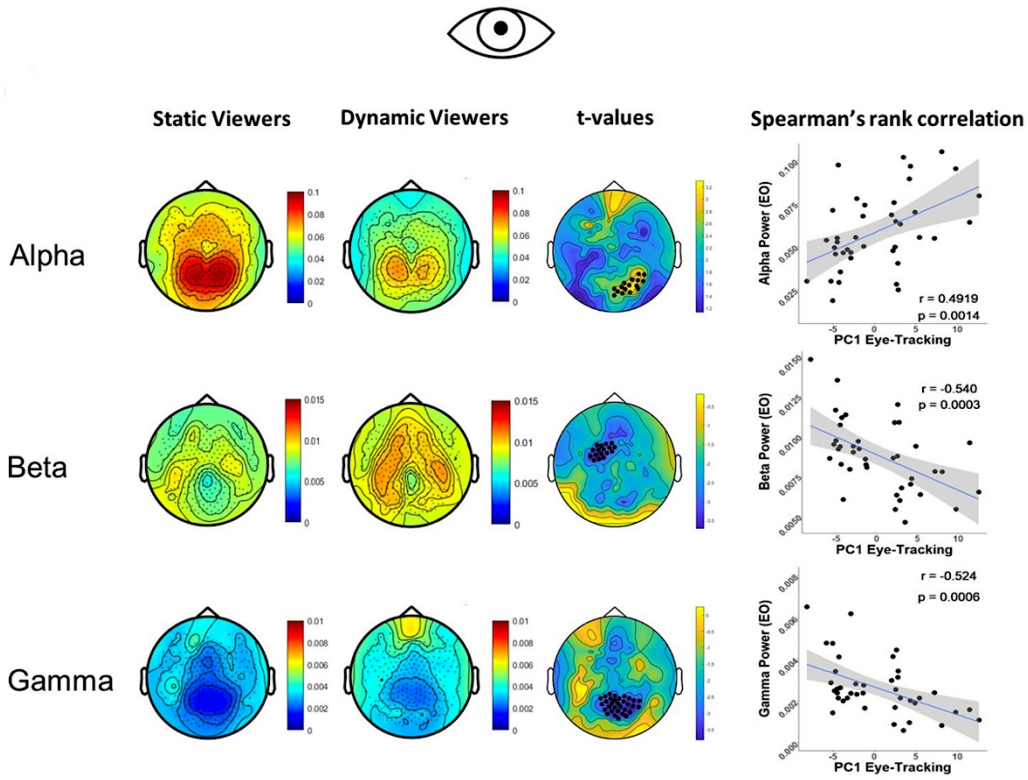


Figure 22: Spectral analysis results. *Eyes-open condition (N=40 subjects) for alpha (7.5–12 Hz), beta (12.5–32 Hz) and gamma (32.5–45 Hz) relative power spectral analysis and t-value maps for the cluster-based permutation analysis, which provided in all three cases significant results (black dots) with cluster alpha at $p < 0.01$ (two-tailed) and alpha $p < 0.05$ (two-tailed)*[32]*. The right panel shows the Spearman's rank correlation between PC1 and averaged power in the significant cluster of electrodes (with Spearman's r, p-value and 95% CI)* [32].

Mutual relationship between alpha and gamma bands (which can also be addressed to in terms of interplay between activatory and inhibitory frequencies) that reflect also an index of internally/externally directionality of attention is reflected trough subjects clustering[32]. *Static Viewers*, showed higher mean alpha power and would, coherently being characterized by intense external stimuli inhibition, according to a baseline cortical activation shifted towards internal processing[32]. Contrarily, *Dynamic Viewers* would present attention more directed up to external stimuli, according to lower alpha inhibition, and a concomitantly resting profile closer to that seen during stimulus processing and selective attention to stimuli[32]. Finally, frontal beta band power appeared to be lower in *Static* than *Dynamic Viewers*, both during eyes-closed and eyes-open. Considering the role of beta band rhythms in coupling a *dynamic core* of hubs and preserving status quo of central stations of functional connectivity during rest but also during natural visual exploration (scenario statistically close to spatiotemporal priors for external visual stimuli), recordings suggest that *Static Viewers* might maintain at rest sensorimotor cortical areas in heightened reactivity state[32,110].

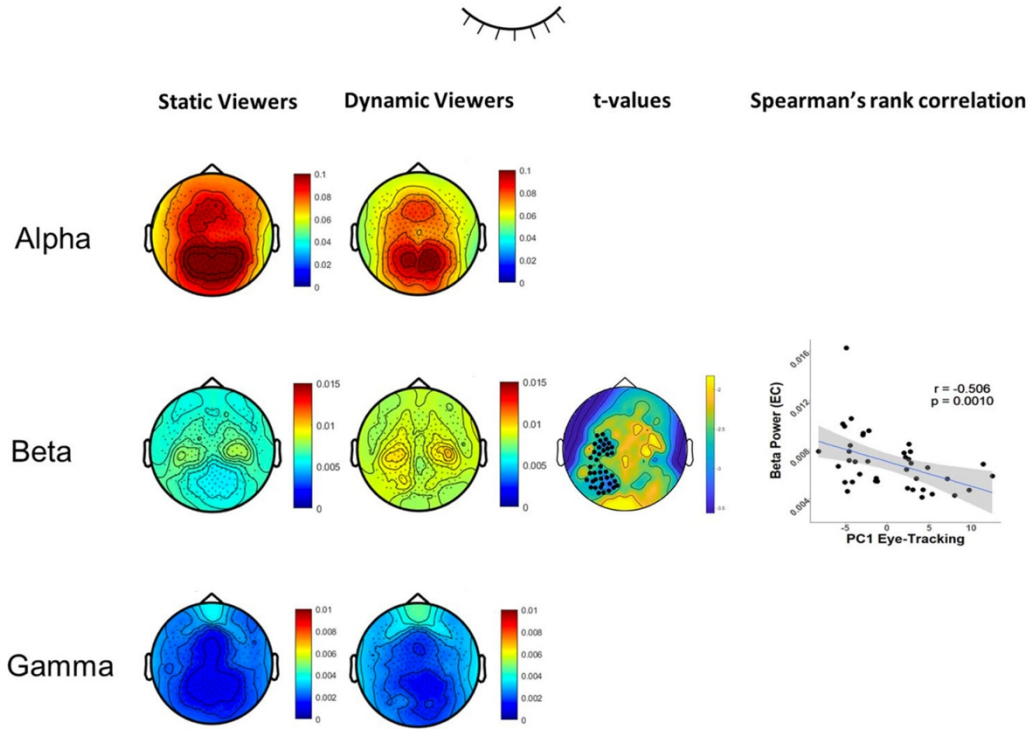


Figure 23: Spectral analysis results. *Eyes-closed condition (N=40 subjects) for alpha (7.5–12 Hz), beta (12.5–32 Hz) and gamma (32.5–45 Hz) relative power spectral analysis and t-value maps for the cluster-based permutation analysis, which provided in all three cases significant results (black dots) with cluster alpha at $p < 0.01$ (two-tailed) and alpha $p < 0.05$ (two-tailed)*[32]*. The right panel shows the Spearman's rank correlation between PC1 and averaged power in the significant cluster of electrodes (with Spearman's r, p-value and 95% CI)* [32].

Statistically, PC1 resulted (both computing EEG recordings data overall all subjects or when the two phenotypes cluster were considered as separated) to be positively correlated with alpha power, and negatively with beta and gamma frequencies[32,33].

4.2.2. Alpha frequency band

Classically, since late sixties, alpha power has always been associated, in terms of cognition, with an "*idling state*" (cortical areas not processing sensory information or motor output[134]) recorded manly over occipitoparietal cortex electrodes, especially during relaxed alert states electrodes in subject with eye closed[125,127]. Moreover, it has been showed to be also an important functional rhythm across sensorimotor cortex when limbs are at rest (there called μ rhythm, 11-12 Hz sub-band), auditory cortex and association cortices[129,131,135]. Magnitude of alpha amplitude in eyes closed resting condition, predicts a greater or lower level of brain activation when suppressed (simultaneously occurs an increase in the amplitude of FDG-PET signal[136]) during visual exploration and cognitive processing; inter-individual differences in amplitude and level of suppression, relate to IAF[137] (see 4.2.3) but also to endophenotypes of visual exploration (as seen in 4.2.1) and cognitive performances[129,138].

Over years, following the so called "*neural efficiency hypothesis*"[139] (which states that effective cognition is not a function of "how hard" the brain works but rather of how efficiently it works[129], so that good performance may be achieved with less contingent cortical activation[139]) alpha upper band frequency started to be seen as an index of *top-down* processing, by growing signal-to-noise ratio within the cortex, thus inhibiting non-essential or conflicting processes[129] which in turn may reflect facilitation on task performance[140]. Consistently, the "*inhibition–timing hypothesis"* clears how, although mirroring anyway a state of information process, ERD (event-related desynchronization, the classically known occipital alpha suppression when transitioning from eye closed idling state to an eyes-open explorative one, also referred to as "*Berger effect*"[137], or when increasing cognitive load[129]) reaches its maximum when task-related processes occur and reflects a low processing selectivity, in other words a state of high overall excitability[140]. It differs from ERS (event-related synchronization, elicited for instance when subjects

withhold or control the execution of a response) which characterizes sites that probably are under, or exert, inhibitory *top-down* control[140]. The latter is a highly selective process because inhibition helps to establish a highly selective activation pattern: it is a timing mechanism, an inhibitory filter that enables to achieve an high signal-to-noise ratio by allowing only (comparatively) a small number of cells to process information selectively, and by silencing the majority of other cells[140].

In line with this interpretation findings suggest that alpha activity increases, (especially in parieto-occipital sulcus) with load retention in working memory dynamics, while disengagement or inhibition, of non-essential visual dorsal stream processes occurs in order to devote structures for working memory maintenance.[129,141]. Moreover, the higher the frequency of cyclical oscillations in the alpha rhythm the greater the capacity and speed of working memory[129,142].Alpha oscillations are also related to *top-down* processes in the complex sensory-semantic long term memory system: when a task requires specific cognitive operations with memorized data (such as retention, inhibition of retrieval, or manipulation through transformation) alpha synchronizes over respective brain areas[140,129]..

Finally, alpha band activity has been associated to the "*gating hypotesis*" according to which functional connectivity may be shaped by inhibitory gating: pulse alpha band oscillatory inhibition reduces the processing capability of a certain cortical area (irrelevant to those specific task-engagement processes) and routes information to task related cortical areas.[143]. So alpha increase has been suggested to either reflect active processing related to memory maintenance or inhibition of regions not required for the task.

4.2.3. Individual alpha frequency

From a purely physiological standpoint, alpha frequency band recordings led over the years to the determination of more than 20 arbitrary frequency boundaries[129]. This variability depends on the interaction of genetically determined (it is now evident that alpha peak frequency reflects inter-individual genetic influences as polymorphisms[144]) multiple signaling pathways at all levels[129]: Ca^{2+}T-channels[144], metabotropic receptors GABA-B[145], metabotropic glutamate receptors (mGluRs) [145] , synapsin and the amount of vesicles exocytosis depending on regulation on action

potentials by those previous genes[129,146], COMT gene locus polymorphisms[147] and many other factors regulating cellular growth[148], energy homeostasis[149]and protein trasduction[129,148,150]. Calcium channels (thalamic relay cells with high density of Ca^{2+}T-channels which have a pacemaker role producing a temporary depolarization at approximately 10 Hz rate[144]) and metabotropic receptors, modulate thalamo-cortico-thalamic network action potentials which then affect the activity of all the other factors pointed out before[129,151]. In addition, also non-genetic mediated phenomena explain variability of alpha band width, such as the level of brain activation state and efficiency of cognitive performance[152,153], which also changes according to age (from 3 to 20 years especially) and through learning[129].

This huge amount of variability of alpha frequency band thresholds (whitin- and between-variability[154]) in frequency, amplitude, duration, and recurrence[155] led over the years to the evaluation of different strategies in order to distinguish between individually based lower and upper frequency boundaries of the alpha band (Individual alpha frequency, IAF)[129]. Some authors consider it as the peak frequency [156], which is also the approach followed by Celli et. al, defining it as the highest absolute value in the 7–13 Hz range on the average spectrum across occipital electrodes (both automatically detected and visually checked) in the eye closed recordings[32,154]. The IAF of the human EEG reflects systemic properties of the brain, is highly heritable, and relates to cognitive functioning[154].

As already addressed exposing the "*inhibition-timing hypothesis*"[140] (as seen in 4.2.2), IAF has an established relationship with inhibition and processing rapidity (according also to the lower rhythms modulation operated to gamma frequencies activity[157]). *Dynamic Viewers* displayed higher IAF (while presenting lower alpha power amplitude) than *Static Viewers*[32], consistently to their faster saccades dynamics and shorter fixation time[33]. IAFs, in fact, have been proved by some studies to be inversely related to the amplitude of the alpha-rhythm at rest, but at the same time being a predictor of the alpha rhythm amplitude during stimulation[158]. Moreover, it has been showed to be related to the amplitude of visual evoked potential (VEP) and, finally, to the hemodynamic oxygenation response to visual stimulation (relationship between IAF and neuro-vascular responses originates from the size of the network recruited for visual processing)[158]. High IAF, such as in

Dynamic Viewers, predicts a low alpha amplitude at rest, a small VEP amplitude and a small oxygenation response[32,158].

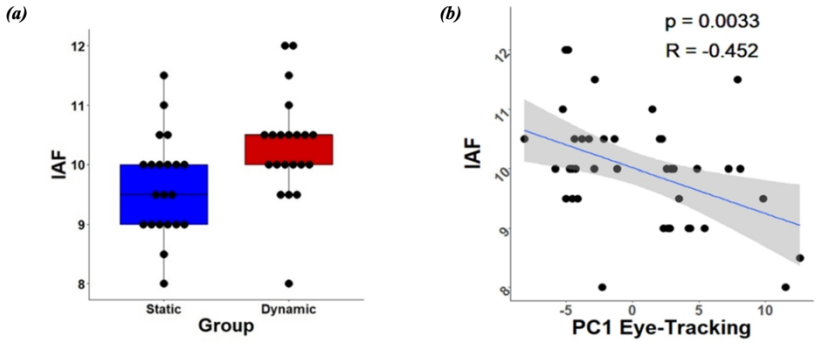


***Figure 24**: **Individual alpha frequency results**. **(a)** Boxplot concerning individual alpha frequency values in the two identified groups: (Static n = 19), median = 9.5 Hz; Dynamic (n = 21) median = 10.5 Hz. **(b)** Spearman's rank correlation between PC1 and Individual Alpha Frequency values.*

Finally, referring also to the "*gating hypothesis*" an higher IAF in *Dynamic Viewers* relates with stronger intracortical inhibition (quicker fixations disengagement) and highly specialized activation patterns eventually resulting in faster task performance (reflected also by a higher number of fixations overall, consistently with the negative correlation between PC1, loaded on fixation duration and IAF)[32,33,143]. *Dynamic Viewers* should be also quicker in attentional tasks and visual processing[32].

4.2.4. Beta and gamma frequency bands

Classically described as the inhibitory rhythm of the motor cortex[32], sensorimotor beta band frequency (15-30Hz) undergoes ERD during movement preparation and execution and then, before returning to a resting state, exceeds the pre-movements level with an ERS, or a post-movement beta rebound (PMBR)[159,160]. The latter, PMBR, occurs around 300 ms after movement is done and persist up to several minutes bilaterally (but especially contralaterally)[161]. The further, ERS, may also be enhanced once *top-down* directed attentional or cognitive processes occur, when subject is asked to observe or imagine a movement[160,162]. Both represent a state of motor cortical inhibition mediated by GABA receptors, but also, in a modern view, participate to hub status quo, based on evidence of increasing beta synchronization during tasks in which a setting is maintained over time[32,163].

Neuronal synchronization in the gamma band (30–100 Hz) accompanied by a decrease in alpha band activity reflects active processing in the engaged brain regions. Accurate identification of the true gamma oscillations requires the application of appropriate statistical analyses, and additional experiments to differentiate between power increases (caused by those specific band oscillations) and those, on the other hand, arising from increased spiking activity[157]. Studying the brain as a network involves exploration of the cross-frequency interactions between gamma and alpha activity (see 4.2.6)[143]. Gamma-band rhythmogenesis, which is usually brief, relies instead on coordinated interplay of excitation and inhibition, realized by reciprocal interaction between pyramidal neurons and interneurons (which depend upon the interactions of GABA-A and AMPA receptors with the pyramidal cell membranes time constant[164]), typically occurs with single-neuron firing. Cell assemblies, on the other hand, can act coordinately in order to promote a collecting firing, which can also discharge postsynaptic neuron in the critical time window of the spike-timing-dependent plasticity[157,165].

4.2.5. Long - range temporal correlations

This EEG metric measures the temporal structure of oscillations and relates it with the concept of neuronal *criticality* of operating brain, trough avalanches organized as a fractal system, affecting cognitive, perceptual and, of course, behavioral processes[32,166]. Previous studies already proved how significant are temporal correlations between alpha, mu and beta fluctuations, which reverberate at least for a couple of hundreds of second during resting states (both with eyes open and eyes closed assessments); then a decay of correlation characterized by power-law scaling properties occurs, differentially connotated, according to the band considered, due to their distinct functional foundation[155].

Although neuronal avalanches appear as a distinct phenomenon from LRTCs, involving much shorter spatial dimension and time scales (10^{-3}- 10^{-1} vs. 100-10^{3} s, respectively), their power-law exponents of size and lifetime distributions have been showed to be strongly correlated to LRTCs' ones[166]. Probably, neuronal avalanches and oscillations demonstrating LRTCs emerge simultaneously in near-critical brain states, indicating the propagation of neuronal activity across extensive spatial and temporal scales[166]. The metastability of critical systems optimizes their

computational power, dynamic range and storage capacity. Fractal self-similarity and power-law (or inverse) scaling behavior features, are typical of systems displaying “avalanche dynamics” which operate within a critical or self-organized critical state[166–168].

A detrended fluctuation analysis (DFA) was performed by Celli et al, extracting a scale-free exponent in order to depict temporal structure of the signal in terms of statistical properties across scales (as self-similarity[32], which was expected to be highly invariant across subjects[155]) and long memory[32,169]. Assessing the rate at which fluctuations grow as a function of the scale, by estimating root mean squared errors at different scales and their relationship with window log, DFA exponents were determined[32]. According to other studies, DFA can be also used in order to study fixational eye movements at different timescales, once operated the removal of micro-saccades (which were not considered by Zangrossi et al. and Celli et. al studies) that impact manly horizontal movements at short time scales (see 2.2.3), while at long time correlations vertical and horizontal eye movements behavior crossover and scaling exponents become similar[79]. Scaling exponent is, indeed, a stationary and significant characteristic of eye movements dynamics[79].

This study by Celli et al. is the first to run DFA for eye movements temporal correlations, according to the hypothesis that also the eye movement time series could show fractal properties[32,170]. So DFA was ran both for the brain-data (corresponding to the alpha band filtered EEG signal) and for the behavioral-data (which are the fixation timeseries); correlation between exponents (of the temporal structure of alpha rhythm and of the temporal structure of eye movements) were established, and their value resulted to be comprehended within the 0,5 – 1 interval (where exponent of 0.5 stands for uncorrelated signal, and an exponent of 1 for strong long-range temporal correlations)[32].

All DFA exponents extracted from the eye movements time series, as expected, were proved to be within the range 0.5–1, demonstrating long memory and LRTCs for that behavioral-data signal[32]. Moreover, DFA exponents, representing the temporal structure of fixations, were supposed to be strongly related with PC1 which is, indeed, a static feature of fixation timings: Spearman’s rank correlation (*r*

$= 0.465, p = 0.002$) confirmed the hypothetical relation, according to the fact that, above all, the two (DFA exponents and PC1 values) are, from different perspectives, measurements of the same phenomenon[32].

Finally, exploring the association between mean of brain and behavioral exponents across subjects, a positive correlation (Spearman's rank correlation, $r = 0.40, p = 0.009$) emerged during eyes-open recordings trough alpha band[32]. In particular, computing Spearman's correlation by using nonparametric permutation and cluster correction, n=30 electrodes (in the occipital area) showed significantly positive correlation; their DFA exponents positively correlated with behavioral DFA exponents, but it is important to underlie that alpha DFA exponents were highly different between *Static* and *Dynamic Viewers*[32]. Moreover, the correlation between behavioral DFA exponents and alpha band DFA exponents appeared to be absent in the eyes-closed recordings[32].

Power-law form LRTCs are thought to reflect structural and functional intrinsic systems constrains, that determine recursive regularities in brain signals and behavioral data[32]. *Static viewers* showed stronger LRTCs both in brain-data timeseries (the occipital alpha band) and in eye movements timeseries, mirroring higher self-affinity (consistently with cluster dynamics of emphasized internal processing), complexity and maintenance of signals memory over time[32]. On the other hand, *Dynamic Viewers* showed LRTCs (behavioral and brain sequences closer to white noise, with DFA exponents proximal to 0,5) exhibiting a less complex signal, a partial lack of temporal structure over time and a resemblance to random processes[32].

4.2.6. Alpha band and the interplay with other frequencies trough visual explorative dynamics

Although being neuronal oscillatory coupling often studied within specific frequency bands, different oscillatory classes present different levels of brain integration: synchronization of multiple bands encodes complex temporal patterns and optimizes synaptic reinforcements or weakenings[130]. Spatiotemporal modulation of information processing, is dependent upon ongoing oscillations, which affect local electrical fields and intrinsic excitability of neuronal populations. Tonic shifts in the power of brain rhythms, particularly alpha and gamma bands

(with beta band perpetrating status quo of networks hub[163]), often accompany changes of neural response amplitude, attentional state and perceptual/cognitive performance[171].

Alpha band oscillations, as addressed before, function as a mechanisms through which cognitive control networks implement *top-down* modulatory effects on both local and distributed information processing[131]. For instance, DAN activity and focal alpha (focal disinhibition) desynchronization reflect *top-down* driven dynamics for selective attention, gating irrelevant sensory processing to enhance local activity and information processing[131]. Consistently, (in line with what exposed in 3.2.3), when experiencing task-engagement or memory-retention task (especially in a sensory-dependent assessment) alpha power increases in right parietal cortex (rTPJ, part of VAN[90]) which is progressively inhibited proportionally to the strength of task-focused attention or task shielding, avoiding attentional shifts to task-irrelevant stimuli, thus favoring attention focusing during *top-down* goal-driven tasks[172]. This is not just a matter of directionality of attention, external or internal, in fact the magnitude of alpha power activity may be conceived as a valid indicator of ongoing cognitive processes[172]. This dynamic occurs even when performing mental imagination tasks, creative cognition/ideas formation; those are all situations that involve, also, an interplay between DAN and the generally defined control networks, such as intrinsic stimuli-independent resting networks such as the DMN[172,173].

The cross-frequency coupling of gamma and other rhythms, within the same and different brain regions, forms a multiscale timing mechanism[157]. Modulation of gamma rhythms by slower oscillations occurs, for instance, with theta band frequency (4-8 Hz): variations of the magnitude of theta-gamma coupling, in multiple hippocampal cortical areas, occur proportionally to working memory load. Those phenomena have been addressed to as "*theta phase precession*", which is also conceptually consistent with the preplay/replay theories, asalready argued in chapter 1 concerning hippocampal activity [174,175]. Moreover gamma activity is regulated by interactions with alpha, delta (0,5-4Hz), slow, and infra-slow (broadening what has been exposed in chapter 1) bands freqeuncies[157].

During an auditory task, gamma power synchronization in the frontal and temporal lobes, predominantly occurs through phase-locking with theta oscillations; in visual tasks, phase modulation over occipital areas is, instead, primarily driven by the alpha rhythm[157,176]. Regarding to visuospatial attentional dynamics (expanding what already exposed in paragraph 3.2.3 and previous chapters) in a disengaged resting state VIS areas synchronize to a common alpha idling rhythm in large bilateral spatiotemporal clusters, which must desynchronize (in particular between hemispheres) consistently with the intra-hemispheric *top-down* directional influences from DAN regions, developing small local clusters which enable visual processing[6]. During a visuospatial attentional task, *top-down* dynamics occur profoundly modulating in strength and directionality (but not topography) the connections between dFEF or pIPS and intermediate areas in the visual hierarchy, V3a–V7 and MT, via superior longitudinal fasciculus (although connections between FEF and IPS, within DAN, lie on the same white matter tracts of the superior longitudinal fasciculus, they're not affected at all)[6]. These mechanisms have been proved also by BOLD-fMRI recordings and transcranial magnetic stimulation over frontoparietal regions (IPS and FEF): both reflect alpha desynchronization in occipitoparietal cortex while the allocation of visuospatial attention verifies[6,177]. These mechanisms (such as the decrease of temporal correlations within visual cortex, aligning with the desynchronization of alpha rhythms observed during anticipation, spatial attention, or visual processing[178]) favor the occurrence of gamma power oscillations, so that alpha frequency, enhanced manly by the FEF (right in particular) effectively routes cortical information flow by modulating gamma-band activity[6,179]. This gamma power supports perception by synchronizing the processing and trafficking of information within and across areas of visual cortex; furthermore, over time, research has revealed that the characteristics of induced gamma activity are determined by low-level stimulus attributes (contrast, color, suppression of surround phenomena, characteristics of image stimuli; any of this concurs in shaping amplitude but also peak frequency of local gamma band activity)[180].

Some studies demonstrated also that the spontaneous power of neural oscillations significantly impacts visual perception, leading to threshold for stimuli, which are intermittently detected or missed depending on the phase (accounting for a

minimum of 16% variability in performance) of previous of spontaneous brain oscillations[171] (major effects of prestimulus phase have been often found to be centered around 10 Hz in the alpha band,[181] while some other studies found it around 7 Hz, at the crossover between theta and alpha bands frequencies[171]). The issue can be seen as the spike timing that may be "clocked" by the phase of prestimulus ongoing alpha activity in visual cortex, as analyzing V1 area[182].

Once again, taken together these finding (which are also closely related to behavior) support the strong interaction theory between *bottom-up* and *top-down* processing, which also reflects trough oscillations interplay among multiple bands frequency. DAN within-network functional connectivity stability might reflect his role as a *prior* for incoming information, tuned even at rest in order to anticipate attention clues, far away from the influence of sensory stimuli[6]. Beta band, finally, has a role in providing this stability and, consequently, the stability of predictive *priors*.

First of all, while alpha oscillation activity (as just argued) generated by infragranular deep cortical layers in FEF/IPS phasically regulates *top-down* modulation[182] of superficial VIS cortical layers gamma activity[183] (which carries feedforward signals) as well as spiking activity evoked by visual stimuli[182], frontal feedback control is employed through synchronization of oscillation in the lower alpha and beta (8 –20 Hz) frequency ranges[179]. While information about stimulus features are carried by gamma oscillations, which determine temporal windows for synaptic plasticity proportionally to their cycle length[130], beta synchronization carries feedback signals which influence the functional activation of relevant cell assemblies (with no circuitry structural change enhanced) mediating the functional coupling of neurons and regions over much longer distances, where high gamma frequency promotes local processing[110,184]. Refining concepts of paragraphs 1.5: during development, repeated exposure to sensory or motor signals enhance reverberation in the post-stimulus period and imprint traces in the spontaneous activity (according also to Hebbian plasticity, see 1.5[42]), so that metrics describing sensory external environment and biomechanical body properties, shape networks topography and dynamics[110,185]. Gamma frequencies are thought to encode for quick environmental changes and error predictions, while beta coupling fluctuations should slowly enhance weighted integration of incoming information and *prior*

inferences, computing the slower temporal structure of somatosensory events and the outputs obtained by the interactions between predictive models and environmental engagement. Those development-shaped internal models, stable yet still malleable in adults (an efficient brain is one that can employ predictions but monitoring for errors during the interactions with the occurrences in the surrounding world, adjusting its models when necessary), act as spatiotemporal *priors* which allow the brain to exploit stored knowledge in order to predictively anticipate the statistically most likely outcome of the upcoming stimuli and movements (balancing specificity and entropy of explanations)[110]. Spontaneous activity determine biased (optimized) recruitment of the task-driven patterns, forming spatiotemporal scaffolding of brain possible responses: this translates to a low dimensionality of cognitive and behavioral (just as in visual explorative dynamics[33]) dynamics across task and across individuals. At the same time this justifies the similarity between task-engaged and resting state functional connectivity[13,110].

Secondly, just as alpha band activity, beta band oscillations operate a *top-down* modulation linked to different cognitive functions (such as visual attention, perception, emotion, working memory), operating that selection bias in task-networks recruitment, in order to predictively preserve computed expectations about the sensory environment and the internal models of body representations, or to plan subsequent exploratory eye movements dynamics in case of unexpected interactions outputs[110]. To do that, beta band synchronizations act enabling long-range within-/between-networks (such as PCC of DAN with DMN[186] or IPS of DAN with SMA of SMN[187]) coupling, creating dynamic interconnections within hubs (hence creating a *"dynamic core", by* overlapping functional hubs with "*rich-club*" regions of structural connectivity) and thus generating highly efficient brain states. Beta band oscillations dynamics account for over the 70% of the efficiency peaks (configuration where nodes of networks can easily connect with other nodes), optimizing communications among distinct functional domains[110,187].
So beta band activity stands as a neuronal correlate of *cognitive synergies* (by joint fluctuations of the *core network* hubs in the beta band) enhancing information transmission to *top-down* bias of the functional coupling between other network regions, applying predictive prior-mediate previsions about task-responses[110].

Coherently, when experiencing both naturalistic visual exploration and scrambled movie visualization, alpha band spatiotemporal activity, compared to rest, decreases within the visual system, but also between VIS and DAN interactions[110], as exposed before[6]; beta band activity, instead, decreases only in the second scenario, which doesn't fit with the idea of temporal *priors* coding during natural vision purpose of those joint fluctuations between dynamic hub regions of association cortexes[110].

Beta rhythms are indeed pivotal in maintaining the *"dynamic core"* composed of central hubs regions, acting in the maintenance of the current sensorimotor or cognitive state, thus maintaining cognitive and behavioral priors (temporal connectivity priors[13]) for real-world events interactions; all of that, while preserving stability, yet flexibility of upgrades, of the status quo of central cortical areas as a pivot around which brain activity realizes itself, practicing the highest global efficiency possible[110,163].

After addressing all these theoretical issues, the significance of observers style profiling by Celli et al. may be more clear in broadening the findings concerning behavioral and intrinsic activity fingerprints by the Zangrossi et al. (see 3.4) study. *Static Viewers*, showed higher mean alpha power and would coherently being characterized by intense external stimuli inhibition, according to a baseline cortical activation shifted towards internal processing[32]. Contrarily, *Dynamic Viewers* would present attention more directed up to external stimuli, according to lower alpha inhibition, and a concomitantly resting profile closer to that seen during stimulus processing and selective attention to stimuli[32]. Finally, frontal beta band power appeared to be lower in *Static* than *Dynamic Viewers*, both during eyes-closed and eyes-open recordings, suggesting that *Static Viewers* might maintain at rest sensorimotor cortical areas in heightened reactivity state[32,110].

4.3. Eyes as a window to the soul

William Shakespeare once stated "the eyes are the window to your soul". Indirectly relating to this idea, over the years many research lines investigated relationship between eye movements and cognitive processing or personality traits. Also Zangrossi et al. addressed these issues, by examining whether eye movement

spatiotemporal features described by PC1 scores were related to individual characteristics, such as cognitive scores (inhibition, visuospatial and verbal memory) and personality traits (Big Five scores: agreeableness/antagonism, neuroticism, conscientiousness/undirectedness, extraversion, openness to experience[188]) administering multiple standardized tests, focusing on *visuospatial long-term/working memory* and *executive functions* (inhibition/impulsivity) following studies that correlated these two models to visual behavior[33].

Recent studies concerning *visuospatial memory* proposed that eye movements do not only mirror the retrieved content, but the facilitatory influence of gaze position on visuospatial episodic remembering (which is considered to depend on the interaction between retrieval cues and stored memory traces), particularly affecting memory for the spatial relationship between objects and balancing it with encoding, increases the likelihood of successful episodic recalling[189]. Moreover, some other studies have demonstrated the comparability between eye movements when inspecting a scene (or hearing a scene description) and when visualizing it from memory[190]. Another research has shown that oculomotor events during recall are not merely reinstatements of those produced during encoding; additionally, when gaze dynamics are restricted, scene recollection is altered and impaired, regardless of the encoding modality[191].

Concerning executive functions, on the other hand, impulsivity may be defined as *"acting without forethought"* and it stand opposite to inhibition[192]. Anticipatory eye movements, which reflect the functioning of anatomical loops between the frontal cortex and basal ganglia, via the thalamus (corticalstriatal frontal loops), reflect brain dynamics related to the "forethought"[192]. Contrarily to the general understanding of 'impulsivity' (related to faster responses), affecting cognitive processing of information needed to anticipate future events, it results in delayed and slowed eye movements: higher scores of impulsivity in healthy subjects showed to be related to smaller anticipatory saccades, longer smooth pursuit latencies and lower anticipatory pursuit velocities[192]. The information extracted from this questionnaire can be seen as complementary to those taken from the Stroop Test, thus, taken together, they allow to investigate impulsivity both from cognitive and behavioural points of view.

First of all, Zangrossi et al. administered a Depression Anxiety Stress Scale (DASS), an 42-item self-report measure (which may be employed also as the 21-item test version) of anxiety, depression and stress with impressive psychometric properties[193], which was employed in order to remove from computation participants with high levels of anxiety, depression, and/or stress to prevent biased eye movement data[33]. Other studies findings, in fact, point out for example in the case of anxiety impairs processing efficiency (response times and mental effort increased) and *top-down* attentional control across different task constraints, influencing search strategies[194].

Then, forward and backward versions of the Digit and Corsi span tasks were administered[33]: they're frequently used to assess verbal and visuospatial short-term memory, which are affected by age and literacy[195]. In particular: forward versions primarily evaluate working memory functioning exploring phonological loops for verbal data and visuospatial draft for visuospatial data, backward versions to primarily address central executive resources[33,195]. The Rey-Osterrieth Complex Figure (ROCF), a psychological test used to evaluate visuospatial abilities, memory, attention, planning, and executive functions, was administered, but only the delayed recall task version was considered[196]. This decision was made because healthy participants achieved excessively high scores when asked to reproduce the figure immediately. In this setting, the initial copy serves solely as a mnemonic imprint, which is then recalled ten minutes later[33,196,197]. Finally, a brief version of the Stroop Test was performed, which addresses executive functions such as cognitive control, attention, and processing speed, but also is considered as a metric for impulsivity[33,198]. The shortened version typically includes fewer items and can be administered more quickly, making it practical for use in clinical and experimental settings[199]. Furthermore, impulsivity in complex behaviors has been assessed by means of the behavioral inhibition system (BIS) and a behavioral activation system (BAS)[200].

After the recording and the testing, subject were asked by Zangrossi et al. to complete the form Neo Five Factors Inventory (NEO-FFI)[33]: big five personality factors were proved by many studies to be related to multiple oculomotor features

such as fixation patterns (for example openness was related to longer fixations), number, duration, and positioning time[33,201]. Trough machine learning approach applied to recordings during everyday task, studies proved the possibility to delineate consistently and accurately personality traits, as level of one or more of the Big Five; moreover was also showed to be possible automated analysis of a large set of eye movement characteristics, ranking them by their importance for personality trait prediction[112].

Lastly, were also examined the relationship with demographic information (age, sex, and education)[33]. Despite common fixational patterns to the most informative regions of a scene (locations with people) and of a person (face, in particular the region around the eyes), studies proved that, on average, women exhibit more exploratory behaviors, making more fixations (shorter but more frequent than men) particularly on non-face locations and a more spread out fixation distribution[202]. Beside these pure behavioral differences, the lower, central, and left subfields of the human retina are thicker in men than in women[202,203]. This anatomical difference means that when women fixate slightly below a target, the light hits a thinner part of the fovea, leading to eye movements that are systematically lower at the most informative locations[202,203]. This phenomenon is heightened under threat conditions due to estrogen's influence on the D2 receptor, which moderates eye movements and emotional salience of danger[202,204]. Furthermore, visual behavior in extroverts is likely to increase the probability of forming different interpretations and seeking different visual information[192]. Conversely, individuals with a high conscientiousness trait are highly organized and focused, and their information-gathering strategies are less influenced by their interpretations[192]. Differences in two impulsivity sub-dimensions (premeditation and perseverance) may also explain part of the variation in fixation distributions between men and women[192]. Premeditative individuals, who value information highly, tend to make more fixations on the eye regions of faces, while perseverant individuals (mostly women) are inclined to continue gathering visual information from new locations, resulting in wide, high-entropy distributions[192].

Overall, significant relationship were observed on age ($t = 2.66, p = 0.009$), and impulsivity (i.e., Stroop test score; $t = -2.36, p = 0.021$); reliable was the

significancy trend for the NEO-FFI factor (out of the big five) "openness" (*t = 1.93, p = 0.057*)[33]. Specifically, *Dynamic Viewers* were younger, showed higher impulsivity (lower inhibition of automatic responses at Stroop test), and a non-significant tendency for being less open[33]. Celli et. al then proved with occipital power results that *Static Viewers* are profiled with a cortical inhibition/internal processing-biased baseline cortical activation, while *Dynamic Viewers* are characterized by a profile biased toward cortical excitation and external processing [32].

These findings compose a cognitive profiling of these two phenotypes of subjects, with *Static Observers* showing a slightly stronger visual working memory, and *Dynamic Observers* a weaker inhibition to salient but irrelevant stimuli[32,33]. Furthermore, this aligns with the perspective that cognitive processing is interactive and broadly distributed across anatomical scales. Looking behavior emerges from cognitive processes that span various scales of space and time (rather than a componential assembly line) as the summation of independent contributions from separate components[205].

EXPERIMENTAL STUDY

5. AIM

Many research lines over the last decades provided new perspectives: the brain can be no more addressed to only as a reflexive sensory-motor analyzer but has to be reconceptualized as a generator of predictive models. These models, optimized during resting-state endogenous activity, act in order to anticipate and interact with the environment more effectively. Characteristics of spontaneous brain activity can predict eye movement dynamics during unconstrained viewing, reflecting an integration of *top-down* and *bottom-up* processing with endogenous dynamics, thus highlighting a novel role of visual exploration as a window into the cognitive-behavioral functional organization of the brain.

Laid this groundwork, the scope of this study was to replicate two previous ones: “Visual exploration dynamics are low-dimensional and driven by intrinsic factors” (Zangrossi et al., 2021) and “One-year-later spontaneous EEG features predict visual exploratory human phenotypes” (Celli et al., 2022). The findings discussed in these papers suggested the intrinsic nature of visual exploration, its low dimensionality, and introduced new characterizations of many subjects' visual explorative style fingerprints, employing eye-tracking and high-density EEG data analysis. Indeed, individuals were shown to be clusterable into two main explorative phenotypes, *Static* and *Dynamic Viewers*, primarily according to fixational and saccadic spatiotemporal features. These features were shown to be manly independent from the *bottom-up* processing of surrounding visual stimulation, trough unconstrained viewing and even more trough resting state eye tracking recordings were stimuli were almost absent at all. The intrinsic delineation of the visual exploration phenotypes previously highlighted indicated the opportunity to investigate brain dynamics trough high density EEG recordings of the neuronal dynamics underlined, proving distinctive fingerprints of the subjects from the two clusters relating to three different EEG metrics, enabling to infer the possibility to accurately profile those subjects based on their endogenous cognitive-behavioral standpoints.

The replication aimed to validate these results on a new sample, exploring the connection between eye movement dynamics, memory recall of visual stimuli, and intrinsic brain dynamics measured through the simultaneously eye-tracking and EEG recording. In particular, we aimed to strengthen and generalize the findings of the previous studies on a wider sample, with contemporary recordings, and collecting data to delve further in the characterization of the two visual explorative phenotypes.

In this framework, the specific objectives were:

- To replicate the previous results highlighting a low-dimensionality of oculomotor dynamics and the relative independence of these PCs from saliency and semantics of visual stimulation, being driven mainly by intrinsic features.
- To reproduce the profiling of subjects' explorative style.
- To evaluate the relationship between oculomotor phenotypes and resting-state brain functioning through hdEEG recordings.

Additionally, the study aimed to examine the relationship between eye movements and brain activity, and to identify distinct patterns in eye tracking and hdEEG data for potential clinical applications.

6. EXPERIMENTAL SETTINGS

6.1. Selection of the subjects: inclusion and exclusion criteria

Healthy participants (n=64 satisfying inclusion criteria; 31 male and 33 female) have been recruited among students (age range: 18 - 35; mean = 23,57, SD = 2,901) of the University of Padua (years of education: mean = 16,93, SD = 1,751) to ensure consistency with Zangrossi et al. (2021)[33]. All of them were Italian except for a girl from Kirghizstan (who didn't undergo cognitive neuropsychological test: most of them are spoken language-based), had normal or corrected-to-normal vision (n = 31 had vision defects and wore glasses; n = 25 suffering from myopia and/or n = 12 of astigmatism), 53 of them right-handed.

The project was funded by a BIAL foundation grant, so they have been compensated 20 euros for the participation; moreover, the data collection for this experiment is part of a larger project funded by that grant, and the thesis focuses only on a subset of the collected data (resting state and unconstrained free-viewing data, see further at Recording Phases, paragraph 6.4.4). The use of human subjects was previously approved by the Ethical Committee of the University of Padova.

All participants signed an informed consent form and completed an anamnestic questionnaire in order to confirm the absence of absolute exclusion criteria, before the experimental session. The absolute exclusion criteria were as follows:

- The presence of any moderate and/or severe chronic (e.g., epilepsy, neurodegenerative disorders, psychiatric conditions, brain tumor) or acute (e.g., recent traumatic brain injury, stroke) neurological condition;
- The presence of any moderate and/or severe ophthalmic disease (e.g., glaucoma, color blindness);
- The assumption of any neuroleptic medication (e.g. antipsychotic), anxiolytic, or any other drug that could affect CNS due to primary pharmacodynamic mechanisms or side effects, including both depressants and stimulants;
- The presence of any dermatologic condition of the scalp (e.g. dermatitis, psoriasis) could interfere with recording or cause pain or discomfort.

Clinically, 11 participants reported suffering from headaches and 4 from migraines. Four of them experienced head trauma in their life, and 6 underwent a prior clinical EEG recording. Consistent with the exclusion criteria, no subject reported previous blackouts, seizures, strokes, brain surgeries, or brain tumors.

Furthermore, participants were instructed to avoid consuming coffee for at least an hour and a half prior to the session (although 7 of them reported the assumption within that amount of time) and to ensure they had an appropriate amount of sleep the night before, defined as at least 6 to 8 hours (mean = 7,33 , SD = 1,234). No face makeup was allowed, nor recently applied hair dye.

6.2. Eye-Tracker: machine, calibration, validation, data collection

Eye-movements data have been acquired by means of a state-of-the-art eye-tracking system (Eyelink 1000 plus desktop mount, SR Research) at a sampling rate ranging from 1000 to 2000 Hz (frames per second)[206].

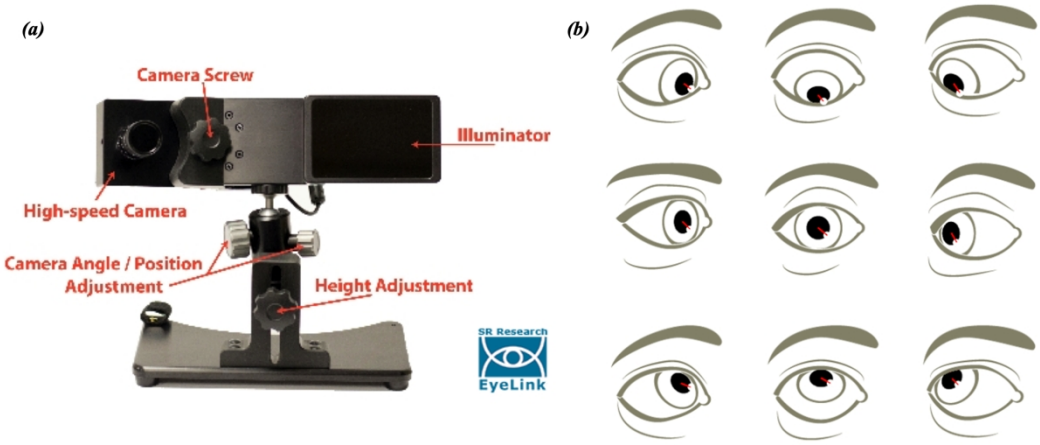


***Figure 25**: **Eye tracker machinery: its structure and functioning**. **(a)** Parts of the EyeLink 1000 Plus Desktop Mount[207]. **(b)** The relative difference in location of the pupil center (red lines indicating the distance between pupil center and corneal reflection center) and corneal reflection (white dots) allows for deduction of the gaze direction[208].*

The tool employs a single high-speed camera capturing up to 2000 images of both eyes per second. The other primary component of an eye tracker is the infrared (IR) emitters (illuminator)[206]. The IR light source ensures accurate measurement of gaze direction by clearly delineating the pupil and detecting reflections from the cornea. The eye tracker's functionality relies on tracking the positions of the pupil center and the corneal reflection to determine eye position and head orientation[206]. The IR

source is aimed at the cornea, and the camera captures the corneal reflections. EyeLink systems determine the participant's gaze location on the screen within 3 milliseconds of capturing the eye image, utilizing image processing algorithms to identify key points: the pupil center and the corneal reflection center[206].

Participants have been sitting on a chair in front of a PC screen with their head stabilized with the using of a chinrest, inside a Faraday cage. This settle was adopted in order to favor the ease and comfort of participants, isolate them from as many sensorial stimuli as possible (light and sounds mostly) and setting them free from any kinds of external constrictions. The images presented were subtend 27.1° × 20.5° (width × height) degrees of visual angle on a screen subtending 31.6° × 23.9°.

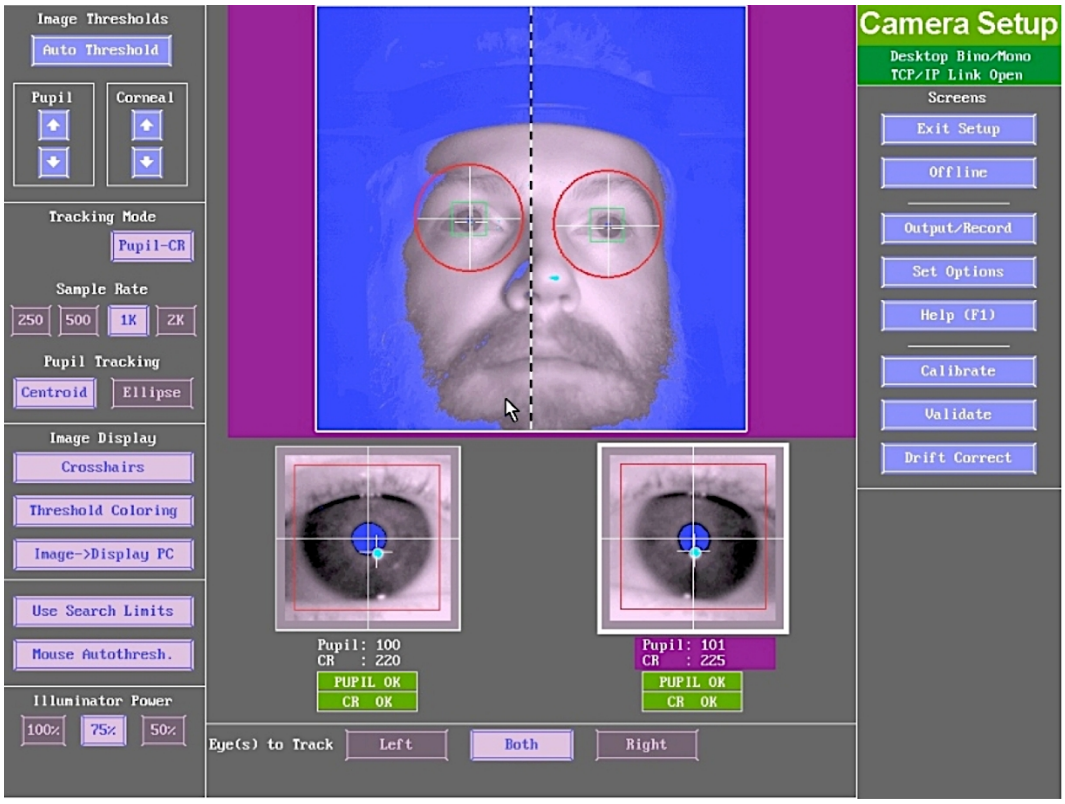


***Figure 26**: Camera setup screen desktop mount, binocular recording*[207].

Prior to the data acquisition, participants were asked to perform series of fixations in order to acquire data for the calibration and validation procedures, aimed at improving tracking accuracy. The quality of calibration is crucial in determining the reliability of the dataset, acting as a first-level quality check; values in the calibration phase are then considered when computing data. In fact, calibration affects the accuracy of gaze calculation, and to be performed at its finest, have to be

selected optimal focus and optimal thresholds for pupil and corneal reflections, for both eyes when accomplishing a binocular recording (see Figure 27, below).

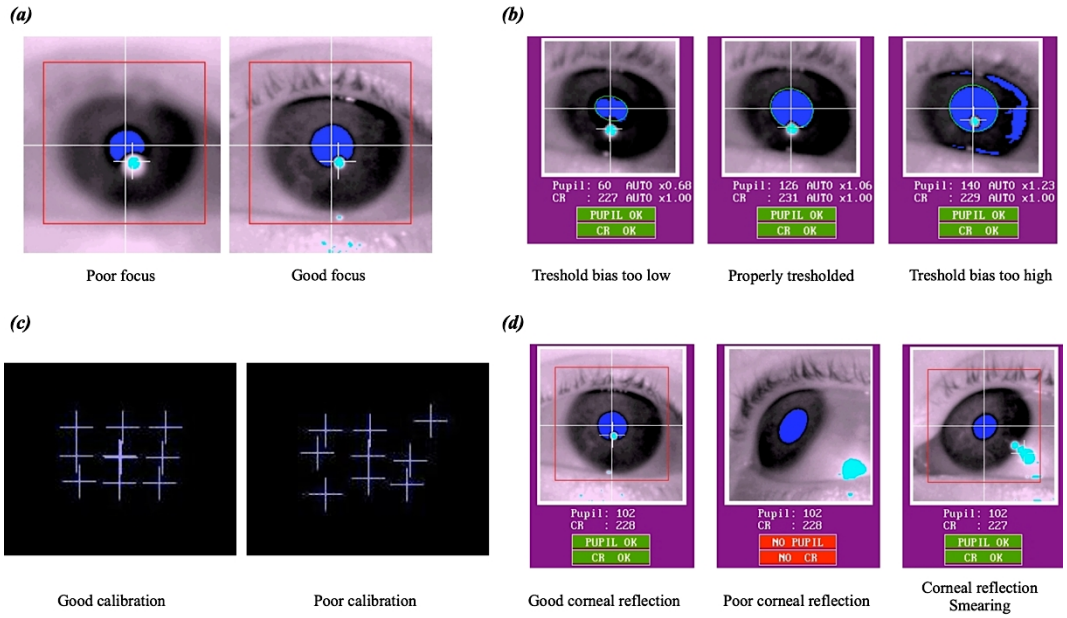


***Figure 27**: **Modifiable parameters and calibration.** **(a)** Focusing the desktop mount camera. **(b)** Pupil and Corneal reflection thresholds and bias values. **(c)** Calibration grid. **(d)** Corneal reflection*[207].

6.3. EEG recording: machine, data collection

EEG activity has been recorded with the PNC's high-density EEG system (hdEEG) consisting of a 256-channel Hydrocel Geodesic Sensor Net[209], the high impedance amplifier Net Amp 400 and the Net Station 4.3 (Electrical Geodesics Inc.).

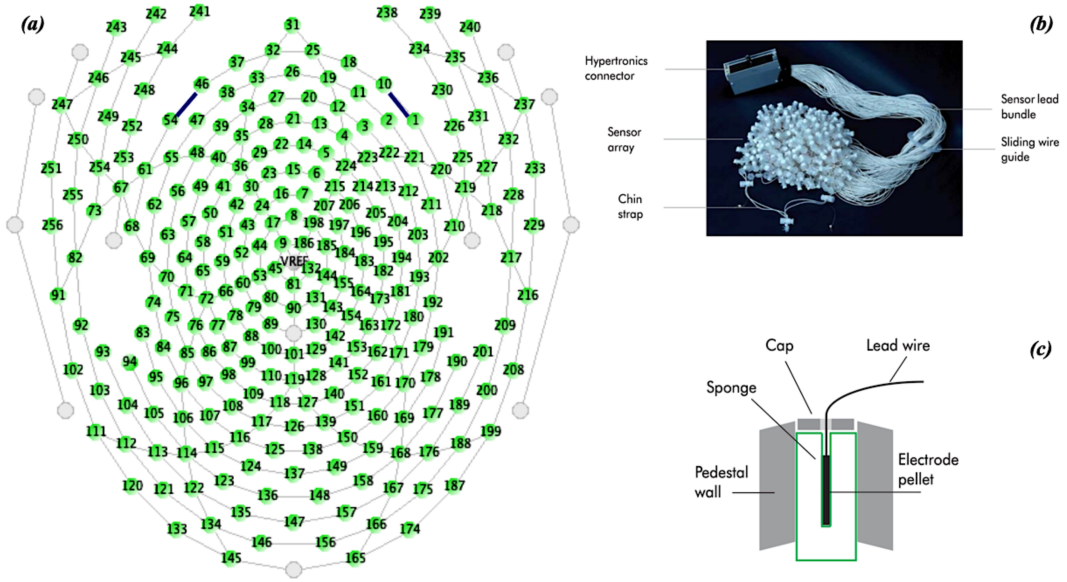


***Figure 28**: **256-channel Hydrocel Geodesic Sensor Net**. **(a)** Net sizing and sensor layout. **(b)** 256-channel machinery components **(c)** Sensor cut-away view*[210].

Prior to every testing phase, impedances were measured and adjusted to be kept below 50 kΩ. All electrodes were referenced online to the electrode placed over the vertex (Cz in the 10/20 international system) . EEG data have been then digitized with a sampling rate of 500 Hz. The recording took place in a sound/electric-shielded Faraday recording cage in order to reduce electromagnetic noise and stimulus interaction with subject brain activity[212].

6.4. Recording setting and phases

Each participant was received at VIMM (Veneto Institute of Molecular Medicine, Padova, Italy) division PNC (Padova Neuroscience Center) and escorted to the hdEEG facility room.

6.4.1. EEG setup

Upon arrival, head circumference was measured to any participant in order to select the appropriate size of the hdEEG cap; once chosen, the latter was submerged for 10 minutes in an electrolytic water solution containing potassium chloride, KCl, (in order to amplify conductance of the electrodes, any of them provided of a little sponge, then soaked in the electrolytic solution) and shampoo. HydroCel Saline KCl electrolyte solution was made according to EGI instructions.

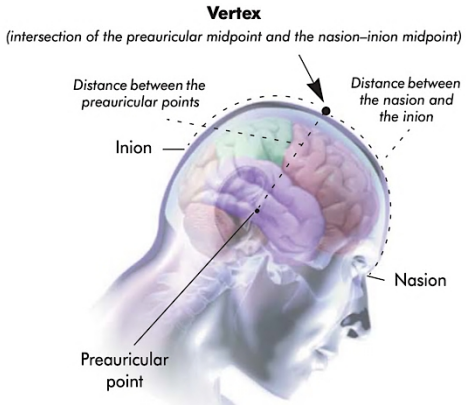


Figure 29: *Skull landmarks for EEG positioning*[210].

While waiting for the preparation time to expire, each subject signed an informed consent form, completed an anamnestic questionnaire, filled out a reimbursement form, and had their ID card registered. Subsequently, each participant underwent another head measurement, this time to determine the intersection between a

sagittal plane fronto-occipital diameter (*nasion-inion*) and the coronal diameter between the *preauricular points* (as seen in Figure 29). That point served as a landmark to locate Cz (*vertex*) during the positioning of the hdEEG cap. Finally, we ensured that all the electrodes adhered to the scalp skin by removing any interposed hair.

The participant was then led into the Faraday recording cage, and the hdEEG was connected to the Net amplifier. Subsequently, the impedance of each electrode was assessed and verified utilizing a software on the host PC outside the cage; additional electrolytic solution was applied where needed to maintain impedances below the 50 kΩ threshold. By wetting the sponge placed between the electrode and the scalp skin, it was possible to modify the conductance to cope with that treshold, selected in order the maximize the quality of the recording.

From the host PC, we, the examiners, could evaluate the signal prior to recording and identify any issues related to potential noise, such as movement and movement-related artifacts from body or facial muscles (electromyogenic influences). Consequently, we could instruct the participant to prevent these solvable artifacts from affecting the recording. We could also address positioning problems, including those affecting eye tracking settings, or solve eventual excessive tension (due to incorrect positioning) in the cables connecting the cap to the amplifier, which could induce wide oscillations, infra-slow activity, that were later cleaned up in the EEG data pre-processing phase if not solvable immediately. Furthermore, we could detect the presence of sweat, which, due to its electrolytic properties, could alter the characteristics of the conducted electric signal.

6.4.2. Eye tracker setup

Positioned their head on the chinrest, any participant had to undergo calibration and validation procedures of the eye tracking system, due to contain the error of the recording under 1,00° for both eyes.

First of all, had to be adjusted from the host PC screen pupil and corneal reflection (CR) detection thresholds; then multiple other options could possibly be customized such as tracking mode, sample rate, threshold coloring, aligning eye window, illuminator power etc. Some patients had to wear glasses for optimal acuity: this

sometimes interfered with the detection of a stable corneal reflection, particularly when the lenses had a thick anti-reflection coating or were progressive lenses. Nonetheless, glasses were preferred over contact lenses because the machine could not accurately determine the position of the corneal reflection with contact lenses, which lie directly on the eyeball, unlike the glass lenses that are positioned at a distance from the cornea. The recording was binocular at all times, except for sporadic cases where the characteristics of the participant's eyeglasses made it impossible to capture both eyes simultaneously.

The eye-tracker requires information on the participants' points of fixation on the display, calibration is the necessary preliminary step that allows to compute the correspondence between the pupil position in the camera image and gaze position on the Display PC Screen. We progressively one by one displayed 13 targets at fixed locations, and the participant had to fixate them; we manually approved the pupil-CR position for each dot when satisficed by the position and then the gaze positions were computed. Graphically, the result was hopefully a regular square shape, that meant the pursuit correspondence between targets on the screen and gaze position was accurately acquired: the eventual level of discrepancy from that shape would underlie the severity of the poor calibration occurring.

After completing this, subjects were once again asked to fixate at the proper moment, to the dots displayed, this time in order to validate the calibration: another fixation, with an error of less than 1.00° for both eyes, confirmed the previously established correspondence between the pupil position in the camera image and the gaze position on the display. Once validation was confirmed, participants were instructed to maintain steady their position until the end of the first phase, to preserve all the procedures realized until that moment.

Subsequently to the end of any recording phase, the process involving EEG and eye-tracker setup had to be repeated. This allowed the subject to relax for a few minutes but especially it served to maximize recording quality for subsequent session.

6.4.3. Images presented

The stimuli proposed to the participants were n=90 images taken from the Places365 dataset, a scenes dataset designed to train artificial systems for image recognition, and selected among those used in a previous paper (Zangrossi et al., 2021)[33,213]. The dataset's images were organized into three hierarchical levels. At Level 1, the most general, images were classified into three categories: indoor, outdoor man-made, and outdoor natural. In Level 2, each Level 1 category was further divided into four to six subcategories. For example, the *"indoor"* category at Level 1 included subcategories such as *"shopping and dining"* and *"home or hotel"* at Level 2. Finally, Level 3 comprised 365 specific categories that described the exact type of scene, such as art gallery, bakery shop, etc[213].

In the previous research, the initial selection of 185 Level 1 images was based on size. Then the images selection was refined through an overlap-based process, superimposing saliency and semantic maps[33]. An additional selection process was conducted differentially to the previous pool in order to establish the database for the present study: 90 level 1 images were chosen from the previous study pool, based on the variance observed among participants explorative dynamics. Each one of the 185 images was treated as a distinct feature, with selection criteria focusing on those exhibiting the lowest similarity and highest variance compared to subjects' fixations and saccades. This approach aimed at facilitate the emergence of *top-down* spontaneous explorative dynamics in the second experiment while minimizing the influence of stimuli relevance driven *bottom-up* processes. Given the absence of goal-driven tasks in the two phases (REST1 and FREE) considered by this study, decisions regarding the saliency and semantics of the images made them have a comparatively lesser impact on shaping the explorative style, thereby enabling the study of endogenous spontaneous bioprint.

6.4.4. Recording Phases

Once all set and done, we started the session, articulated in different phases:

1. **REST1** (*Resting-state 1):* hdEEG and eye-tracking recorded for 5 minutes with eyes open while watching a blank grey screen without stimulation. Unlike the experimental paradigm used in a previous study (Zangrossi et al., 2021)[33] there was no central cross to focus on, allowing the subject to freely explore the screen within its perimeter according to their natural resting-state exploratory behavior. No additional constraints or instructions were provided.

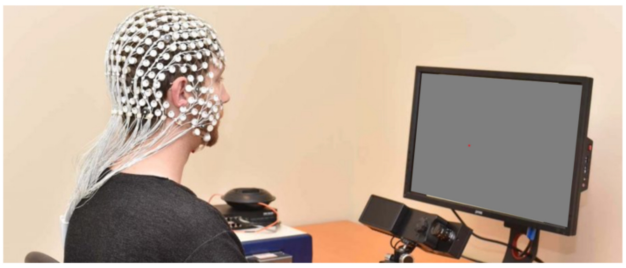


Figure 30: Resting state setup*: subjects were asked to look at a grey screen for 5 minutes, while relaxing and not focusing on particular thoughts. The assessment aims at indagate a disengaged cognitive state.*

2. **FREE (***Free-viewing)*: participants were asked to look at n=90 real-world scenes for 5000 ms each, with an inter-trial interval (ITI) of 1500ms, for a total of 10 minutes while hdEEG and eye-tracking data were recorded. In contrast to the setting of the previous experiment[33], each trial automatically followed the previous one after the ITI period, eliminating the need for participants to manually advance to the next trial by pressing the spacebar.

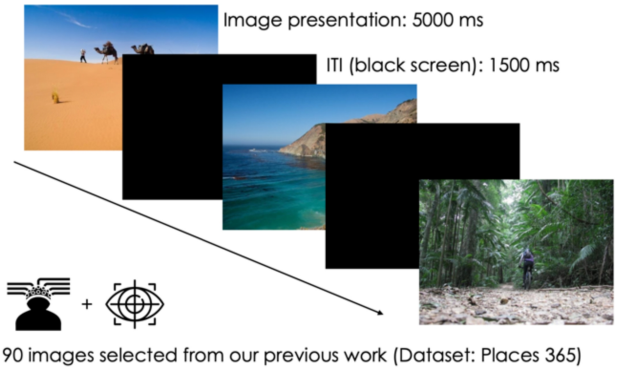


Figure 31: Free-viewing setup*: subjects were asked to look at 90 real-word scenes in sequence, each followed by an ITI. The assessment aims at indagate the unconstrained naturalistic visual explorative behavior.*

3. **FORC** (*Forced-viewing*): participants were asked to fixate specific elements of the scenes (whose locations and movements reflected the

fixations previously recorded during free-viewing on each trial) while hdEEG and eye tracking data were collected. These portions of the scenes were highlighted by a sharp circle while the rest of the image remained blurred. The duration of this phase was variable depending on the amount of the cumulative fixations time per trial in the previous phase.

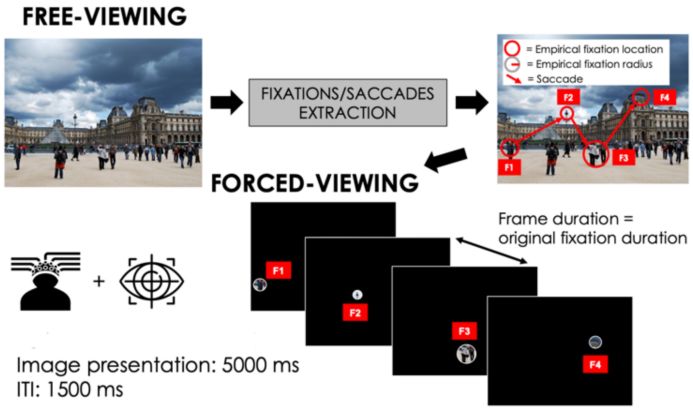


Figure 32: Forced-viewing setup*: subjects were asked to look at 90 images where a portion was on focus, according to their previous fixation pattern in the free-viewing phase. The assessment aims at indagate a constrained visual explorative behavior*

4. **REST2** (*Resting-state 2)*: participants were presented with the same grey screen adopted in the first phase (same setting of the REST1).

For the purpose of the present study, only phases 1 (REST1) and 2 (FREE) data have been considered.

Exclusion criteria concerning the eye-tracking recording data comprised the following: individuals with excessive data loss, defined as items with more than 50% missing data and subjects with more than 50% of items with more than 50% missing data[113] (n=1). Further, another subject was excluded due to a mild cognitive deficit, which appeared clear during the recording and was then stated by the participant herself (n=1). Regarding EEG data, this latter subject was excluded, but apart from this, all other data were eligible for the study's aims. Problems and artifacts that could not be resolved on-site were addressed during data pre-processing.

Overall 62 out 64 participant recording data have been considered eligible to be included in the final sample for data processing and statistical analysis.

6.5. Cognitive and behavioral tests

Subsequent to Eye-tracking and hdEEG recording, participants were asked to undergo a battery of neuropsychological tests aimed at evaluating a range of cognitive domains. Models computing tests scores and PCs have been computed in order to further characterize subjects' traits, allowing correlation with some of the behavioral dynamics indirectly assessed by the experiment, thus strengthen and broadening profiling features.

The following tests can be administered to patients with neurological or psychiatric conditions resulting in cognitive-behavioral impairments or, as we did in this experimental design (with appropriate adjustments and considerations in administration and scoring, such as considering only delayed recall of Rey−Osterrieth Complex Figure) to healthy participants:

1. Barigazzi's prose memory test: neuropsychological assessment tool designed to evaluate verbal memory and reproduction of verbal information, providing insights into memory function and potential memory impairments [214]. Normally, it involves participants listening to a prose passage and then recalling it, both immediately and after a delay[214]. In our assessment, with a sample of healthy subjects, only the delayed recall was administered and errors regarding principal events, secondary events and details were evaluated.

2. Rey−Osterrieth Complex Figure (ROCF): neuropsychological test used to evaluate visuospatial abilities, memory, attention, planning, and executive functions. It involves the subject copying a complex geometric figure, both immediately (copy phase) and after a delay (recall phase)[193]. Standard version valuation is stratified as follows: A precise copy made quickly (<3) suggests normal processing, while a correct but slow copy may indicate perception or execution issues. A slow, poor copy can suggest mental disability or dementia[193,194]. Here considering only health participants, only recall phase have been considered[194], 10 minutes after the copy phase, consistently with Zangrossi et. al. [31]

3. Forward and Backwards Digit Span: neuropsychological test aimed at measure working memory and attention, assessing the capacity to temporarily store and manipulate information[195]. The examiner recites aloud

a numerical sequence at a rate of one digit per second, and candidates have to repeat the sequences; up to two attempts are allowed for sequences of each length. Subsequently, candidates must repeat the digit sequences in reverse order, again with up to two attempts permitted for each length[195]. Results refer to Verbal IQ and the Full Scale IQ, referring to all Wechsler's intelligence scales, both Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Intelligence Scale for Children (WISC), together with the Wechsler Memory Scale[215]. Weinberg et al. in 1972 discovered that patients with right hemisphere damage had difficulty with the backward digit span task but not the forward task. They proposed that the backward task involves mentally scanning a visual image (visuospatial processing) of the digit sequence, a process impaired by visual neglect, typically seen as left-sided neglect in these patients[216]

4. Forward and Backwards Corsi's test: visuospatial memory span test that assesses how much visuospatial information can be held in recent or working memory[217]. Using a board with nine numbered cubes (arranged asymmetrically), the examiner touches the cubes in increasing sequence lengths, which the subject must then replicate[217]. The test score depends on the longest sequence correctly reproduced, indicating the subject's memory span. Studies show no gender differences in adults and the elderly, but male university students often perform better in spatial tasks[217].

5. Stroop Color-Word Test: neuropsychological assessment that measures primarily the ability to inhibit cognitive interference, where processing one feature of a stimulus interferes with another[195,199].It evaluates executive functions like cognitive control, attention, and processing speed, and is also a metric for impulsivity[195,199]. The shortened version is quicker to administer, making it practical for clinical and experimental settings. Success involves inhibiting automatic reading responses[199]. This test is widely used for diagnosing ADHD, schizophrenia and assessing brain injury patient[218].

METHODS AND EXPERIMENTAL RESULTS

7. EYE MOVEMENTS'DATA

In this phase of data analysis we considered recordings' data collected during the FREE phase, when subjects were asked to look freely at 90 real-world scenes, exposed for 5000 ms each, with an inter-trial interval (ITI) of 1500 ms. During these total 10 minutes, hdEEG and eye-tracking data were recorded.

Gaze movements data are here considered and analyzed in order to reproduce on a different sample, and with a different eye tracker (a state-of-the-art Eyelink 1000 plus, SR Research, eye-tracker) the findings from the previous study by Zangrossi et. al. concerning low dimensionality of eye movements, which appeared to be driven mostly by intrinsic factors, partially independent from *bottom-up* stimuli[31]. These data allowed to profile subjects according to their endogenous visual explorative phenotype features, clustering them consequentially into two distinct groups[31]. The reliability of these findings will be examinated in the following paragraphs, confirming with this replication the generalizability of those results.

7.1. Eye movements features extraction

After completing the recording phases, we began the statistical analysis of the raw eye movement data a with minimal pre-processing, including only gaze samples where both eyes had the highest validity value: a validity code of 0, indicating that the eyes were found and the tracking quality was optimal throughout the whole recording duration. Next, we extracted a comprehensive set of features that encoded the multiple characteristics of eye movements, in order to accurately describe visual behaviors: a set of 49 features was extracted for each subject (see below, Table I) for capturing the spatiotemporal dynamics of eye movements and fixations, rather than their spatial distribution.

Three main sources of information were considered:

- Fixations: identified employing a velocity-based threshold algorithm (detection threshold lambda = 15), which is the most popular, adequate and robust algorithm design for saccade detection[33,219]. Although the lack of a *gold standard* saccade recognition method, this algorithm is utilized by the

majority of studies whose dataset is based on static infrared eye-tracking systems, as in the case of this experimental assessment[219]. Trough previous chapters, the importance of *saccades-fixations strategy* has been widely exposed from a mere oculomotor perspective; moreover, from a cognitive standpoint, fixations represent information processing, and their duration is linked to the depth of the cognitive engagement of the subject performing them[220].

- Pupil diameter: as seen in paragraph 2.4.1, non-luminance-mediated (as in this experimental assessment, where the recordings have been conducted in an almost dark room) changes in pupil diameter correlate with cortical (especially with ACC and PCC) and subcortical neuronal activity (LC, for example). Those are involved in a broad variety of cognitive processes such as arousal, attention[92], cognitive load and effort [221], salience and decision biases[89–91].

- Gaze steps: computed from the raw gaze data as the Euclidean pixel distance between two consecutive gaze positions (avoiding distinctions between saccades and microsaccades, both thought to be controlled by the same neuronal mechanisms)[205,222].

Features	Code	Description
N of steps	n_jumps	Number of gaze steps
Length of Steps (M)	dist_mean	Mean of gaze steps length
Length of Steps (SD)	dist_sd	Standard deviation of the gaze steps length
Length of Steps (MAX)	dist_max	Maximum gaze steps length
Length of Steps 25% (M)	dist_mean25_1	Mean of the gaze steps length in the first quarter visual exploration
Length of Steps 25% (SD)	dist_sd25_1	Standard deviation of gaze steps length in the first quarter visual exploration
Length of Steps 25% (MAX)	dist_max25_1	Maximum gaze steps length in the first quarter visual exploration
Length of Steps 25-50% (M)	dist_mean25_2	Mean of the gaze steps length in the second quarter visual exploration
Length of Steps 25-50% (SD)	dist_sd25_2	Standard deviation of gaze steps length in the second quarter visual exploration
Length of Steps 25-50% (MAX)	dist_max25_2	Maximum gaze steps length in the second quarter visual exploration
Length of Steps 50-75% (M)	dist_mean25_3	Mean of the gaze steps length in the third quarter visual exploration
Length of Steps 50-75% (SD)	dist_sd25_3	Standard deviation of gaze steps length in the third quarter visual exploration
Length of Steps 50-75% (MAX)	dist_max25_3	Maximum gaze steps length in the third quarter visual exploration
Length of Steps 75-100% (M)	dist_mean25_4	Maximum gaze steps length in the last quarter visual exploration
Length of Steps 75-100% (SD)	dist_sd25_4	Standard deviation of gaze steps length in the last quarter visual exploration
Length of Steps 75-100% (MAX)	dist_max25_4	Maximum gaze steps length in the last quarter of visual

		exploration
N of Fixations	fix_n	Number of fixations
Fixation Rate (per second)	fix_rate	Number of fixations per second on average
Total Fixation Duration	fix_time_tot	Global time spent in fixations
Fixation Duration (M)	fix_mean	Mean fixations' duration (i.e., mean interval between consecutive saccades)
Fixation Duration (SD)	fix_sd	Standard deviation of fixations' duration
Fixation Duration (MIN)	fix_min	Minimum fixation duration
Fixation Duration (MAX)	fix_max	Maximum fixation duration
Fixation Duration 25% (M)	fix_mean25_1	Mean duration of the first 25% of fixations timeseries
Fixation Duration 25% (SD)	fix_sd25_1	Standard deviation of fixations duration in the first quarter visual exploration
Fixation Duration 25% (MIN)	fix_min25_1	Minimum fixation duration in the first quarter visual exploration
Fixation Duration 25% (MAX)	fix_max25_1	Maximum fixation duration in the first quarter visual exploration
Fixation Duration 25-50% (M)	fix_mean25_2	Mean duration of the fixations from 25% to 50%
Fixation Duration 25-50% (SD)	fix_sd25_2	Standard deviation of fixations duration in the second quarter of visual exploration
Fixation Duration 25-50% (MIN)	fix_min25_2	Minimum fixation duration in the second quarter visual exploration
Fixation Duration 25-50% (MAX)	fix_max25_2	Maximum fixation duration in the second quarter visual exploration
Fixation Duration 50-75% (M)	fix_mean25_3	Mean fixations duration in the third quarter of visual exploration
Fixation Duration 50-75% (SD)	fix_sd25_3	Standard deviation of fixations duration in the third quarter visual exploration
Fixation Duration 50-75% (MIN)	fix_min25_3	Minimum fixation duration in the third quarter visual exploration
Fixation Duration 50-75%(MAX)	fix_max25_3	Maximum fixation duration in the third quarter visual exploration
Fixation Duration 75-100%(M)	fix_mean25_4	Mean fixation duration in the last quarter of the visual exploration
Fixation Duration 75-100% (SD)	fix_sd25_4	Standard deviation of fixations duration in the last quarter visual exploration
Fixation Duration 75-100% (MIN)	fix_min25_4	Minimum fixation duration in the last quarter of visual exploration
Fixation Duration 75-100% (MAX)	fix_max25_4	Maximum fixation duration in the last quarter visual exploration
Pupil Diameter Left (M)	pd_sx_mean	Mean of left pupil diameter (in mm)
Pupil Diameter Left (SD)	pd_sx_sd	Standard deviation of left pupil diameter (in mm)
Pupil Diameter Left (MIN)	pd_sx_min	Minimum of left pupil diameter (in mm)
Pupil Diameter Left (MAX)	pd_sx_max	Maximum of left pupil diameter (in mm)
Pupil Diameter Right (M)	pd_dx_mean	Mean of right pupil diameter (in mm)
Pupil Diameter Right (SD)	pd_dx_sd	Standard deviation of right pupil diameter (in mm)
Pupil Diameter Right (MIN)	pd_dx_min	Minimum of right pupil diameter (in mm)
Pupil Diameter Right (MAX)	pd_dx_max	Maximum of right pupil diameter (in mm)
N of flips on X-axis	flipX_n	Number of flips (i.e., change of direction) on X-axis
N of flips on Y-axis	flipY_n	Number of flips (i.e., change of direction) on Y-axis

Table I: Eye movements' features, corresponding statistical analysis code, and description. *Differing from Zangrossi et al*[33]*., exploration time was not considered as a main source of information, reducing the number of features considered from 58 to 49.*

7.2. Eye-movements data reduction

Concerning the unconstrained free-viewing (FREE) dataset, a features correlation matrix (62 participants x 49 features) was obtained, and then a principal components analysis (PCA) was ran in order to reduce it to some fewer meaningful components.

As already pointed out in paragraph 3.3.1, PCA is a statistical technique used to simplify a dataset by reducing its dimensions, while retaining most of the original variability in the dataset[119]. It does this by transforming the original variables into a new set of uncorrelated variables, referred to as principal components (PCs), operating this way a *data compression* but also a *noise reduction*, by focusing on the components accounting for the highest variance[223]. Moreover, it allows to simplify data dimensionality to two or three dimensions for easier *visualization* and *interpretation*[223]. Finally, often PCA is employed as a pre-processing step in machine learning to improve model performance and reduce computational cost burden[33,224].

Once operated a standardization of the dataset (especially being the variables on different scales) features are computed on a covariance matrix, in order to define how those variables are related to each other[223]. Next, the *eigenvalues* are calculated, which are scalar that computationally, for a given square matrix, result in the same effect as applying the matrix transformation to a specific vector, called the *eigenvector*, when multiplied by it[119,225]. These values are indexes that serve as indicators of how effectively a component summarizes the data, determining the magnitude of a new feature "space": the amount of variance each principal component captures[223]. *Eigenvectors* (in other words, PCs) on the other hand, are non-zero vectors that, when the matrix is applied to them, change only in magnitude (and occasionally in direction if the *eigenvalue* is negative) but often not in direction [119,225]. Indeed, PCA is understandable as an adaptive data analysis technique that involves solving an *eigenvalue/eigenvector problem* to reduce the dimensionality of the data[112].

In addition to the raw standardized data loadings (the scaled and mean-centered full set of features extracted from the gaze data acquired during the exploration of

images[33]), PCA loadings have been also "rotated" by applying an *oblique rotation (Promax)*. This consists of a statistical technique employed in factor analysis to further explore the underlying relationships between variables[33,226,227] (both loadings are reported by the data in Table II below). This technique enables factors to exhibit correlations with each other, facilitating interpretation and incorporating factor correlations[212,213]. By allowing those correlation, it often provides a more accurate and meaningful representation of the underlying structure of the data[212,213].

Features	Raw PCA loadings				Rotated PCA loadings		
	PC1	PC2	PC3		PC1	PC2	PC3
n_jumps	0.221	0.089	-0.09		0.246	0.026	-0.06
dist_mean	0.115	-0.237	0.006		0.026	-0.258	-0.069
dist_sd	0.092	-0.287	0.091		-0.022	-0.315	-0.003
dist_max	0.029	-0.148	0.098		-0.034	-0.167	0.047
dist_mean25_1	0.116	-0.207	0.06		0.031	-0.243	-0.008
dist_sd25_1	0.096	-0.248	0.064		-0.003	-0.274	-0.017
dist_max25_1	0.078	-0.191	-0.007		0.008	-0.2	-0.067
dist_mean25_2	0.113	-0.23	0.03		0.023	-0.255	-0.043
dist_sd25_2	0.092	-0.255	0.086		-0.01	-0.285	0.002
dist_max25_2	0.086	-0.136	0.049		0.028	-0.165	0.004
dist_mean25_3	0.109	-0.235	-0.019		0.023	-0.248	-0.092
dist_sd25_3	0.091	-0.264	0.099		-0.015	-0.295	0.011
dist_max25_3	0.024	-0.176	0.11		-0.05	-0.194	0.051
dist_mean25_4	0.099	-0.227	-0.05		0.02	-0.23	-0.119
dist_sd25_4	0.06	-0.264	0.078		-0.043	-0.28	-0.008
dist_max25_4	0.024	-0.129	0.12		-0.034	-0.154	0.074
fix_n	0.213	0.096	-0.108		0.243	0.039	-0.075
fix_rate	0.213	0.096	-0.108		0.243	0.039	-0.075
fix_time_tot	-0.09	0.066	-0.217		-0.039	0.14	-0.185
fix_mean	-0.243	-0.042	-0.021		-0.239	0.049	-0.031
fix_sd	-0.235	-0.094	-0.001		-0.251	-0.005	-0.028
fix_min	-0.058	0.066	0.012		-0.033	0.077	0.033
fix_max	-0.18	-0.128	-0.015		-0.21	-0.052	-0.053
fix_mean25_1	-0.209	-0.042	-0.033		-0.206	0.04	-0.043
fix_sd25_1	-0.204	-0.044	-0.056		-0.2	0.042	-0.065
fix_min25_1	-0.034	0.099	-0.132		0.016	0.132	-0.095
fix_max25_1	-0.164	-0.039	-0.064		-0.16	0.035	-0.071
fix_mean25_2	-0.233	-0.048	-0.016		-0.232	0.039	-0.029
fix_sd25_2	-0.218	-0.106	0.004		-0.24	-0.023	-0.027
fix_min25_2	-0.032	0.074	-0.015		-0.003	0.082	0.009
fix_max25_2	-0.169	-0.144	0.004		-0.208	-0.075	-0.039
fix_mean25_3	-0.234	-0.043	-0.007		-0.232	0.042	-0.018

fix_sd25_3	-0.217	-0.09	0.002		-0.234	-0.009	-0.024
fix_min25_3	-0.042	0.109	-0.04		0.002	0.123	-0.003
fix_max25_3	-0.183	-0.121	0.016		-0.214	-0.051	-0.021
fix_mean25_4	-0.218	-0.025	-0.024		-0.21	0.057	-0.028
fix_sd25_4	-0.202	-0.066	0.01		-0.212	0.007	-0.009
fix_min25_4	-0.013	0.038	-0.08		0.01	0.057	-0.065
fix_max25_4	-0.17	-0.085	-0.001		-0.188	-0.019	-0.026
pd_sx_mean	0.001	-0.112	-0.384		0.004	-0.016	-0.4
pd_sx_sd	-0.007	-0.121	-0.372		-0.008	-0.024	-0.392
pd_sx_min	-0.028	0.06	-0.166		0.013	0.102	-0.139
pd_sx_max	0.01	-0.101	-0.36		0.013	-0.014	-0.375
pd_dx_mean	0.008	-0.129	-0.377		0.004	-0.036	-0.4
pd_dx_sd	0	-0.145	-0.357		-0.012	-0.051	-0.385
pd_dx_min	-0.062	0.042	-0.06		-0.037	0.073	-0.044
pd_dx_max	0.033	-0.119	-0.238		0.015	-0.066	-0.264
flipX_n	0.199	0.062	-0.144		0.222	0.021	-0.12

Table II: Principal component analysis raw and rotated loadings.

The *eigenvectors* are subsequently arranged in descending order, sorted depending on their corresponding *eigenvalues*[223]. According to the *Keiser rule*[227,228], only components with *eigenvalues* greater than 1 are considered (consistently with Zangrossi et al.) [31]. A value of 1, indeed, implies that the factor carries the same amount of information as a single variable[229], so only factors explaining a wider amount of variability are eligible to be taken into account. The first principal component is the direction that maximizes explanation of the variance in the data, the second principal component is orthogonal to the first and captures the next highest variance, and so on[229]. By selecting the first *n* principal components (PC*n*, with *n* as a number lower in value than the original number of variables), PCA reduces the dimensionality of the data while preserving as much variability as possible[119].

As can be seen in the Scree Plot (a line plot of the principal components in an analysis, the *eigenvalues* of factors[223]) of Figure 33 below, three principal components (PC1, PC2, and PC3, whose relatively explained variance can also be appreciated in figure 34(a), the correlation matrix) have been found to be able to globally explain 60,2% of eye movement dynamics of the 62 observers recruited, who performed the unconstrained free-viewing task.

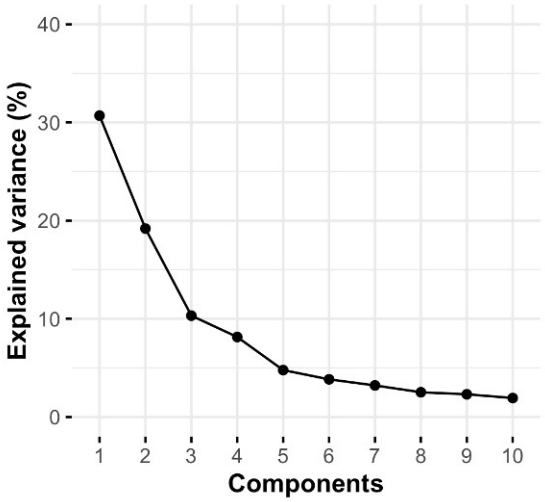


Figure 33: Scree plot showing the variance explained by different PCs*. To be further selected, a component had to account for a percentage of the variance of at least 10%[33]: PC1 (30,7%), PC2 (19,2%) and PC3 (10,2%), satisfying this criteria. Graphically, according to some researchers, the correct number of components is the one appearing prior to the "elbow"[229] on the line pot, as in this case.*

This low dimensionality is extremely consistent with the findings of Zangrossi et al. where a three latent variable model, as well, accounted for the 60% of variance of visual exploratory eye movement dynamics trough the unconstrained free-viewing task underwent by the subjects, as already exposed in 3.3.1.

In particular, as can be seen in the matrix in Figure 34(a) below, in the sample of this replication, the first component (PC1) accounts for 30,7% of variance and is loaded mostly on features describing fixations duration statistics, consistently with the first component of the previous study, which represented the 31,1% of variance and was mainly charged with feature describing time spent during fixations[33]. The second component (PC2), explaining for 19,2% of variance, is essentially loaded on features concerning statistics of gaze step length; differentially the second novel variable in the previous study was mainly charged with exploration time, number of steps and number of flips, thus represented for 16,5% of variance[33]. The third one (PC3), accounts for 10,3% of variance, and is primarily loaded on pupil diameter width statistics features; in the previous study third component explained 12,2% of variance and was charged on gaze steps' length statistics[33] (as is PC2 in this study).

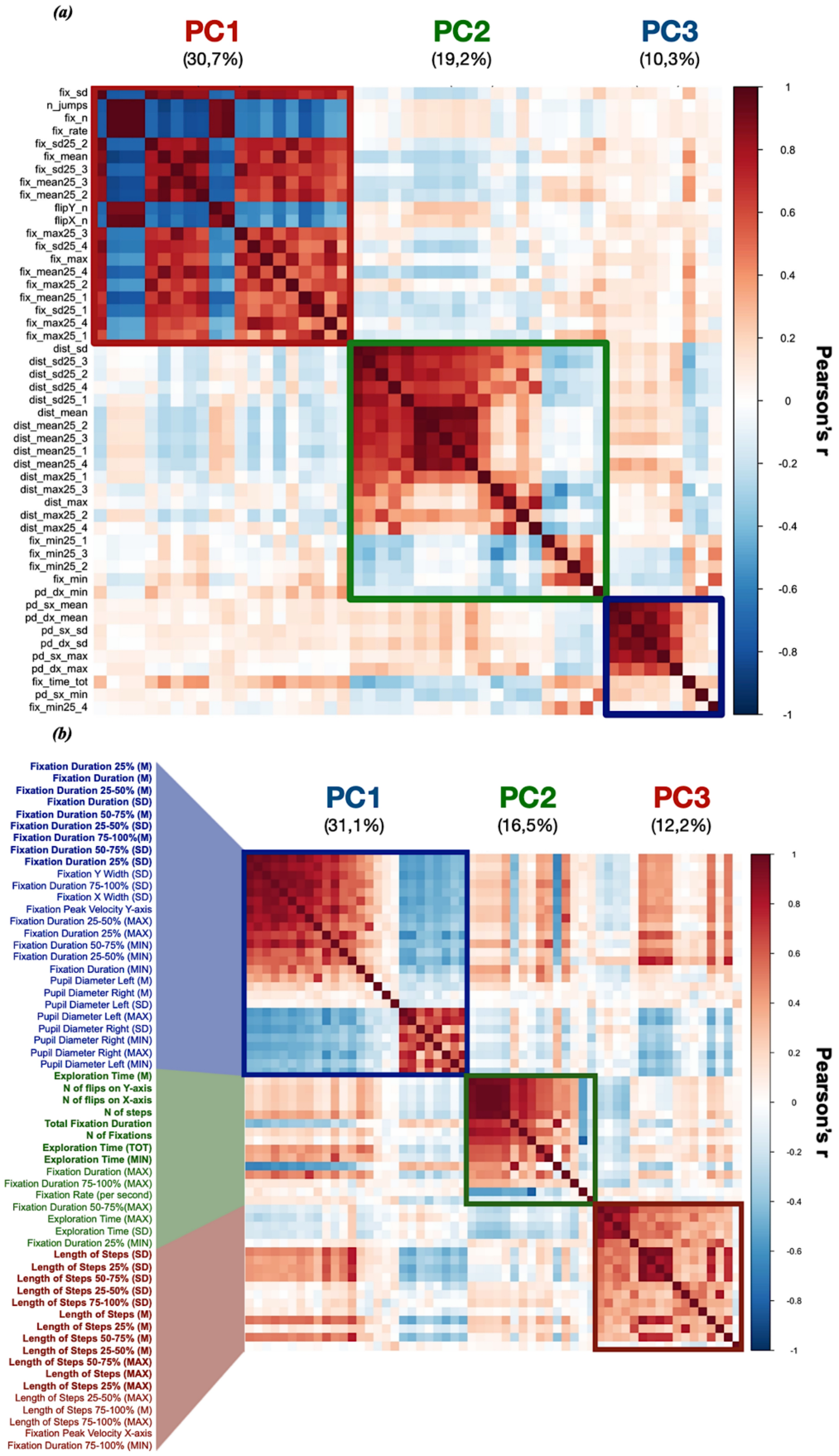
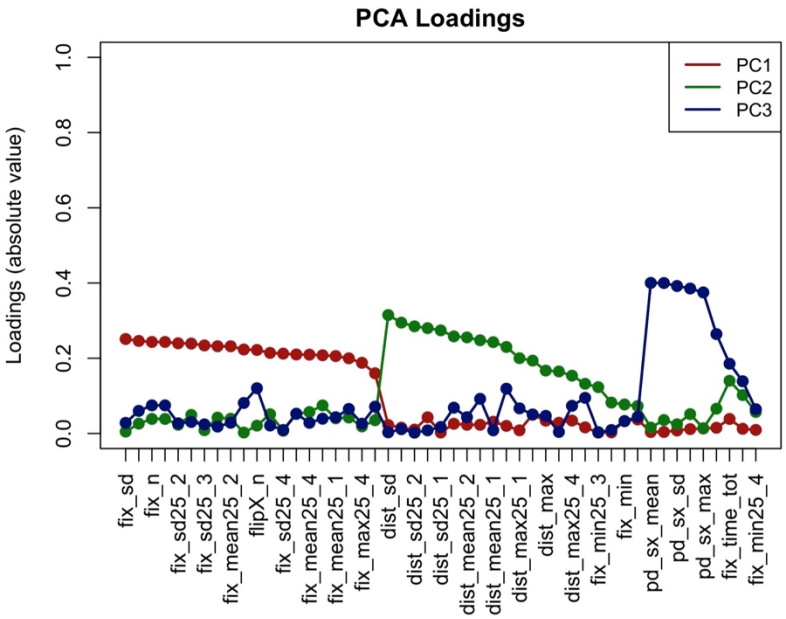


Figure 34: Comparison between Correlation Matrixes from the present study (a) and from Zangrossi et al. (b – already presented as Figure 19 in paragraph 3.3.1) *The matrixes shows correlations (Pearson's r) between features, which are ordered according to their loadings in the first three PCs. The color of Y-axis labels*

indicates the PC with the highest loading for the corresponding feature. The aim of this comparison is to show the striking consistency of the replication study ***(a)*** *with the original* ***(b – already presented as Figure 19 in paragraph 3.3.1)****: both display a low dimensionality of spatiotemporal visual explorative dynamics, a coherent number of novel variables (3), each accounting for a comparable amount of variance. Referring to the present study, PC1 accounts for 30.7% of the variance and is mainly loaded on fixation duration features, similar to the PC1 of the previous study (which explained 31,1% of the variance). PC2 explains 19.2% of the variance, relates to gaze steps' length features, whereas the PC2 of the previous study focused mostly on exploration time features and number of gaze steps and flips (explained 16,5% of the variance). PC3 accounts for 10.3% of the variance, focusing mainly on pupil diameter, while the PC3 of the previous study linked it to gaze steps' length statistics (accounted for 12,2% of variance).*

Specifically, all three components are loaded differentially concerning their features also from a single feature value standpoint (figure 35, below). 34 out of the 49 initial features survived the loading threshold of 0,2 in absolute value (Figure 36, below), suggesting a substantial role for components' definition.



	PC1	PC2	PC3
n_jumps	0.246		
dist_mean		-0.258	
dist_sd		-0.315	
dist_mean25_1		-0.243	
dist_sd25_1		-0.274	
dist_max25_1		-0.2	
dist_mean25_2		-0.255	
dist_sd25_2		-0.285	
dist_mean25_3		-0.248	
dist_sd25_3		-0.295	
dist_mean25_4		-0.23	
dist_sd25_4		-0.28	
fix_n	0.243		
fix_rate	0.243		
fix_mean	-0.239		
fix_sd	-0.251		
fix_max	-0.21		
fix_mean25_1	-0.206		
fix_mean25_2	-0.232		
fix_sd25_2	-0.24		
fix_max25_2	-0.208		
fix_mean25_3	-0.232		
fix_sd25_3	-0.234		
fix_max25_3	-0.214		
fix_mean25_4	-0.21		
fix_sd25_4	-0.212		
pd_sx_mean			-0.4
pd_sx_sd			-0.392
pd_sx_max			-0.375
pd_dx_mean			-0.4
pd_dx_sd			-0.385
pd_dx_max			-0.264
flipX_n	0.222		
flipY_n	0.223		

Figure 35; Figure 36: Features correlation values within first three PCs: line plot and table. (35) *The Line Plot represent absolute loadings value of features loaded on the three major components PC1, PC2 and PC3: here only strong and mild positively correlated feature for each component have been reported. More in detail, the* ***(36)*** *features value table shows positive and negative correlation values, of all the features taken into account, for each component loading,*

In line with the previous experiment of Zangrossi et al. we proved once again, on a different sample and with slightly different (although conceptually identical) experimental design, that a relatively low number of dimensions enables to explain

a great amount of variability concerning of eye movements dynamics (e.g., amplitude, velocity), fixational spatiotemporal properties (e.g., duration, rate), and pupil parameters across numerous subjects and many visual scenes. This part of the replication, accomplishing the results exposed trough paragraphs 7.1 and 7.2, enabled us to speculate once again concerning low dimensionality of eye movements dynamics, supporting the research lines which posit that eye movements and fixations patterns across subjects can be explained with a few components, relatively independent of stimulus content and mostly driven by a visual explorative phenotype which may be endogenous, identitarian and a reflection of spontaneous brain activity, so propelled by intrinsic factors.

7.3. Detection of clusters in visual behavior and their interpretation

A broad dimensionality of exploratory visual behavior would correlate with distinct eye movements dynamics across different subjects or would be more dependent on the images' features that would this way drive different eye movement patterns (or both). On the other hand, as sustained by this study, the low dimensionality (as in this case) of visual explorative dynamics, may stand for the possibility to explain visual behavior of various subjects across different images as a reflection of *top-down* endogenous dynamics, partially independent from *bottom-up* salience and semantics visual stimulation. Consequently, we then investigated whether distinct spatiotemporal visual behaviors could be summarized by the means of two phenotypical groups' characteristics, in order to replicate the results of Zangrossi et al., and reproduce the clustering they identified, splitting the participants' sample between *Static Viewers* and *Dynamic Viewers*[33] (see 3.3.2).

In line with that previous study, a k-means cluster analysis, splitting the sample into two groups ($k=2$), was performed and best separation was obtained along both PC1 and PC2 loadings (see Figure 37, below). K-means clustering method can be employed in order to enable the partitioning of n objects, each having measurements concerning p variables, into k classes[230]; often, as in this case with PCA, it is performed following the application *a priori* of a data reduction techniques[119,230]. The K-means algorithm aiming to split a set of data points into k clusters, each data point is then relocated into the cluster with the closest mean[230]. Therefore, each group is indeed identified by a centroid or mean point[230]. The algorithm initially

creates k partitions and assigns the input points to each partition; then it calculates the centroid of each group. Those processes are subsequently reproduced, constructing new partitions by assigning each input point to the group whose centroid is the closest and recalculating the centroids for the new groups[230]. In this way, finally, it creates the most appropriate separations of the dataset into a number of clusters.

The reliability of the two-cluster solution was evaluated by comparing multiple clustering outcomes, obtained obviously from k-means cluster analysis, but also by different hierarchical clustering algorithms. Several distance metrics and different k values have been employed in order to compare the wider range of possible computational processing and thus elect the most robust clustering solutions. The similarity between those solutions was quantified applying the *Jaccard index* (which, considering two sets of data, measures their similarity/dissimilarity analyzing which members are shared or distinct; it is computed dividing the size of the intersection by the size of the union of two clusters[231]) which indicated that the two-cluster solution (*k=2*), was the most consistent across different methods.

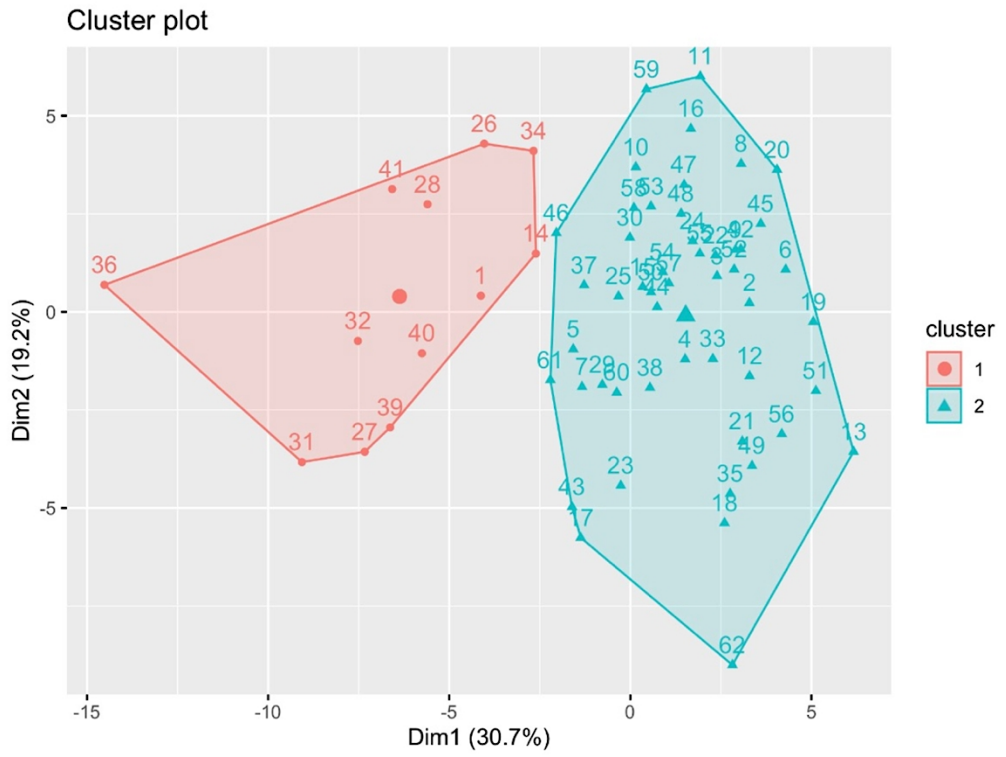


Figure 37 : The cluster plot. *It shows the distribution of the participants between the two groups concerning the best separation obtained, along both PC1 dimensionality (Dim1, 30,7% of variance accounted) and PC2*

(Dim2, 19,2% of variance accounted) loadings. "Cluster 1" describes Static Viewers (n=12) principal components values, "Cluster 2" describes Dynamic Viewers (n=50) principal components values.

In the previous study by Zangrossi et. al, *Static Viewers* (subjects with high PC1 values) showed longer fixation time, longer spontaneous viewing time, smaller mean pupil diameter and a lower fixation rate (less frequent but longer fixations)[33]; they were characterized by an average of higher amplitude and more numerous gaze steps, just as more gaze and a distribution of gaze steps more similar to a power law (see 3.3.3)[33]. On the other hand, *Dynamic Viewers* (subjects with low PC1 values) showed opposite features such as more numerous fixations, performed at a higher rate, wider mean pupil diameter and a distribution of gaze steps less similar to a power law[33].

In line with Zangrossi et al.'s findings, the sample can once again be divided into those two groups of observers, demonstrating through our experiment the possibility of profiling subjects according to their visual explorative behavior. On the other hand, in this experimental assessment, observers with high PC1 scores (principal component mainly loaded on features describing fixations' time and dynamics, consistent with PC1 from the previous study, see paragraph 3.3) are now identified as *Dynamic Viewers*. This occurs because, unlike the previous study, some features that were positively correlated in the previous assessment are here correlated with PC1, but expressing a negative value in this assessment, making subjects with high values *Dynamic explorers*, contrary to what took place in the other study. In the computational assessment of PCA, the algorithm assign a numerical value that, regardless of its positive or negative sign, describes the correlation between the feature and the *eigenvector*. In other words, while the positive/negative sign of a number is not important, it is the absolute value (especially if greater than 0.2) and the type of feature considered that are crucial in describing the correlation. For simplicity, hereby we refer to "positively" and "negatively" correlated referred to the sign of the value describing the strength of the correlation of that feature concerning the PC considered, and not to a statistical significance of the bond of between the feature and the principal component. All the features further nominated are significantly related to the PC considered.

Dynamic Viewers are characterized by (positively correlated), for example, a high number of fixations (*fix_n feature*), a high number of fixations per second on average (*fix_rate feature*), a high number of gaze steps (*n_jumps feature*) and coherently an high number of gaze flips on both axis (*flipX_n and flipY_n features*) . Conversely, they are negatively correlated with features that were positively correlated with PC1 values in the previous study, such as mean fixation duration (*fix _mean feature*), standard deviation of fixation duration (*fix_sd feature*), maximum fixation duration (*fix_max feature*), and other various statistical metrics (such as mean, maximum, and standard deviation) of most quartiles of fixation time features. These latter features, negatively correlated with positive values of PC1, thus indicating a negative relationship when considering *Dynamic Viewers'* visual behavior. Those features are indeed positively correlated with low values of PC1 scores: this occurs when considering *Static Viewers* phenotype, which is profiled by the meanings of those features.

Moreover, although *Dynamic Viewers* cluster has a more homogeneous distribution concerning PC2 values, *Static Viewers* are typified by slightly positive values of PC2 scores, consistently to the fact that those principal component values are negatively correlated with features related to the statistics metrics (mean, maximum and standard deviation) of gaze steps length.

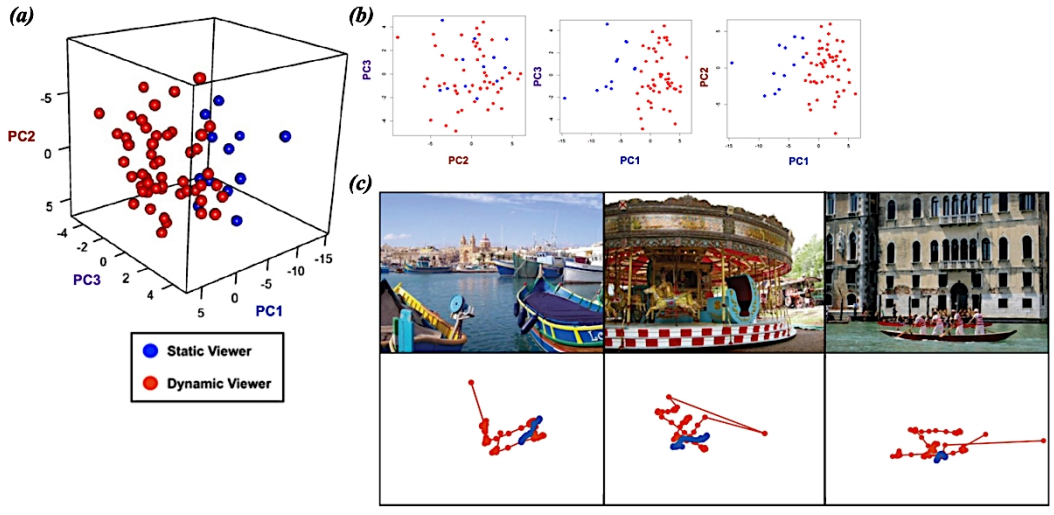


***Figure 38: Subjects' clustering and PCs**. **(a)** Three-dimensional space, defined by the first three PCs, clusters' projection. **(b)** Two-dimensional PC scores relationships: PC1 values are once again those best describing the two clusters. **(c)** Examples of Static (blue dots) and Dynamic (red dots) Viewers oculomotor dynamics patterns (each dot represents gaze position sampled at a timepoint).*

In summary, despite the opposite relations of PC1 values compared to the previous study, *Static Viewers* were found once again to be characterized by longer fixation durations and longer viewing times, but by a lower number of fixations, a lower fixation rate, fewer gaze steps, and flips. Additionally, considering PC2 values, they are characterized by a lower mean length of gaze steps. Conversely, *Dynamic Viewers* were shown to be characterized by opposite features. These results are consistent with the findings of Zangrossi et al., and the replication can be considered achieved: once again findings suggest that, considering that fixations is the time when foveation of the image (in a dynamical stability, as seen relatively to fixational movements) allows visual processing, the engagement of *Static Viewers* in longer fixations suggests deeper processing of fewer stimuli[33]. Conversely, *Dynamic Viewers* tend to scan more rapidly and superficially across multiple items in a visual scene[33].

8. EEG DATA

In this section of data analysis we focused on the data collected during the REST1 phase, where participants were instructed to gaze quietly at a blank grey screen for 5 minutes. Our objective was to replicate the findings of Celli et al. regarding resting state brain activity, in a eyes-open condition[32]. Additionally, we aimed to support, from a frequency analysis perspective, the characterization of subjects within the *Static* and *Dynamic viewer* clusters (identified by Zangrossi et al. based on their oculomotor features[33]).

We verified, in the previous chapter, the robustness of those results on a new sample proving the replicability of Zangrossi et. al. findings (on a distinct cohort of participants, employing a distinct eye-tracker and slightly different task conditions) concerning low dimensionality of oculomotor behavior, which appear to be partially independent by stimuli and mostly driven by intrinsic factors: those factors allowed us to split participant, once again, into two clusters of observers based on their eye movements features. In this section, we aim to prove the link highlighted by Celli et. al. findings (with a shorter resting state recording and slightly different conditions) between those intrinsic factors (drivers of eye movements dynamics) and the possibility to verify an oscillatory brain activity fingerprint of participants' endogenous neural dynamics, sustaining the possibility of subjects profiling in the two clusters identified, *Dynamic* and *Static viewers*.

8.1. EEG pre-processing

Pre-processing of EEG data was structured employing MATLAB (The MathWorks, Inc) scripts based on functions from the EEGLAB toolbox, an open source software developed to allow processing of single-trial and/or averaged EEG data collections of any number of channels[232]. First of all, data have been band-pass filtered with cut-off frequencies defining a 0,75 – 80 Hz interval, different to the one defined by Celli et al. in the previous study, in order to optimize pre-processing dynamics depending on the characteristics of the present dataset analyzed. In particular, the four filters employed were also different:

- High-pass filter with 0,75 Hz cut-off to sort out lower frequencies.

- Two Notch band-pass filters which sorted out frequencies within 49 – 51 Hz and 99 – 101Hz intervals respectively. They were utilized in order to delete frequencies ranges that could have been contaminated by alternate current frequency peaks.
- Low-pass filter with 80 Hz cut-off to sort out higher frequencies.

The rationale of operating this frequency (or temporal) filtering, which consists of an attenuation of signal components bands, is to reduce noise in the recordings data, preserving the signal of interest and increasing, consequently, signal-to-noise ratio[233]. Although pivotal, frequency filtering criteria have to be carefully selected because they cannot separate signal from noise in the same band (considering that sometimes noise and signal of interest are separated, but mostly overlapped) but either they delete or attenuate anything in the targeted band, causing by the way changes in local temporal signal.

Automated detection of noisy and/or non-reliable channels was then conducted but also was followed by confirmation through visual inspection, each aimed to remove inadequate signal, in order to isolate actual *brain* signal from noise. The selection processes relied on five criteria, with thresholds determined by a preliminary dataset examination to optimize detection:

A. Flat signal (in other words, with no detected signal) for more than 5 consecutive seconds. This one is the only absolute criteria.

B. Standard deviation greater than 3 for the spectral test (*index_SPECTRUM*), which help identify and remove artifacts by analyzing power spectrum shape of the EEG data.

C. Standard deviation bigger than 5 for the probability test (*index_PROB*). This test helps in detecting segments of the data that exhibit improbable values or patterns that deviate significantly from what is expected based on the rest of the dataset.

D. Standard deviation greater than 5 for the kurtosis test (*index_KURTOSIS*). Kurtosis test is a statistical technique employed in order to identify significant deviations from the normal distribution in EEG data[234]. Being EEG signals essentially a reflection of non-stationary process, kurtosis

values indicate the presence of improbable signal features, enabling to filter them out from the actual signal. Strongly positive values, when the distribution is peaky (for instance during a transient strong muscle activity) or negative ones when reflecting alternate current or direct current artifacts[234,235].

E. Raw channel signal amplitude, absolute value greater than 650.

Channels selected by the criterium A, the only absolute, or at least two between B, C, D or E criteria, were interpolated using spherical splines[230], to estimate average surface reference potential, allowing a better evaluation of the potentials relative to infinity than the discrete average computed over superior scalp electrodes, and showing greater accuracy in density mapping[236,237].

8.1.1. Independent Component Analysis

Once, then, re-referenced the EEG data to the average of all electrodes, independent component analysis (ICA) was employed to definitely remove ocular, muscular and movement artefacts. In particular, a FastICA package[238] enabled the use of a deflation-based fast fixed-point ICA algorithm with the hyperbolic tangent as a cost function. ICA identifies a coordinate system where the data projections have minimal temporal overlap and to do so its mathematical foundation is to minimize mutual information among the data or to maximize their joint entropy[232]. ICA can be considered an alternative method to PCA: the latter, when applied to temporal domain, aims to ensure that each PC explains as much of the uncorrelated variability with previously determined components as possible, while ICA focuses on finding maximally independent sources (ICs)[232].

Adjacent EEG scalp electrode channels are highly correlated and they capture signals from multiple sources, both biological and non-biological. ICA has proven effective in isolating the distinct source generator processes that underlie these recordings[239]. Independent components (ICs) were classified as “primarily brain-related” or “non-brain-related”, specifically into seven classes, employing the ICLabel toolbox:

- Brain ICs: for the first category, containing activity believed to originate from locally synchronous activity in one or two well-connected cortical

patches, which are typically small and produce smoothly varying dipolar projections to the scalp. They usually display power spectral densities where frequency and power are inversely related[239].

- Muscle ICs: electromyographic signals characterized by broadband activity at high frequencies (above 20–30 Hz) derived from many motor unit action potentials during muscle contractions or periods of static tension[239]. Often they can appear as dipolar, but being their source located outside of the skull, their pattern is more localized and recognizable than brain signal[239].
- Eye ICs: activity induced by an electrical dipole (positive pole at the cornea, negative at the retina) consequent to the high metabolic rate of the retina[240]. Frontal scalp projections of this standing dipole change according to the type of eye movement: clear quick shifts for blinks and sustained "square" shifts for vertical or horizontal movements[239].
- Heart ICs: rare electrocardiographic signal projected to the scalp (if electrode is situated for example over a superficial artery, closely approximates a diagonal linear gradient from left-posterior to right-anterior) recognizable by the clear QRS-complexes waveform in their time series[239,240].
- Channel Noise ICs: portion of the recorded signal, statistically independent from those of other channels; can be caused by high impedances or physical movements of the electrodes, and typically indicates poor signal quality or significant artifacts affecting individual channels[239].
- Line noise ICs: influence of line current noise, depending on poorly grounded EEG amplifiers for example, identifiable as high concentration of power at either 50 Hz or 60 Hz[239].
- Other ICs: non-explicit category which accounts for ICs that fit none of the previous ones. Mostly it concerns ICs containing indeterminate noise or ICs containing multiple signals that ICA decomposition could not separate well [239].

All the ICs classified as Brain ICs or Other ICs (but with Brain as second highest probability) were kept.

8.1.2. Artefact Subspace Reconstruction

In order to remove any possible residual artefact, the Artefact Subspace Reconstruction (ASR) was employed in our pipeline: it consists of an adaptive spatial filtering approach where the artefacts characterized by an high variance (muscle and motion signals for instance in our pre-processing) are identified and adaptively removed using reference data which are free from any type of artefacts, and so "clean"[241]. Although typically applied after the high-pass temporal filter, we decided to implement it downstream in the pipeline, consistently with Celli et al., allowing us to concentrate its processing efforts and effectively clean any persistent post-ICA artefacts[33,241].

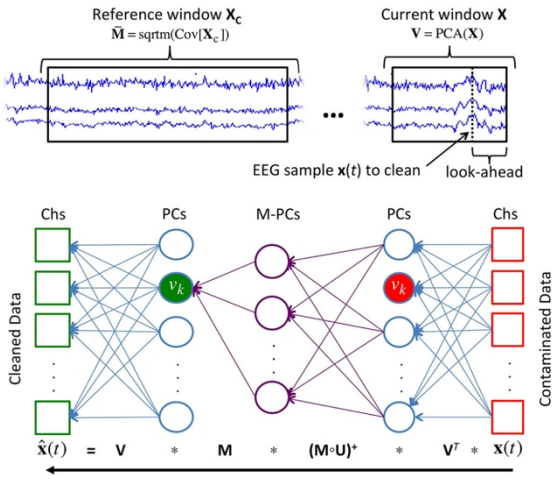


***Figure 39: The ASR method**. Artifacts with high variance (compared to a reference dataset or window) are detected and dynamically eliminated from the dataset through a sequence of linear subspace projections.*

Data segments were detected as noisy employing a 1 s sliding-window PCA. If PCs exceeded 35 standard deviations from the "cleanest" dataset portions, a mixing matrix computed from the latter, was utilized to substitute the artifactual data identified.

8.2. Spectral analysis

The power spectral density was computed applying a Welch's overlapped segment averaging estimator (which employs a fast Fourier transformation, considering mean values across time windows), in order to obtain in a 1-80 Hz frequency range, a frequency resolution of 0.5 Hz[232]. Every channel had its spectral density extracted, computed and then converted from dB to $\mu V^2/Hz$. To normalize each spectrum to

the relative frequency power, it was finally divided by the total power obtained through trapezoidal integration of the entire spectrum.

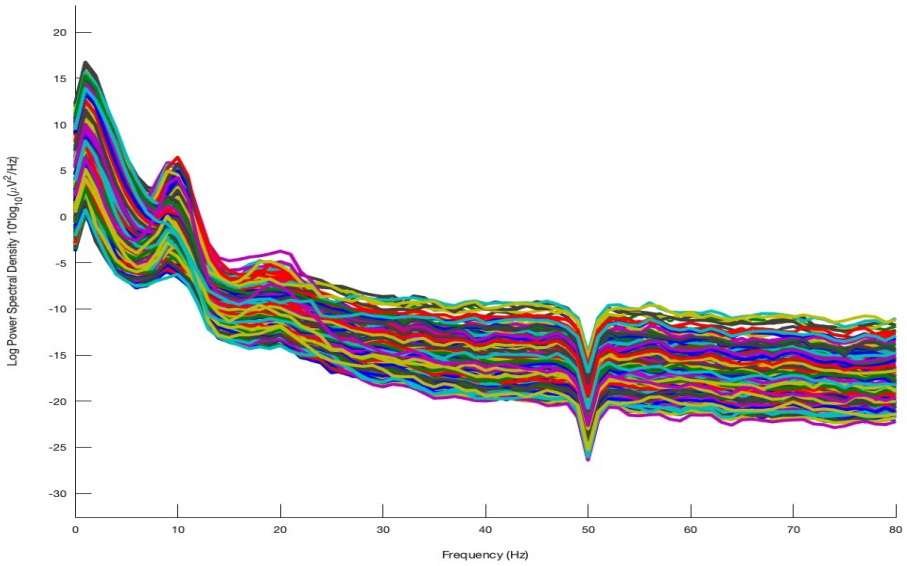


Figure 39: Example of a spectrum. *The spectral analysis represent all subjects' EEG channels spectrum, in a 0 to 80 Hz interval, obtained by running the spectopo() function on EEGLAB, with a frequency resolution of 0,5 Hz. Note the sorted out frequencies within the 49 – 51 Hz interval consequently to the Notch band-pass filter feature.*

8.3. Statistical analysis (spectral analysis)

Referring to the eyes-open condition only, we employed the Fieldtrip toolbox, which enables to perform structured analyses of large MEG, EEG, and other electrophysiological datasets using the MATLAB command line and scripting[242], to operate a nonparametric permutation technique with cluster correction[243].

Firstly, an average of frequency power into five bands was ran. Those, listed in descending order of frequency, are: gamma (32,5 - 45 Hz), beta (12,5 - 32 Hz), alpha (7,5 - 12 Hz), theta (3,5 - 7 Hz) and delta (1 - 3 Hz) bands. The frequency power for each band was averaged across all 256 electrodes, obtaining distinct global frequency powers, which were then compared to the PC1 values across the 58 subjects considered: we aimed at testing statistical correlations between distinct power bands and PC1 in a continuous fashion. Only 58 out of the 62 participants whose oculomotor dynamics were analyzed, were considered here, as 4 recordings

were eliminated due to poor data quality or incomplete registration caused by technical issues.

Nonparametric permutation approach is often employed in MEG or EEG statistical data analysis, as in this case, because of the multiple comparisons problem: due to the extremely large number of (sensor, time)-pairs, the multiple statistical comparisons (usually a number of the order of several thousands) operated, make it impossible to handle with classical procedures, the so called family-wise error rate (FWER), which consists of the probability of incorrectly inferring that there may be differences between the experimental conditions at one or more (sensor, time)-pairs [243]. In other words, there's an increased risk of obtaining false positives when conducting statistical tests on a large number of data such as EEG signals from many electrodes recorded over time[244,245]. Nonparametric permutation with cluster correction addresses this issue by identifying clusters of contiguous data points showing significant differences between experimental conditions: thus it evaluates those entire cluster dimensions, in terms of (frequency, time)-samples on the basis of spectral and temporal adjacency, rather than individual data points as (sensor, time)-pairs[243].

Specifically, we chose to ran as appropriate statistical test, a Spearman's rank correlation coefficients, computed in each electrode between the distinct frequency bands and eye-tracking PC1 values. The null hypothesis was tested by the nonparametric permutation approach with cluster correction. We computed 1000 resamples with two-sided 95% confidence intervals, corresponding to an alpha level of 0,05. In detail, cluster correction method aimed at creating the maximum cluster size possible, and employed a nonparametric two-tailed cluster threshold set to 0,05. Clustering of channels was completely data-driven: the function employed, highlighted the contiguous electrodes (data points) showing a level of correlation with the variable exceeding that predefined significance threshold. Dimension (i.e., number of electrodes) of clusters, as it can be seen in Figure 41 below, was different according to the frequency band. Finally, Spearman's rank correlation is computed between frequency bands power exponents and PC1 exponents only for the cluster of electrodes identified in the previous step.

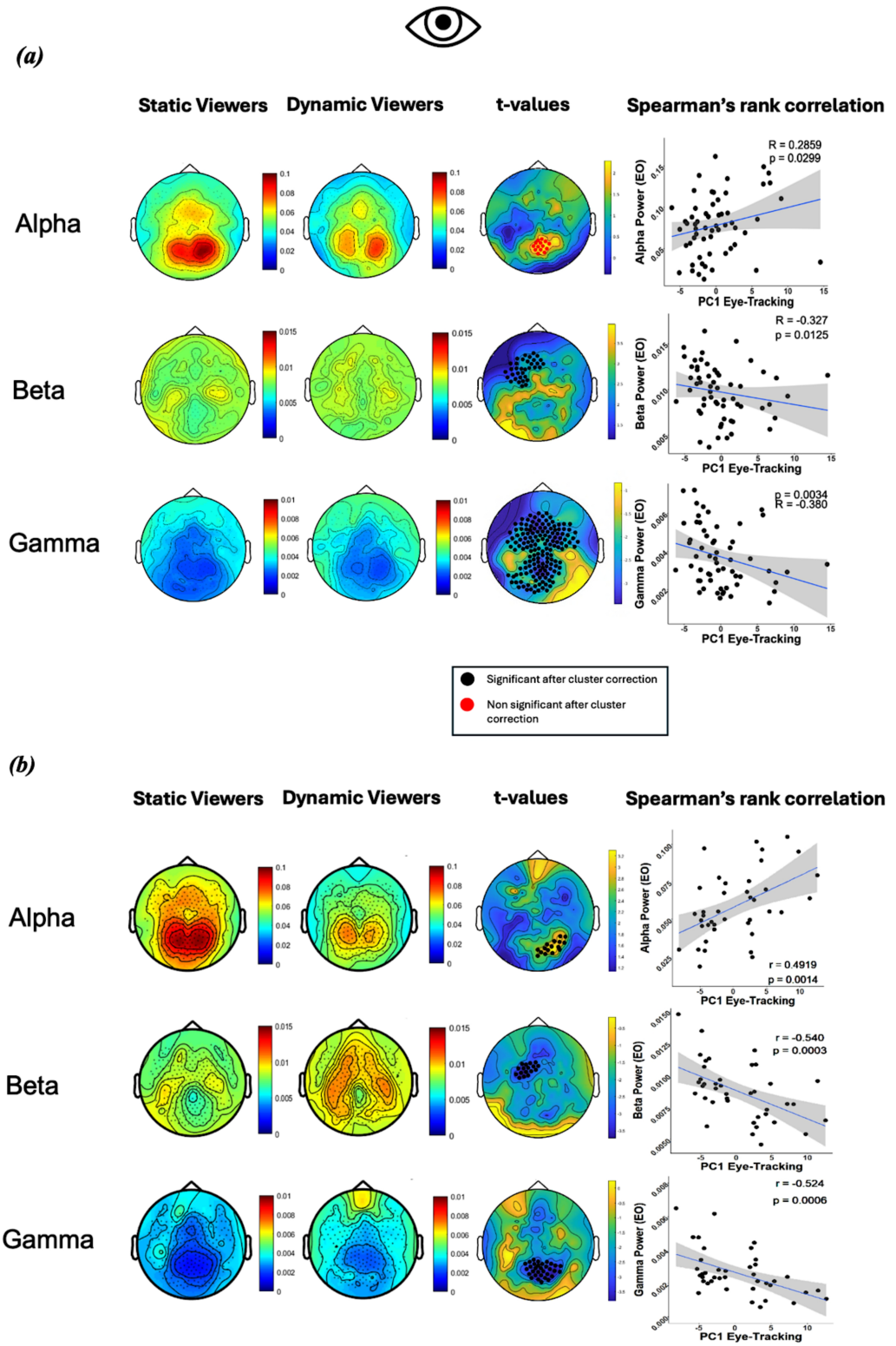


Figure 41: Comparison between the eyes-open resting state spectral analysis results from the present study (a) and from Celli et al. (b – already presented as Figure 22 in paragraph 4.2.1) to highlight the remarkable consistency of the results. (a) *Group scalp maps in eyes open condition for alpha (7.5–12 Hz), beta (12.5–32 Hz) and gamma (32.5–45 Hz) relative power and t-value maps for the cluster-based permutation analysis with cluster correction operated as a continuous analysis (differentially to b where t-maps are obtained by a comparative analysis), following the reversal of PC1 values for qualitative consistency with the previous study's graphical representation. Significant results for the high-frequency bands beta (p = 0,01; number of electrodes = 35) and gamma (p = 0,002; number of electrodes = 159) after cluster correction, while alpha band results*

*were showed to be non significant (p = 0,051; number of electrodes = 14) after cluster correction. Black dots index significance with cluster alpha at p < 0.05 (two-tailed) and alpha p < 0.05 (two-tailed), while red dots index non-significance(N=58 subjects, continuous correlation analysis). The right panel shows Spearman's rank correlation coefficients, which are computed in each electrode between frequency power in each band and PC1 values. Null hypothesis testing is conducted by using the nonparametric permutation approach with cluster correctio with cluster alpha at p < 0.05 (two-tailed) and alpha p < 0.05 (two-tailed)(N=58 subjects, continuous correlation analysis). Relative power spectral analysis qualitatively relate to the ones of the previous study and so have been referred to extreme PC1 values subjects representing for each visual explorative style. (N = 20).**(b – already presented as Figure 22 in paragraph 4.2.1).** Group scalp maps in eyes open condition for alpha (7.5–12 Hz), beta (12.5–32 Hz) and gamma (32.5–45 Hz) relative power and t-value maps (where the comparison yielded significant results) for the cluster-based permutation analysis. Black dots index significance with cluster alpha at p < 0.01 (two-tailed) and alpha p < 0.05 (two-tailed). The right panel shows the Spearman's rank correlation between PC1 and averaged power in the significant cluster of electrodes (with Spearman's r, p-value and 95% CI). (N = 40, subjects with the highest 20 and lower 20 PC1 values, analyzing the extreme representations of the explorative styles).*

The statistical assessment of the frequency bands averaged powers in the present study, although differentially designed according to the distinct experimental assessment (e.g. 10 minutes vs 5 minutes) and to the different sample dimension (e.g. 120 vs 58), confirmed and strengthened the results of Celli et. al.[32] (see paragraph 4.2.1) in the eyes-open resting state condition (see Figure 41(b) or 22).

In this study, referring to the t-value maps, we evaluated the correlation between power bands and PC1 values across all 58 subjects, while in the previous study only 40 subjects (that showed extreme PC1 values a year before in the study of Zangrossi et al.[32]) were recruited. Consequentially this time we conducted a continuous correlation analysis, which comprehended both extreme and mild values correlation with PC1 scores, evaluating all the variations within the continuum in characterizing subjects as belonging to one or the other exploratory styles; in the previous study the spectral statistical analysis have been conducted on data relating only to strongly characterized explorative styles. Above all these differences, we confirmed the clustering of electrodes which topographically, considering all the three averaged power bands, are extremely consistent with the ones highlighted by the previous study. This result is extremely robust and relevant, especially given that the analysis was conducted without any "prior knowledge" of the topography of the t-test results from the previous study. By using two different statistical tests, each appropriate to the computational approach, the dimensions and characteristics of the respective samples, we obtained two results that are remarkably consistent in terms

of t-values. In addition, we performed a Spearman's rank correlation, which has a qualitatively informative scope, consistently with the previous study, between significant clusters and PC1 values.

In the beta band (12,5–32 Hz) averaged power, the cluster based permutation revealed a significant negative correlation between PC1 and beta power in a frontal cluster of electrodes ($p = 0,01$; number of electrodes = 35); computing the Spearman's rank correlation between electrodes in the significant cluster of the global beta power and PC1 values, can be confirmed a negative correlation ($r = −0,327$, $p = 0,0125$). In the gamma band power (32,5–45 Hz) the cluster based permutation revealed a significant negative correlation with PC1 in a cluster of electrodes in occipito-parietal but also frontal areas ($p = 0,002$; number of electrodes = 159); Spearman's rank correlation, also, reported a negative correlation in the significant cluster between global gamma power and PC1 ($r = −0,380$, $p = 0,0034$). All those values and topographical features are significant and consistent with the ones of the previous study, highlighting how subjects with a lower fixation duration and an higher fixations rate, as in *Dynamic Viewers*, tend to be characterized by higher beta and gamma band power activity.

An occipital cluster of electrodes in the alpha band (7,5–12,5 Hz) averaged power, although characterized by non significant values of correlation with PC1 ($p = 0,051$; number of electrodes = 14) at the cluster based permutation and cluster correction (probably due to reduced sample dimensions), show a trend comparable to ones of the previous study in terms of positioning but above all in terms of direction of correlation with PC1 values. That trend, consistently to the one of the previous study, is to be progressively increased in a almost linear relation with the rising of PC1 values (again, following the reversal of the PC1 values obtained through eye movements analysis, to be qualitative consistent with the previous study). This is confirmed also by the Spearman's rank correlation between global alpha power in the cluster, although non significant, and the PC1 values ($r = 0,2859$, $p = 0,0299$).

In summary, for the significant clusters in the beta and gamma averaged powers, as well as for the trend highlighted by the identified alpha averaged power cluster, a directional relationship is confirmed between increasing PC1 values for the latter

and decreasing PC1 values for the formers. Once again, subjects with longer fixations time and lower fixations rate, pivotal loadings in the PC1 (again, here considered with opposite values than the ones obtained in the PCA previously performed for observers profiling trough oculomotor features, to be graphically and statistically coherent with Celli et al.[32]), identified as characterized by a mild or progressively stronger *Static Viewing* fashion, appear to be characterized by higher (progressively increasing according to greater PC1 values) occipital alpha band power. Conversely, subjects with progressively shorter fixations time and higher fixation rate, referred to as *Dynamic Viewers*, exhibit progressively higher frontal beta power and occipito-parieto-frontal gamma power, in line with their lower alpha occipital power (see low-high frequency bands interplay described in paragraph 4.2.6). In addition, topographically, clusters identified by Celli et al[32]. in subjects with extreme PC1 values, are remarkably coherent in terms of spatial distribution with the ones highlighted in the present assessment.

Finally, the topoplots, presented here for illustrative purposes only, have been computed following the same approach as Celli et al[32]: 20 subjects (10 for the *Static* and 10 for the *Dynamic Viewers* groups) recordings were selected due to their extreme PC1 values, which strongly represented the typical profiling features, and their spectral analysis were topographically plotted. Visually we can appreciate, in particular, the higher alpha power and lower gamma power in the occipital spectrum in the *Static Viewers*, and coherently a higher beta frontal power *Dynamic Viewers* such as an higher global gamma band power. These graphics, in other words, although non significant from a mere statistical standpoint, qualitatively strengthen the representation of the explorative phenotypes already individuated, by amplifying its results, as it is based only on subjects with extreme PC1 values. Once again, these findings are extremely consistent with the ones of Celli et al, whose entire analysis was performed on extreme PC1 values' subjects.

8.3. Visual explorative phenotypes: a brief results' review of both eye tracking and EEG data analysis

In summary, computing eye tracking data from the FREE phase of 62 healthy subjects we observed a low dimensionality of oculomotor dynamics, with three PCs

accounting for the 60,2% of the variability in oculomotor movements across subjects and scenes. The spatiotemporal features loaded on the PCs were substantially independent from saliency and semantics of the images presented, accounting for the rising role (conceptualized trough research lines) of *top-down* intrinsic dynamics in driving "when" and "how" ocular movements are performed, interacting with *bottom-up* stimulation processing which in a unconstrained free viewing task, still predict "where" fixations will occur. Moreover, based mainly on PC1 values, we were able to split the sample into two clusters, identified by distinct visual explorative styles, according to the hypothesis that intrinsic factors could drive visual explorative behavior. A two groups solution proved to be the most reliable and, proceeding in confirming and strengthen Zangrossi et. al results[32], we profiled subjects into *Static Viewers* (longer fixation duration, longer viewing times, but a lower number of fixations, a lower fixation rate, fewer gaze steps and flips) and *Dynamic Viewers* (with opposite features) based on the features describing their visual explorative style fingerprints, and in particular relating to their PC1 values (and PC2 values to a lower extent).

Then, we analyzed REST1 hdEEG data of 58 out of 62 healthy subjects, employing a nonparametric permutation technique with cluster correction on these eyes-open resting EEG data (previously pre-processed): by the means of cluster based permutation correlations between PC1 and cluster of electrodes in the alpha, beta and gamma bands averaged powers, have been highlighted and two out of three clusters were significant after cluster correction. Concerning the significant clusters in the beta and gamma averaged powers, as well as for the trend highlighted by the identified alpha averaged power cluster, a directional relationship is confirmed between increasing PC1 values for the latter and decreasing PC1 values for the formers.

Spearman's rank correlation between electrodes in the significant clusters of the beta and gamma bands and the PC1 values sustained those results, by exhibiting values of $r = -0{,}327$, $p = 0{,}0125$ for the beta band and values of $r = -0{,}380$, $p = 0{,}0034$ for the gamma band. Although cluster correction proved a non significance relationship with cluster alpha band electrodes, the Spearman's rank correlation values ($r = 0{,}2859$, $p = 0{,}0299$) were, once again, consistent with the correlation

direction between bands and PC1 values, confirming the profiling results exposed just before. Finally, also topoplots (ran on 20 equally divided between the groups subjects, representing for each of them the extremely strongly defined phenotypes) although being pure qualitatively descriptive, highlighted the means of this characterization.

Observers explore a visual scene with different eye movement exploration styles, and these styles relate to intrinsic properties of EEG brain signals. Baseline intrinsic brain activity influences cortical circuitries during visual exploration. Altogether these replication results are remarkably consistent with Zangrossi et al. e Celli et al. findings, confirming the characterization of explorative styles and the generalizability of those results.

9. SAMPLE DEMOGRAPHIC AND NEUROPSYCOLOGICAL TESTS

Once collected all recording phases, 55 out of the 64 subjects were asked to undergo a battery of standardized neuropsychological tests in order to address some of the cognitive domains, such as[246,247]:

- Learning and Memory: processes related to the encoding, storage, and retrieval of information; it includes short-term memory, working memory, procedural memory, semantic memory, visuospatial memory and long-term memory[246,247]. In these assessment, mostly prose memory, verbal memory and visuospatial memory have been investigated.
- Language: it includes all aspects of language function, receptive language, expressive language, verbal memory including speaking, reading and writing[246,247]. Receptive language and verbal memory were the ones mostly investigated by the test administered.
- Complex Attention: refers to the ability to focus, sustain, and shift attention as needed, including aspects like selective attention, sustained attention, and divided attention[246,247]. The tests proposed investigated mostly selective and sustained attention skills.
- Executive function: involves higher-order cognitive processes that regulate, control, and manage other cognitive processes, including for example inhibitory control, cognitive flexibility, and decision-making[246,247]. Primarily inhibitory control and cognitive flexibility have been exanimated in this section.
- Visuospatial Skills: the ability to understand and remember the spatial relationships among objects[246,247]. It includes visual perception, spatial orientation, and the ability to manipulate visual and spatial information

As already exposed in the introduction section, the close relationship between cortical-subcortical oculomotor control and visuospatial-attentive areas lead us to investigate deeply mnemonic and visuospatial domains in order to assess (although adjusted for age, sex, education, language and culture; all the participant that underwent tests, n = 55, were Italian) cognitive status of the sample of the

participants. The results presented below are qualitative and descriptive, with no significant differences observed between the clusters.

Category	Measurements' topic	Variable	Sample (n=55) Mean (SD)
Demographic		Age	23,570 (2,902)
		Sex	26 F; 29 M
		Years of education	16,930 (1,751)
Cognitive	Prose Memory	Barigazzi Prose - secondary events	30,26 (9,841)
		Barigazzi Prose - principal events	7,981 (2,603)
		Barigazzi Prose -details	4,130 (1,805)
		Barigazzi Prose - total	42,370 (1,280)
	Woking Memory	Digit Span Forward	6,436 (1,198)
		Digit Span Backward	5,545 (1,051)
	Visuospatial memory	Corsi Forward	6,722 (1,204)
		Corsi Backward	6,130 (1,150)
		Rey-Osterrieth Figure – Recall	39,370 (8,956)
	Impulsivity	Stroop Test Words – time (s)	11,514 (2,366)
		Stroop Test Words – errors	0,036 (0,189)
		Stroop Test Colors – time (s)	14,100 (2,372)
		Stroop Test Colors – errors	0,273 (0,449)
		Stroop Test Color - Word - time (s)	21,750 (4,674)
		Stroop Test Color - Word - errors	0,436 (0,688)
		Stroop Test Interference - time (s)	8,780 (3,821)
		Stroop Test Interference – errors	0,282 (0,692)

Table III: Demographic characterization *of the sample (n=55 subjects, 26 F and 29 M);* ***Cognitive Measurements*** *investigated by different parameters of tests scores. Brief summary of the principal statistical metrics (mean and standard deviation).*

	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	SD	NA's	Static Mean (SD)	Dynamic Mean (SD)
Barigazzi Prose - principal events	6,00	24,00	32,00	30,26	37,00	48,00	9,84	10,00	29,5 (10,9)	30,5 (9,67)
Barigazzi Prose - secondary events	4,00	5,25	9,00	7,98	10,00	13,00	2,60	10,00	7,27 (2,76)	8,16 (2,56)
Barigazzi Prose - details	1,00	2,63	4,00	4,13	5,50	7,50	1,80	10,00	4,14 (2,16)	4,13 (1,73)
Barigazzi Prose - total	11,00	34,00	44,25	42,37	52,25	63,50	1,28	10,00	40,9 (14,3)	42,8 (12,6)
Rey-Osterrieth Figure	20,50	34,00	41,00	39,37	45,00	64,00	8,96	9,00	38,2 (9,66)	39,7 (8,86)
Digit Span Forward	4,00	6,00	6,00	6,44	7,00	9,00	1,20	9,00	6,91 (0,83)	6,32 (1,25)
Digit Span Backward	4,00	5,00	5,00	5,55	6,00	8,00	1,05	9,00	5,73 (1,01)	5,50 (1,07)
Corsi Forward	4,00	6,00	7,00	6,72	7,00	9,00	1,20	10,00	6,27 (1,19)	6,84 (1,19)
Corsi Backward	4,00	5,25	6,00	6,13	7,00	8,00	1,15	10,00	5,82 (1,17)	6,21 (1,15)
Stroop Test Words – errors	0,00	0,00	0,00	0,04	0,00	1,00	0,19	9,00	0,18 (0,41)	0,00 (0,00)
Stroop Test Colors – errors	0,00	0,00	0,00	0,27	1,00	1,00	0,45	9,00	0,00 (0,00)	0,34 (0,48)
Stroop Test Color - Word - errors	0,00	0,00	0,00	0,44	1,00	3,00	0,69	9,00	0,36 (0,51)	0,46 (0,73)
Stroop Test Interference – errors	-0,50	0,00	0,00	0,28	0,75	2,50	0,69	9,00	0,27 (0,61)	0,28 (0,72)
Stroop Test Words – time (s)	8,42	9,93	11,03	11,51	12,60	21,69	2,37	9,00	12,9 (3,38)	11,2 (1,93)
Stroop Test Colors – time (s)	8,00	12,54	14,01	14,10	15,16	19,43	2,37	9,00	15,4 (2,57)	13,8 (2,23)
Stroop Test Color - Word - time (s)	11,54	18,61	21,16	21,75	23,73	35,65	4,67	9,00	22,4 (4,30)	21,6 (4,79)
Stroop Test Interference - time (s)	0,00	6,59	8,10	8,78	10,76	21,11	3,82	8,00	8,25 (2,75)	9,11 (3,87)

Table IV: Extended summary of neuropsychological tests scores, complete sample*. In particular, last columns show mean and standard deviation concerning the two subsets, of Dynamic and Static viewers.*

To evaluate verbal memory and reproduction of verbal information, the *Barigazzi's Prose Memory test* was employed: normally it involves the participants listening to a prose passage and then recalling it, both immediately and after a delay[214]. In our assessment, with a sample of healthy subjects, only the delayed recall was administered and errors regarding principal events, secondary events and details were evaluated, alongside to the total scores.

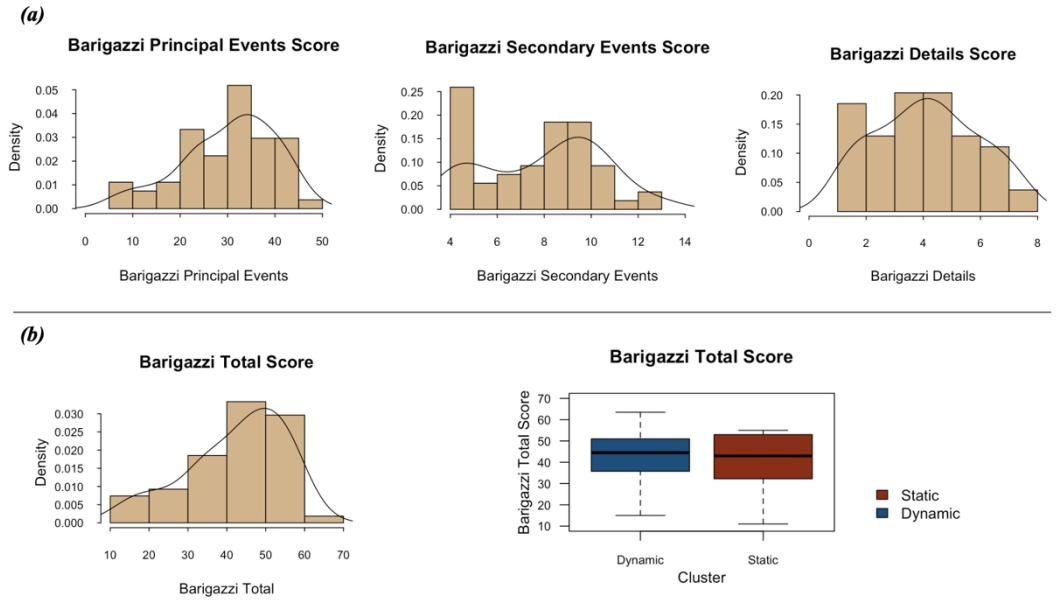


Figure 42: Barigazzi Prose Memory test plotting. (a) *Principal events score, secondary events score, details score histograms with kernel density curve superimposed.* ***(b)*** *Total score complete sample histogram with kernel density curve superimposed.; total score sorted by cluster boxplot.*

The *Rey−Osterrieth Complex Figure (ROCF)*, employed to evaluate visuospatial abilities, memory, attention, planning, and executive functions, involves the subject copying a complex geometric figure, both immediately (copy phase) and after a delay (recall phase)[193]. Here, again, considering only health participants, the recall phase (10 minutes later than the copy phase) was the only one considered[194].

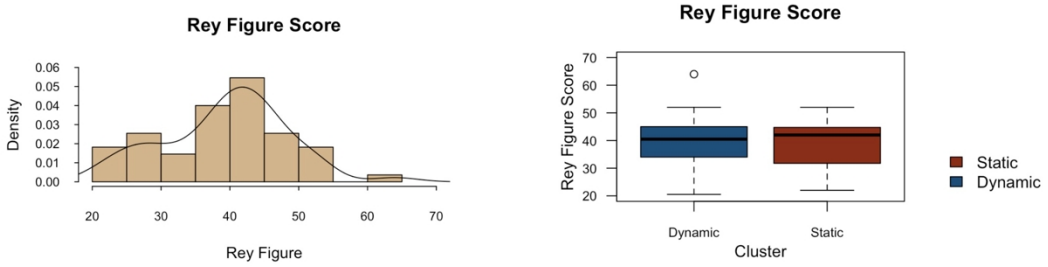
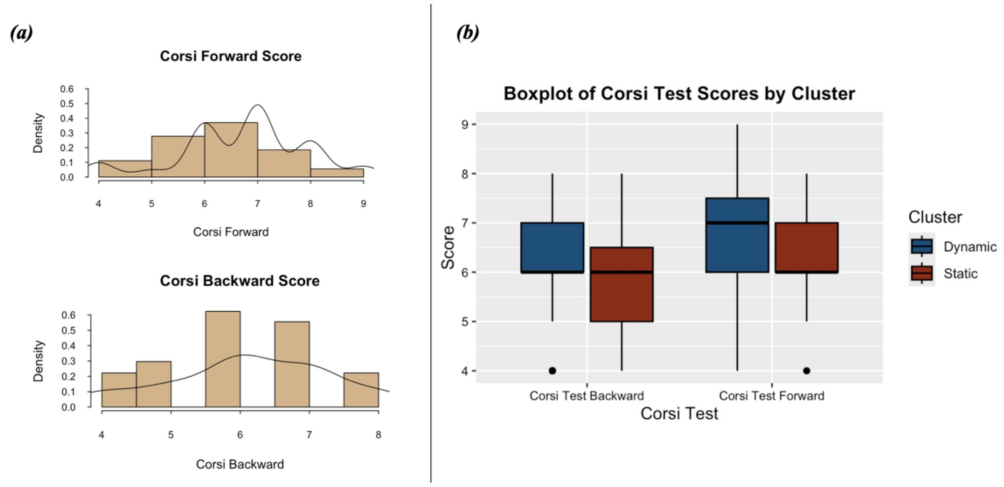


Figure 43: Rey - Osterrieth Complex Figure scores. *Complete sample histogram with kernel density curve superimposed; boxplot sorted by Cluster.*

The same cognitive domains were assessed also employing the *Forward and Backwards Corsi's tests*, which are, again, visuospatial memory tests able to evaluate how much visuospatial information can be held in recent or working memory[217]. Using a board with nine numbered cubes (arranged asymmetrically), the examiner touches the cubes in increasing sequence lengths, which the subject must



then replicate: the longest the sequence reproduced, the higher memory span[217].

Figure 44: Corsi Test Backward and Forward scores. (a) *Corsi Test Forward and Corsi Test Backward scores histograms with kernel density curve superimposed.* ***(b)*** *Corsi Test Backward and Forward sorted by Cluster.*

In order to examine working memory and attention capabilities, *Forward and Backwards Digit Span tests* have been proposed to the participants; they assess, in particular, the capacity to temporarily store and manipulate information. Examiner verbally articulates a numerical sequence at a pace of one digit per second and candidates are required to repeat aloud those sequences of digits; up to two trials are allowed for sequences of each length.

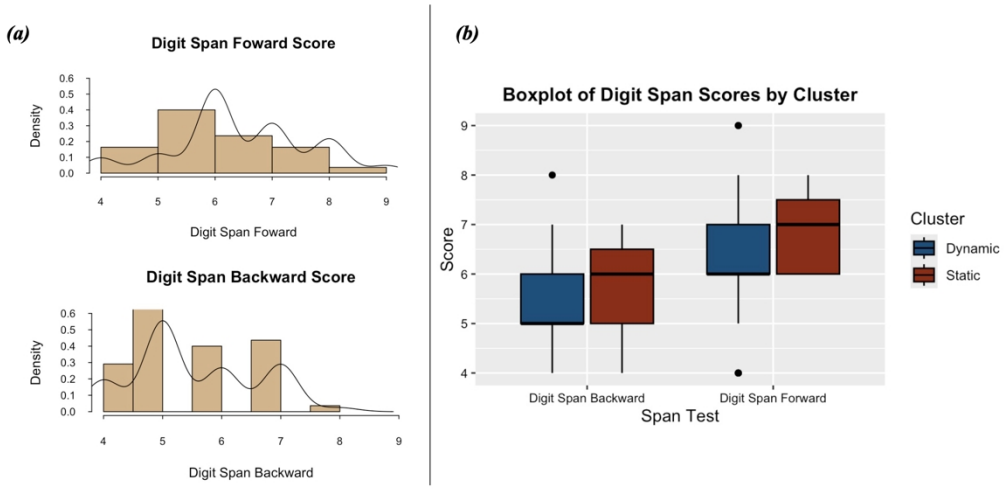


Figure 45: Digit Span Backward and Forward scores. (a) *Digit Span Forward and Backward scores histograms with kernel density curve superimposed.* ***(b)*** *Digit Span Backward and Forward sorted by Cluster.*

Finally, the *Stroop Color-Word Test* was employed, to measure primarily the ability to inhibit cognitive interference, where the processing of one stimulus interferes with another one[195,199].It evaluates executive functions such as cognitive control, attention, and processing speed, and it is furthermore a reliable metric for impulsivity[195,199].

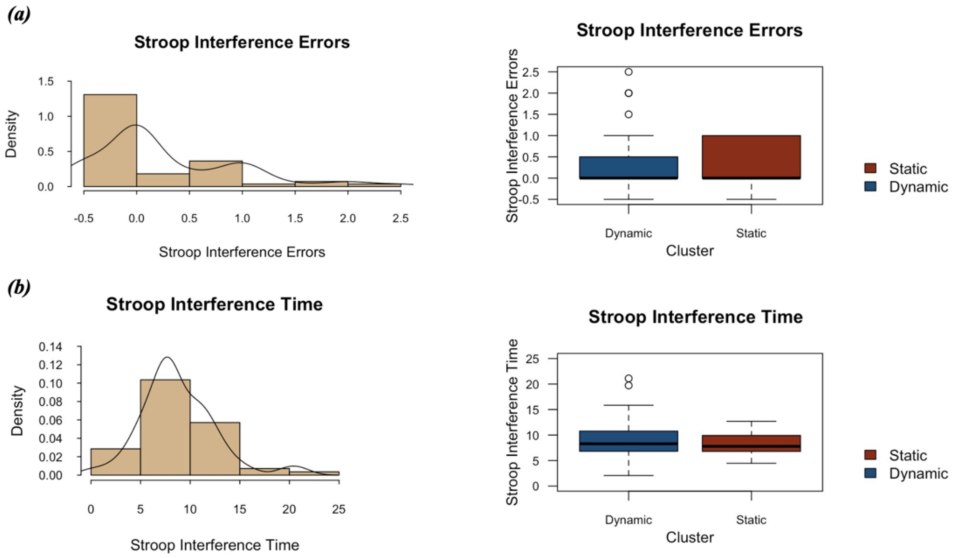


Figure 46: Stroop Interference Errors and Time. ***(a)*** *Stroop Interference Errors histogram with kernel density curve superimposed; boxplot sorted by Cluster.* ***(b)*** *Stroop Interference Time histogram with kernel density curve superimposed; boxplot sorted by Cluster.*

DISCUSSION, FUTURE PERSPECTIVES AND CONCLUSIONS

10. STUDY RESULTS AND RATIONALE

10.1. Study results' discussion: both oculomotor and oscillatory activity fingerprints

In the present study we measured simultaneously in 64 healthy participants eye movements dynamics and oscillatory brain activity, employing respectively a infrared state-of-the-art static eye tracker and a 256 channels electroencephalograph, in order to highlight the role of spontaneous brain activity in determining distinct visual exploratory phenotypes. Our purpose was to replicate, on a new sample and with slightly different experimental settings, two previous studies of Zangrossi et.[33] al and Celli et al.[32] We aimed at proving the generalizability of their findings concerning the role of endogenous activity in shaping subjects explorative styles and, consequently, the possibility of clustering the participants in two distinct groups of observers, each with different oculomotor dynamics and brain resting state activity fingerprints.

First of all we computed the eye tracking data (62 participants' data out of the 64 of the original sample were qualitatively considerable) obtained with an unconstrained free viewing task, where subjects were asked to explore without any type of limitation a set of 90 real images for a total of a 10 minutes session. Consistently with the previous experiment of Zangrossi et. al.[33], we ran a principal component analysis (PCA) to reduce dimensionality of the numerous features (related to fixations, gaze steps and pupil diameter width) extracted and to test whether a low or high dimensionality model was the one able to describe explorative style dynamics. A three novel feature model (low dimensional) describes 60,2% of the variability in visual exploration dynamics; PC1 in particular, mainly loaded on features describing fixations duration statistics, described the 30,7% of variability.

The low dimensionality of visual explorative dynamics, may stand for the possibility to explain visual behavior of various subjects across different images as a reflection of *top-down* endogenous dynamics, partially independent from *bottom-*

up stimulation. Critically, PC1 scores were not explained by features associated with saliency or semantic weights of the objects part of the scenes presented, deposing for a pivotal role of intrinsic factors in driving oculomotor dynamics. The spatiotemporal features loaded on the PCs were substantially independent from saliency and semantics of the images presented, accounting for the rising role (conceptualized trough researches) of *top-down* intrinsic dynamics in driving "when" and "how" ocular movements are performed, interacting with *bottom-up* stimulation which in a unconstrained free viewing task, still predict "where" fixations will occur.

Consequently, we then investigated whether distinct spatiotemporal visual behaviors could be summarized by the means of two phenotypical groups' characteristics, in order to replicate the results of Zangrossi et al.[32]: we identified that a two-group solution *(k=2)* was the most effective and so spitted the participants' sample into *Static Viewers* and *Dynamic Viewers* groups based on the features describing their visual explorative style fingerprints and so according to their distribution foremost in relation to the features values loaded on PC1 (and to a lesser extent with the ones of PC2). In particular, subjects with low PC1 values, exhibiting longer fixations duration, longer viewing times, but a lower number of fixations, a lower fixation rate, fewer gaze steps and flips, were profiled in the *Static Viewers* cluster. Conversely *Dynamic Viewers* were identified by opposite features and so by high PC1 values.

The engagement of *Static Viewers* in longer fixations suggests that they perform a deeper processing of fewer stimuli, exploring images for a longer time; conversely, *Dynamic Viewers* tend to scan more rapidly and superficially, according to their higher fixational rate, across multiple items in a visual scene. Moreover, *Static Viewers* showed a distribution of gaze steps closer to a power law distribution, higher mean amplitude and more numerous gaze steps and flips, other than a smaller pupil diameter mean width. *Dynamic Viewers* showed higher pupil diameter mean width and a distribution of gaze steps less similar to a power law. These results confirm and strengthen the findings proposed by Zangrossi et. al[33].

Based on the theory that spontaneous brain activity plays a fundamental role in cognition, providing spatiotemporal and connectivity priors (acting as a generative model of spatiotemporal patterns of activity) then employed during behavioral tasks [6], we tested the hypothetical relationship of these two visual explorative behaviors with intrinsic brain dynamics, measuring EEG oscillations at rest (58 participants' data out of the 62 that underwent oculomotor dynamics processing, were qualitatively eligible to be taken into account) .

We show that eye movements dynamics have robust neural activity correlations in spontaneous eyes-open resting EEG oscillations, by conducting a continuous correlation analysis between power bands and PC1 values across the 58 subjects considered. This computation process comprehended both extreme and mild values of eye movements' dynamics correlation with PC1 scores, evaluating all the variations within the continuum in characterizing subjects as belonging to one or the other exploratory styles. We analyzed, employing a nonparametric permutation technique with cluster correction, the pre-processed EEG data: cluster of electrodes maps relating to the alpha (7,5−12,5 Hz), beta (12,5–32 Hz) and gamma (32,5–45 Hz) bands averaged powers, have been highlighted and two out of three clusters were significant after cluster correction. The alpha band, which displayed non significant ($p = 0,051$) correlation, exhibited anyway a direction correlational trend consistent with the previous study by Celli et al.

That previous study proved that the EEG analysis could further characterize the visual explorative phenotypes identified a year earlier: *Static Viewers* showed higher alpha power and lower gamma power in occipital electrodes, while exhibiting lower beta power in frontal electrodes. In contrast, *Dynamic Viewers'* oscillation profiling displayed lower global alpha power and higher high-frequency power (beta and gamma). In our replication, occipital alpha band power increased proportionally to the rising of PC1 values: after reversal of PC1 values for consistency with the previous by Celli et al, the rising of PC1 values relates to a progressively growing *Static explorative* fashion, with higher fixational time that correlates woth higher alpha power. Higher fixation rate, here relating to progressively lower PC1 values would relate with greater high-frequency global powers, relating more to a *Dynamic viewing* fashion.

Spearman's rank correlation between electrodes in the significant clusters of the beta and gamma bands global averaged powers and the PC1 values; although cluster correction proved a non significance relationship with cluster alpha band electrodes, the Spearman's rank correlation values were, once again, consistent with the correlation direction between bands and PC1 values, confirming the profiling results exposed just before. Finally, also topoplots (ran on 20 equally divided between the groups subjects, representing for each of them the extremely strongly defined phenotypes) although being pure qualitatively descriptive, highlighted the means of this characterization.

10.2. Discussion: the pivotal role of endogenous factors

Over the years, intrinsic brain activity has been a topic of increasing interest across many research lines, according to its pivotal functional role in the progressive reconceptualization of the brain functioning, which is seen no longer as a mere reflective sensory-motor analyzer but, from an *inside-out* perspective[8], as a producer of generative models. The resting brain functions as a vast simulator of scenarios, assigning different relative weights to functional patterns, depending on the context, ranging from the maximization of the entropy of explanations and, on the other hand, to the maximization of the accuracy of explanations (to fit data).

Although often explored on behalf of resting state activity recordings, as we did partially also in our experimental assessment, the brain is effectively restless: from a metabolic point of view most of its energy is spent on resting potentials and sub-treshold activities, not spikes. Moreover, intrinsic activity, as showed by Deco et al. [24], has a functional anatomy emerging from structurally and dynamically shaped slow linear fluctuations, whose constraints lean on the underlying anatomical connectivity. Areas of related coherent spontaneous activity have been described as resting state networks, RSNs (many of them have been identified, in terms of both grey matter and white matter mapping[19]), which act as spatiotemporal *priors* (maintaining an high level of coherence of activation topography at rest and during tasks, but also acting as rhythmic streams that shape differential excitability states[6,27]) for task-evoked activity[6]. Finally, this spontaneous activity is coherent at

single-cell, cortical and subcortical levels, and changes during development, learning, health and disease[6].

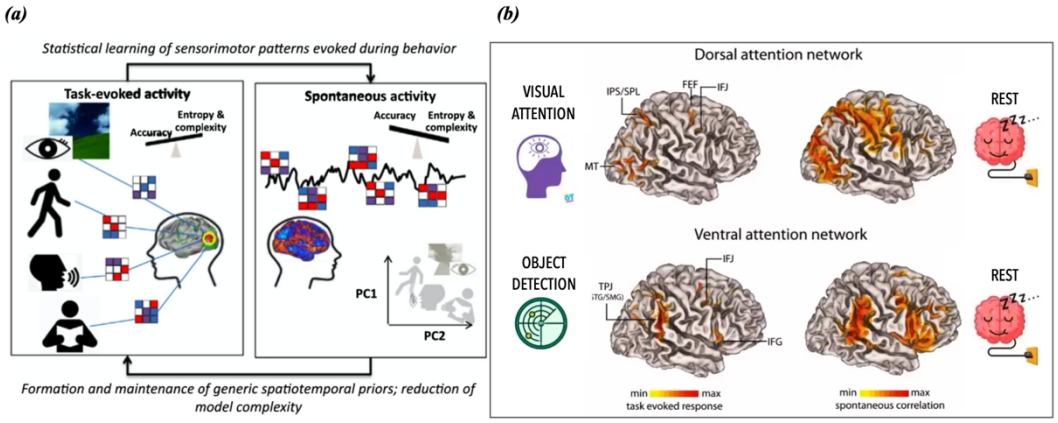


Figure 46: Priors and the Predictive Brain; An example of spontaneous vs task Brain activity concerning visuospatial attentive networks. (a) *Brain generative models continuously integrate the statistical history of co-activatory patterns from past experiences. When at rest, the brain recreates those patterns to optimize its generative model, like compressing data, and prepares general spatiotemporal frameworks for future tasks.* ***(b)*** *Dorsal and Ventral Attention Networks cortical areas activity in a comparison between task-evoked activity and resting state intrinsic activity.*

The idea is that during our lives, genetics shapes preconfigured wide networks of connections, which immediately exhibit (even at the beginning of the central nervous system development, when the baby lies in the mother's womb) some patterns of intrinsic oscillatory activity, which appear to be chaotic in first place but already starts to orchestrate the anatomical connections integration. When born, and during years of development and learning, interacting with the surrounding environments, intrinsic activity drives neuroplasticity, by conditioning both synaptic pruning and connections strengthening. This aims at increasingly refining the capability of interacting with the environment and the information that typically characterizes our experiences, guaranteeing the best possible task engagements outcomes (according to the "*good enough brain"*, see chapter 1).

Whenever the brain is in a disengaged state, spontaneous activity can, (conceptually) oscillating between maximizing the entropy of explanations and maximizing the accuracy of explanations required in tasks, shape and/or reconfigure spatiotemporal *priors* in a continuous development that takes place during growth, learning, and life overall. This makes each of us the most adapted human being possible to predictively interact with everything concerning us,

integrating external and internal projections of the environment. All these mechanisms shape our cognitive-behavioral dynamics (trough health and disease), and being our brain strongly oriented towards visual perceptual processing, on which many brain patterns converge directly or indirectly reflecting in the interplay of *cover-overt* attentional dynamics and oculomotor dynamics, eyes movements are, indeed, a behavioral window (that our study employed as a standpoint to look out from) to the cognitive constraints that modulate our way of behaviorally relate with the internal and external environments. In addition, all these elements should theoretically allow, as we investigated, the profiling of different cognitive-behavioral phenotypes of single individuals and clusters of individuals.

Characteristics of spontaneous brain activity can, indeed, predict single subject profiling[30] and cognitive-behavioral interactions, such as the eye movements dynamics during unconstrained viewing, reflecting an integration of *top-down* and *bottom-up* processing with the endogenous dynamics, thus emphasizing the role of visual exploration as a window into the cognitive-behavioral functional organization of the brain. Zangrossi et al. findings highlighted the importance of endogenous factors concerning visual explorative behavior[33]: the components mainly describing spatiotemporal eye movements features, which are consistent during both unconstrained viewing and resting state recordings, are independent of the image content[33]. Coherently saliency and semantics have a very low influence in explaining their variability (determining, when available, eventually, only "where" topographically direct fixations)[33]. This implies that resting dynamics have an influence on "how" and "when" we move our eyes during visual exploration: stable components are active both in blank screen and free viewing exploration, consistently with the idea that spontaneous neural dynamics act as spatiotemporal *p riors,* predicting task-evoked activity and so potentially revealing stable and biologically determined behavioral fingerprints in the observers[33]. This enables also the clustering of participant into the two groups, of *Dynamic* and *Static Viewers*, whit an accuracy of assignment over 90% across different images, depending on their distinct viewing style, concerning the rate and duration of fixations, pupil diameter, amplitude and number of gaze steps, and number of gaze flips[33].

Already Poynter et al. revealed the possibility, employing eye-tracker recordings in a sample of 40 participants, of evaluating a low dimensionality in the visual explorative dynamics, particularly with regard to the duration and rate of fixations, putatively relating the oculomotor behavior to attentional dynamics[99]. Interestingly, those same features have been two of the main loadings in the PC1s of subsequent studies such as the one conducted by Zangrossi et al.[33] and the present study, each conducted on a bigger sample.

As extensively pointed out in chapter 3, we refer to the "*strategy of saccades and fixations*" because of the multiple level interplay between cortical areas (such as the ones of DAN[31] and VAN[90], see paragraph 3.2.3) and subcortical hubs (such as the brainstem where attentive-oculomotor signals are deconstructed and actuated, the superior colliculus which is the last/first hub of multimodal integration between *top-down* and *bottom-up* dynamics, but also the oculomotor cerebellum, the thalamus and the basal ganglia). Many research lines suggests, coherently, that fixations and saccades, main components of eye movements dynamics, are interdependent processes across time scales, as exemplified by unimodal distributions of gaze-step sizes which are characterized by power-law scaling[102]. At cortical level DAN and VAN closely regulate the interplay between reorienting *covert-overt* attention to novel locations processing and the control of focal processing[90]; visual processing occurs, indeed, during fixations, and is no surprise that DAN and VIS (see 3.2.3) areas are so highly interconnected[6].

Covariance of fixation duration and gaze step distribution, according to cortical areas interplay, can be appreciated observing the different spatiotemporal patterns of the clusters: *Static Viewers*, whose exhibition of longer fixation time may imply more-in-depth processing of fewer stimuli, and *Dynamic Viewers*, who may scan more rapidly, and more superficially, to more items in a visual scene.

In our framework we verified once again how eye movement features during free visual exploration appear to be correlated across subjects and allow the clustering of people in two phenotypes groups, according to their intrinsic style of exploration. Approaching the issue from a predictive brain perspective, we operated also resting state EEG recordings in order to highlight the existence of neurological constraints,

either structural and functional, that may drive visual exploration behavior and predict individual differences, depending on the interplay between *top-down* and *bottom-up* processing with endogenous activity determined *priors*, as pointed out before.

A brain state can be described as a set of oscillatory waves, conceptualized as recurring and sequential patterns of propagating brain activity[248].During wakefulness rest, the restless brain, indeed, instead of globally stabilizing at a homogenous baseline level, exhibits activity fluctuations (with distinct oscillatory EEG signatures) within and between different areas, composing a picture of intertwined yet dissociable dynamic brain processes[249]. In summary, the brains, quoting György Buzsáki are now conceived as "foretelling devices and their predictive powers emerge from the various rhythms they perpetually generate"[60].

The interplay between different resting state power reflect the baseline level of cortical activation which depends upon ongoing oscillations, that affect local electrical fields and intrinsic excitability of neuronal populations. Tonic shifts in the power of brain rhythms, particularly alpha and gamma bands (with beta band power perpetrating the *status quo* of networks hub[166]), often accompany changes of neural response amplitude, attentional state and perceptual/cognitive performance[170], which reverberate through behavioral dynamics[170]. Different oscillatory classes present distinct levels of brain integration: synchronization of multiple bands encodes complex temporal patterns and optimizes synaptic reinforcements or weakenings[130]

Alpha power is no more perceived as only the reflection of an idling state, but the evidences accumulated over the years demonstrate how it may reflect first of all inhibitory dynamics (such as "inattention" at rest[249] or trough visual areas in eyes-closed conditions or in absence of salient visual stimuli) not only directed to non-essential or conflicting processes[129], following the so called "*neural efficiency hypothesis*"[139] (see 4.2.2) but also exhibiting an inhibitory *top-down* control[140] on both local and distributed information processing[131], enabling both the gating (reducing the processing capability of a certain cortical area and routes information to task related cortical areas[143]: "*gating hypothesis*") and the timing (by applying an

inhibitory filter that enables to achieve an high signal-to-noise ratio by allowing only a small number of cells to process information selectively and by silencing the majority of other cells[140]: "*inhibition–timing hypothesis"*). Moreover the magnitude of local alpha predicts a greater or lower level of brain activation when suppressed, as an updating mechanism for processing incoming signals: for example when, by *top-down* regulation from FEF and IPS, VIS within network areas desynchronize in localized cluster to enable visual processing coordinated to attentive-oculomotor dynamics, clocking the higher frequency subsequent activity and enhancing an efficient and precise neuronal recruitment of cells which are in an appropriate state for perceptive mechanism, consequently to the previous alpha synchronization magnitude at rest. These mechanisms (such as the decrease of temporal correlations within visual cortex, aligning with the desynchronization of alpha rhythms observed during anticipation, spatial attention, or visual processing[178]) favor the occurrence of gamma power oscillations, so that alpha frequency, enhanced manly by the FEF (right in particular) effectively routes cortical information flow by modulating gamma-band activity[6,179]

Gamma power, is indeed, deeply dependent by a cross-frequency coupling with other rhythms, reflecting in a multiscale timing mechanism[157], as in this case with the alpha band. Another important example is the one of "*theta phase precession*" (see paragraph 4.2.4), consistent with the preplays/replays theories (see paragraph 1.4). Moreover it also exhibit a functional interplay with delta (0,5-4Hz), slow, and infra-slow bands frequencies[157]. Importantly, also an higher-frequency functional interplay is fundamental concerning the *priors* theory discussed before: while information about stimulus features are carried by gamma oscillations, determining temporal windows for synaptic plasticity, proportionally to their cycle length[130], beta synchronization carries feedback signals which influence the functional coupling of neurons and regions over much longer distances, whereas high gamma frequency promotes local processing[110,184]. Refining concepts of paragraph 1.5: during development, repeated exposure to sensory or motor signals enhance reverberation in the post-stimulus period and imprint traces in the spontaneous activity (according also to Hebbian plasticity, see 1.3[42]), so that metrics, describing sensory external environment and biomechanical body properties, shape networks topography and dynamics[110,185]. Gamma frequencies are thought to encode for quick

environmental changes and error predictions, while beta coupling fluctuations should slowly enhance weighted integration of incoming information and *prior* inferences, computing the slower temporal structure of somatosensory events and the outputs obtained by the interactions between predictive models and environmental engagement. Those development-shaped internal models, stable yet still malleable in adults (an efficient brain is one that can employ predictions but monitoring for errors during the interactions with the occurrences in the surrounding world, adjusting its models when necessary), act as spatiotemporal *priors* which allow the brain to exploit stored knowledge in order to predictively anticipate the statistically most likely outcome of the upcoming stimuli and movements (balancing specificity and entropy of explanations)[110]. Spontaneous activity determine biased (optimized) recruitment of the task-driven patterns, forming spatiotemporal scaffolding of brain possible responses: this translates to a low dimensionality of cognitive and behavioral (just as in visual explorative dynamics[33]) dynamics across task and across individuals. At the same time this justifies the similarity between task-engaged and resting state functional connectivity[13,110].

On the other hand, the alpha-gamma interplay is also tought to reflect the directionality of attention, whether directed towards internal or external processing. DAN activity and focal alpha desynchronization (focal disinhibition) reflect *top-down* driven dynamics for selective attention, gating irrelevant sensory processing to enhance local activity and information processing[131]. Consistently, when experiencing task-engagement or memory-retention task (especially in a sensory-dependent assessment) alpha power increases in right parietal cortex (rTPJ, part of VAN[90]) which is progressively inhibited proportionally to the strength of task-focused attention or task shielding, avoiding attentional shifts to task-irrelevant stimuli, thus favoring attention focusing during *top-down* goal-driven tasks[172].

Neuronal synchronization in the gamma band, accompanied by a decrease in alpha band activity reflect active processing in the engaged brain regions. Decreasing of alpha rhythms may linked to a more externally directed attention, while higher alpha global power might indicate a higher inhibitory baseline of interaction with external stimuli and so more focusing on internal processing. This aligns with

findings concerning *Static Viewers* oscillatory profile and also with their viewing behavior, characterized by longer fixation and more in-depth visual information processing of a fewer number of stimuli. According also to the *efficiency*, *timing* and *gating* hypothesis concerning alpha power functionality, their higher alpha activity baseline can be conceived as a specific reflection of cognitive preparatory activity to their remarkable deeper processing behavior. On the other hand, *Dynamic Viewers,* exhibiting higher global high-frequency baseline level, would be characterized by a resting state profile more similar to a task-engaged state (either on stimulus processing or performing of selective attention). The increase on the global level of gamma-to-alpha power (with a baseline level of more desynchronized global alpha power), consists of an intrinsic different balancing of cross-frequency interplay, which reflects: lower inhibition towards external stimuli, a more reactive state in interacting with surrounding environment and a greater focus on those external stimuli, in order to ensure a better preparatory state for that remarkable higher engagement rate with more stimuli out of the number of stimuli presented, compared to *Static Viewers*.

Those concept fit with the findings of different balancing of parieto-occipital regions gamma-to-alpha ratio, but also with the fact that *Dynamic Viewers* exhibit diffusely a global higher gamma power (occipital-parieto-fontal significative clusters of electrodes). Overall then the occipital power results, align with the cognitive profiles of the two types of subjects (see 4.3), with *Static Observers* showing a slightly stronger visual working memory, and dynamic observers a weaker inhibition to salient but irrelevant stimuli.

Moreover, *Dynamic Viewers* would exhibit also higher frontal beta power: as addressed before, beta rhythms represent the status quo/maintenance of a specific task or motor set and this can be empirically appreciated by observing synchronization during tasks in which a set is maintained over time (e.g., a working memory task). Beta band oscillations are no more conceived only as the inhibitory frequency of sensorimotor cortex, but also as a rhythm which operate a *top-down* modulation linked to different cognitive functions (such as visual attention, perception, emotion, working memory), managing, alongside to alpha power, that selection bias in task-networks recruitment, in order to predictively preserve

computed expectations about the sensory environment and the internal models of body representations, or to plan subsequent movements (and also exploratory eye movements) dynamics in case of unexpected interactions outputs[110]. To do that, beta band synchronizations act enabling long-range within-/between-networks (such as PCC of DAN with DMN regions[186] or IPS of DAN with SMA of SMN[187]) creating dynamic interconnections within hubs, hence creating a *"dynamic core"* and thus generating highly efficient brain states.

Beta band is, indeed, pivotal in maintaining the current sensorimotor or cognitive state, thus cognitive and behavioral *priors* (temporal connectivity priors[13]) for real-world events interactions; all of that, while preserving stability, yet flexibility of upgrades, of the *status quo* of cortical areas as a pivot around which brain activity realizes itself, practicing the highest global efficiency possible[110,163]. From this standpoint, consistently, *Dynamics Viewers* exhibiting that type of beta power pattern appear to be more reactive toward rest-task transitions and adaptations of *prior* predictive models to task performance. On the other hand, *Static Viewers,* exhibiting lower beta frontal power, might maintain at rest a more reactive motor cortex, with a lower beta rhythm to overcome and initiate motor activities. This preparation for coordinated movements with fixations and in-depth visual processing might leave more space for synchronous movements while performing concentration and stimuli processing, and to react to the possible outcomes of processing with subsequent actions.

To conclude the discussion, our replication study consisting of concomitantly recordings of both eye movement and EEG features of healthy subjects, both high temporal resolution methodics, led us to a novel experimental setting on a new sample, that confirmed and strengthened the generalizability of the previous results of the two separate (although conducted on the same sample) studies by Zangrossi et al.[33] and by Celli et al. [32]. We demonstrated that a complex behavior like the oculomotor dynamics of visual exploration can be summarized with a few components loaded on features across many subjects and pictures. This is in line with a growing behavioral literature branch concerning the covariance across subjects, which is progressively proving that many apparently complex behavior underlie a low dimensionality: complex hand movements[250], human city navigation

in cities (with a *returners/explores* consequent phenotypes characterizations)[251], and variability in reward inhibition[252] that may be underpinned by the result of integrate cognitive-behavioral interplay depending on *top-down/bottom-up* dynamics with intrinsic brain activity. At the same time, growing research evidences highlight the low dimensionality of coding through correlated neuronal activity across many neurons in studies concerning face perception[253] and exploratory face movements[254] and hand movements[255].

According to the research lines that highlight the role of intrinsic brain activity in shaping connectivity and spatiotemporal *priors,* as well as to those supporting the spatiotemporal low dimensionality of cognitive-behavioral processes as a reflection of *top-down* and *bottom-up* dynamics interplay with endogenous brain activity itself, we defined a method to push forward our understanding of brain oscillatory rhythms and oculomotor dynamics both as functional fingerprints of distinct visual explorative styles. The reliability of those results enabled us to operate a clustering of the healthy observers, defining their explorative style as *Static* or *Dynamic*. Those styles classification appear to be stable across subjects, as well across experimental setups, enabling to operate a profiling of individual eye movement features and brain oscillatory powers correlates at rest, as an intrinsic characterizations of the subjects investigated. Surprisingly resting oscillatory brain activity was extremely consistent with the results of Celli et. al, both in terms of significative electrodes clusters (or trend of significance) and foremost of directionality of the correlations between distinct power bands and PC1 loaded on the main oculomotor features. These results led us to speculate about future perspective and possibility to push even more further our comprehension of spatiotemporal endogenous brain dynamics and cognitive-behavioral characterization of the uniqueness human brain functional dynamics and phenotypes.

10.3. Strengths and limitations of the present experimental setting

Regarding the present study's limitations, although employing an eye tracker system with a sampling rate from 1000 to 2000 Hz (frames per second)[206] we did not considered for the purpose of this study the dynamics of microsaccades, which

are an important mechanism of fixation and are underlined by the same mechanisms of the saccades and fixation strategy. They might be considered in some of the following publications which will might take into account also the data from the FORC and REST2 phases that were not computed for the purpose of the present study. We tried also, in first place, to design visual exploration recordings in order to pursuit the best natural conditions possible (other than presenting natural visual scenes) such as without the use of a chin-rest support and employing algorithms for head movements correction, or wearable eye-trackers. We then went back to a setting consistent with the one of the previous experiment of Zangrossi et al. in order to maximize the value of this replication study but also to solve many recordings problems that occurred (without the use of the chin-rest in particular) to pursuit the best quality of the recordings data.

In order to strengthen the results of the previous studies form Zangrossi et al., this time we designed a setting with longer blank screen viewing period, of 5 minutes compared to the 30 seconds (prior to the onset of the first image) of those former research fashion. This way ruled out the potential degree of expectation that may be present in the past studies and might influenced the results. On the other hand, we examinated a shorter eyes-open resting state session compared to the one of Celli et. al (10 minutes). By the way, the results of the present study have been extremely consistent with the previous ones, independently of resting state duration, shedding light on the fact that those different recording conditions did not preclude the possibility to capture the oculomotor and oscillatory brain fingerprints of the observers. This time the design implemented only the possibility to push the survey further, both quantitatively and qualitatively; for instance, this time we have been able to detect slower fluctuations of eye movement patterns, as well as non-luminance mediated pupillary responses, related to vigilance fluctuations, and relate them to intrinsic activity.

Still, abstracting from our design, we have to relate with the general problem (which can't be completely solved but only managed) of operationally define what a “resting state” is and to precisely defining its functional characteristics. We tried, anyway to respect the setting standardized by the literature and to create the most coherent and effective environment on which base our setting. Quoting Laufs et al.

"By definition, instructions beyond "lie still and stay awake" are precluded because they would induce specific brain states instead of rest. The precise mental processes (and their timing) during rest hence remain essentially uncontrolled, and this is probably the main limitation to the utility of this condition as a baseline or control."

Moreover, our findings may partially reflect differences in overall arousal and motivation between groups*:* theoretically each individual would be characterized by his or her own baseline arousal level and low-arousal subjects would show an increased low-high global power ratio[256], higher eyes-closed resting state alpha power and lower alpha reactivity when transitioning from eyes shut to open[125,257]. In our setting we considered only a eyes-open resting state phase, partially solving those problems; however, this experiment was not designed to test deeply the level of arousal, which was only considered by computational pipelines.

In addition, the simultaneously recording of both eye tracking and EEG data, solve the objection presented to Celli et al. whether the distinction between *Static* and *Dynamic Viewers* might be considered stable after one year since the eye tracker recordings, although being demonstrated widely in literature the stableness over time of PCs scores loaded on those and similar features[114,258–261]. Whit our design we overcome this potential limitation and show that we are not documenting brain correlates of a "state" recorded a year earlier but "trait", stable at least as long of our investigations concerning reliabilities across subjects, across images and items and across a range of brain states from rest to unconstrained or constrained settings.

Finally, operating a continuous correlation analysis, which comprehended both extreme and mild values correlation with PC1 scores, we were able to evaluate all the variations within the continuum in characterizing subjects as belonging to one or the other exploratory styles. That approach strengthen even more the consistency and generalizability of the results compared to the one of the previous study, which were conducted on extreme phenotypes and computed a comparative analysis.

11. FUTURE PERSPECTIVES AND CLINICAL APPLICATIONS

A final aspect that has to be taken into account, is the potential for applications in a clinical population. Many authors have shown over time the association between some specific patterns of eye-movements dynamics and neurodegenerative conditions. Most of the studies, by the way, employed non-natural recordings, based on specific laboratory tasks (such as anti-saccades tasks), or investigations while reading.

The neural pathways and brain regions involved in eye movements during ocular fixation and gaze control can be abnormal in presence of a neurodegenerative disorder. Careful clinical examinations of oculomotor dynamics in patients with those conditions is pivotal for neurological and cognitive-behavioral assessment. Laboratory recordings, although often being not employed in a diagnostic phase, might provide reliable information concerning disease severity and eventual progressions or regressions[262].

Concerning Alzheimer Disease patients, for instance, hypometric saccades constitute an aspect of their oculomotor pattern that has been widely confirmed in the literature. Etiopathogenetically early amyloid deposition and tau pathology occur in the SC and in some of the principal cortical areas of the DAN, such as FEF and IPS; alteration in the interplay DMN-DAN, deficient motor signals converging from those DAN and other areas, all converging to SC (given its functional positioning as a hub of intersection) and finally distorted signals projected to the brainstem burst neurons, determine all together pathological saccadic dynamics already in early stages of the pathology (often already in mild cognitive impairments stages, an early state of pre-dementia decline in cognitive abilities which anticipates the neurodegenerative drift towards various types of dementia, including AD).

To cite some of the pivotal research lines, already in 1986 Fletcher et al. proved that AD patients performed hypometric saccades that resulted in fewer accurate gaze dynamics than normal subjects[263]. Later, Fernández et al. showed that AD patients displayed a reduced size of outgoing saccades when compared with healthy controls, by employing a reading task. Recently, some research lines pointed to the

possibility of employing eye tracking methodologies as tool to perform early diagnosis: Fraser et al. presented a machine learning analysis of oculomotor features data for the detection of mild cognitive impairments, with two trials where patients were asked to read aloud or read in silence, employing for the data recordings the same eye-tracker as we did[264,265]. Also Biondi et al. developed a deep learning model able to discriminate during reading tasks the oculomotor dynamics of healthy subjects and neurodegenerative patients[266]. Deep Learning approach, being specifically focused in identifying patterns and extracting rich features, has been proven to be reliably suited to this application[264,266]. However, its requirement for large amounts of tagged data has also highlighted its limitations[266]. Eye-tracker based tools may be a sensitive and promising methodology to employ in early cognitive diagnostics; moreover their implementation in wearable and mobile devices (such as smartphones, computer and tablet cameras), which would provide high-frequency longitudinal data collection concerning gaze patterns and pupillary reflexes, might be useful to properly study neurodegenerative diseases and to address diagnosis and monitoring needs.

Alterations in intrinsic eye movement patterns may potentially serve as an early biomarker for neurodegeneration, which may be extremely important considering the fact that now some drugs are capable to slow the degenerative process down, in some cases almost halting its progression. If such device could be implemented early in the diagnostic process improving its potential, the use of those drugs could ideally ensure an increase in life expectancy for these patients, who are facing a serious, irreversible condition, capable of causing an absolute cognitive decline bordering on the loss of self.

Moreover, in those AD patients, a more constrained system generates shorter gaze shifts, and oculomotor dynamics appear to be more similar to a power-law scaling behavior, pairing with the worsening of cognitive performance. This complex cognitive-behavioral perspective opens to the implementation of resting-state EEG recordings as a diagnostic or prognostic tool alongside of eye-tracking recordings, as in our framework.

Moretti et al. designed a EEG study to study the relationship between individual frequencies and relative power bands according to the role of the cholinergic system, cortico-cortical connections, and sub-cortical white matter networks. They studied normal elderly subjects, patients affected by mild Alzheimer disease and vascular dementia patients, (all selected by comparable Mini Mental State Evaluation scores) showing the possibility of discriminating between mild AD from VaD and healthy old participants[267]. In addition, Montez et al. showed that, according to the fundamental role of amplitude modulation of neuronal oscillation in determine cognitive performance, indices of amplitude dynamics may implemented as biomarkers of early-stage Alzheimer disease[268]. Their EEG recordings proved a strongly reduced incidence of alpha-band oscillation bursts over temporo-parietal regions and weaker autocorrelations on long time scales; meanwhile, enhanced theta oscillations in medial prefrontal cortex are thought to reflect a compensatory mechanism.

Taken together, all those findings provide some favorable evidences regarding the existence of both oculomotor and EEG oscillatory early biomarkers. Our study implements these same tools on healthy participants to successfully highlight cognitive-behavioral visual exploratory phenotypes. A reasonable future perspective might involve the extension of these profiling methods to MCI or AD patients, detecting by a simultaneously recording some integrated signatures of early neurodegeneration. Ideally, these investigations should be conducted on a sample of individuals who previously underwent longitudinal recordings employing sensitive wearable eye-tracking tools. These tools, associated with deep learning computational processes, may identify certain types of visual exploratory phenotypes, even at the cost of high false positives (in order to increase the prior probability), which may enable to direct the potential patients to undergo an early simultaneous resting-state EEG and eye-tracking recordings. In an optic of personalized preventive medicine, studies as the present one, which are conducted in almost natural conditions of visual exploration, provide innovative knowledge and deeper comprehension of those cognitive-behavioral assessments and may be the key for future assessments implementations for early-diagnostics and monitoring in clinical populations.

12. CONCLUSIONS

Our replication study results are remarkably consistent with Zangrossi et al. e Celli et al. findings, confirming the low dimensionality of a complex behavior such as oculomotor spatiotemporal dynamics ("when" and "how" ocular movements are performed), which emerge from the interplay between *top-down* and *bottom-up* processing with endogenous activity. Thus we corroborated the possibility to cluster subjects' explorative phenotype according to their eye movements features and their intrinsic oscillatory brain activity.

We profiled subjects into two clusters: *Static Viewers* (longer fixation duration, longer viewing times, but a lower number of fixations, a lower fixation rate, fewer gaze steps and flips) and *Dynamic Viewers* (with opposite traits), based on the features describing their visual explorative style fingerprints, and in particular relating to their PC1 values (and PC2 values to a lower extent). Then, we analyzed hdEEG by the means of cluster based permutation correlations between PC1 and cluster of electrodes in the alpha, beta and gamma bands averaged powers, which highlighted that two out of three clusters were significant after cluster correction and that the directionality of the relations was consistent with the previous study.

Observers explore a visual scene with different eye movement exploration styles, and these styles relate to intrinsic properties of EEG brain signals. Baseline intrinsic brain activity influences cortical circuitries during visual exploration.

We propose that these profiling methodologies can be employed as a window to enlarge our knowledge concerning the innovative *inside-out* brain perspective, but also may have potential implications as an early-diagnostic biomarker of neurodegeneration, within the context of personalized medicine, in relation to the eye movements alterations which usually occur at the impairment onset. Moreover, research lines over the last decades concerning the rising role of spontaneous brain activity may be pivotal to advance our knowledge concerning chronic neurological disorders.

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ICONOGRAPHY

1. Figures

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Adapted from "Nozais V, Forkel SJ, Petit L, et al. Atlasing white matter and grey matter joint contributions to resting-state networks in the human brain. *Commun Biol*. 2023;6(1):726. doi:10.1038/s42003-023-05107-3"

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Adapted from "Raichle ME. The restless brain: how intrinsic activity organizes brain function. *Philos Trans R Soc B Biol Sci*. 2015;370(1668):20140172. doi:10.1098/rstb.2014.0172" and "Vaishnavi SN, Vlassenko AG, Rundle MM, Snyder AZ, Mintun MA, Raichle ME. Regional aerobic glycolysis in the human brain. *Proc Natl Acad Sci*. 2010;107(41):17757-17762. doi:10.1073/pnas.1010459107"

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Adapted from "Deco G, Ponce-Alvarez A, Mantini D, Romani GL, Hagmann P, Corbetta M. Resting-state functional connectivity emerges from structurally and dynamically shaped slow linear fluctuations. *J Neurosci Off J Soc Neurosci*. 2013;33(27):11239-11252. doi:10.1523/JNEUROSCI.1091-13.2013"

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Adapted from "Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci*. 2005;102(27):9673-9678. doi:10.1073/pnas.0504136102" and "Pezzulo G, Zorzi M, Corbetta M. The secret life of predictive brains: what's spontaneous activity for? *Trends Cogn Sci*. 2021;25(9):730-743. doi:10.1016/j.tics.2021.05.007"

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Adapted from "Corbetta M, Akbudak E, Conturo TE, et al. A Common Network of Functional Areas for Attention and Eye Movements. *Neuron*. 1998;21(4):761-773. doi:10.1016/S0896-6273(00)80593-0" and "Corbetta M, Patel G, Shulman GL. The Reorienting System of the Human Brain: From Environment to Theory of Mind. *Neuron*. 2008;58(3):306-324. doi:10.1016/j.neuron.2008.04.017"

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Adapted from "Celli M, Mazzonetto I, Zangrossi A, Bertoldo A, Cona G, Corbetta M. One-year-later spontaneous EEG features predict visual exploratory human phenotypes. *Commun Biol*. 2022;5(1):1361. doi:10.1038/s42003-022-04294-9"

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(b) Adapted from “Zangrossi A, Cona G, Celli M, Zorzi M, Corbetta M. Visual exploration dynamics are low-dimensional and driven by intrinsic factors. *Commun Biol*. 2021;4(1):1100. doi:10.1038/s42003-021-02608-x”

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2. Tables

Table I: Eye movements' features, corresponding statistical analysis code, and description.

Table II: Principal component analysis raw and rotated loadings.

Table III: Demographic characterization of the sample; Cognitive Measurements investigated by different parameters of tests scores.

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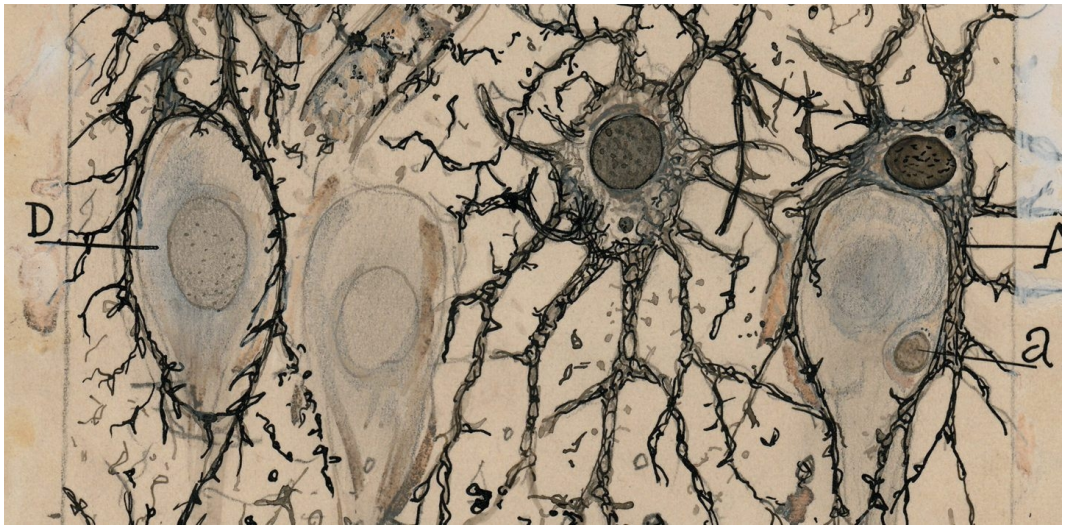
"Ciascuno di noi è una biografia, una storia. Ognuno di noi è un racconto peculiare, costruito di continuo, inconsciamente da noi, in noi e attraverso di noi – attraverso le nostre percezioni, i nostri sentimenti, i nostri pensieri, le nostre azioni; e, non ultimo, il nostro discorso, i nostri racconti orali. Da un punto di vista biologico, fisiologico, noi non differiamo molto l'uno dall'altro; storicamente, come racconti, ognuno di noi è unico".

Oliver Sacks



Santiago Felipe Ramón y Cajal