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BIOMARKERS OF COGNITIVE DEFICITS FOR ASSESSMENT AND REHABILITATION PROTOCOLS IN IMMERSIVE VIRTUAL REALITY

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Abstract

Existing evidence suggests that oculomotors and cardiac metrics may offer non-invasive, objective, real-time means to investigate attentional processes. Recording these measures in environments that closely resemble everyday life, such as immersive virtual reality (iVR), could enhance ecological validity and improve their reliability as clinical biomarkers. These methods could also address limitations of current neuropsychological tools and help in mitigating the pervasive consequences of attention impairments after acquired brain injuries. Therefore, the present work aimed at examining whether oculomotor and heart rate variability metrics, collected within newly developed iVR software, serve as reliable biomarkers of attention and as tools for diagnosis and prognosis. Chapter 1-4 provide a theoretical overview of the neuroscientific principles and neuropsychological challenges around which the thesis is based. Studies in chapters 5 and 6 demonstrated that heart rate variability and oculomotor metrics, collected in iVR, predict attentional performance and clarify how these biomarkers relate to distinct attentional processes. In addition, chapter 6 highlighted the specificity of a set of oculomotor metrics for targeting alertness, spatial and selective components of attention. Based on this evidence, chapter 7 and 8 applied the same iVR-oculomotor approach to patients with attention deficits after brain injuries. In detail, chapter 7 supports clinical translation by accurately distinguishing patients with and without attention deficits and by demonstrating a neuroanatomical foundation. Similarly, results in chapter 8 showed the feasibility of iVR-based rehabilitation to promote improvements in attention components, while concurrently using embedded oculomotor metrics to predict individual recovery trajectories. As discussed in chapter 9, these findings converge in underscoring the value of examining biomarkers within iVR to deepen understanding of their link with attention and to provide reliable methods for assessing, monitoring and rehabilitating attention impairments. Ultimately, the present evidence supports integrating these innovative methods into clinical practices to complement and enhance current neuropsychological procedures.

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Chapter 1

General Introduction

Everyday environment exposes us to a continuous stream of information that far exceeds our capacity to process it. To cope with this complexity, attention processes play a crucial role. Attention represents a fundamental set of neurocognitive mechanisms that enable individuals to be prepared for facing tasks, select relevant stimuli, and allocate limited cognitive resources across multiple activities (Bartolomeo, Thiebaut de Schotten, & Chica, 2012). From this perspective, attention can be better conceptualized as a multicomponent function with an intensity aspect, which determines how much attention is allocated to a given task regulating alertness and vigilance level, and a selection aspect, which allows the focalization of attention on relevant information, spatial location or multiple tasks while inhibiting the irrelevant ones (Posner & Boies, 1971; Posner, Snyder, & Davidson, 1980; van Zomeren & Brouwer, 1994). These multiple processes are underpinned by large-scale cortical networks (Petersen & Posner, 2012; Posner & Petersen, 1990). Particularly, the Dorsal Attention Network, anchored in the intraparietal sulcus and frontal eye fields, and the Ventral Attention Network, centered in the temporoparietal junction and ventral frontal cortex (Corbetta & Shulman, 2002, 2011) along with white matter tracts, including the Superior Longitudinal Fasciculus, as well as the Arcuate Fasciculus and the Inferior Fronto-Occipital Fasciculus, results as the core hub of attentional processing (Alves et al., 2022; Doricchi et al., 2008; Hattori et al., 2018; Thiebaut de Schotten et al., 2014; Umarova et al., 2014). These widespread attention-related neural correlates are highly vulnerable to disruption following acquired brain injuries. Consistently, between 46% to 92% of brain-lesioned patients show impairment in attention domain (Barker-Collo et al., 2009; Spaccavento et al., 2019). These pervasive alterations are commonly linked with disruption in everyday functioning, poorer rehabilitation outcomes, reduced return to work rates and limited social participation, ultimately leading to an overall reduction in quality of life for both patients and caregivers, with effects persisting in the long-term (Barker-Collo, 2009; Gilmore, Katz, & Kiran, 2021; Hyndman, Pickering, & Ashburtn, 2008; Mavroudis et al., 2024; Mellon et al., 2015; Ponsford et al., 2014; Rabinowitz & Levin, 2014). Current neuropsychological practice includes a variety of validated and standardized tools to detect and rehabilitate attentional deficits (Donders, 2020; Cicerone et al., 2019; Zucchella et al., 2018). However, traditional assessment protocols are primarily based on paper-and-pencil or computerized tasks that suffer from low ecological validity (Chaytor & Schmitter-Edgecombe, 2003; Negut et al., 2015; Tupper & Cicerone, 1990), higher variability in administration and scoring (Spreij et al., 2022), and limited sensitivity to the complexity of real-world attentional demands (Houggard et al., 2021; Pieri, Tosi, & Romano, 2023). In rehabilitation, while existing protocols show partial effectiveness, they are often suboptimal in intensity, duration and generalizability, with inconsistent outcomes, particularly at follow-up evaluations (Bogner et al., 2019; Goikoetxea-Sotelo & van Hedel, 2023; Loetscher et al., 2019; Mancuso et al., 2025). Immersive Virtual Reality (iVR) has recently emerged as promising tool in neuropsychology because with its features can potentially address many of these challenges. iVR enables the simulation of multimodal, dynamic, and ecologically valid scenarios that closely mirror real-life cognitive demands, while maintaining a high level of experimental control over stimulus presentation and performance monitoring, thereby increasing the reliability of acquired data (Parsons, 2016; Pieri, Tosi, & Romano, 2023). In rehabilitation, iVR increases the sense of presence, improving motivation and adherence to training protocols (Catania et al., 2024; Perez-Marcos, Sanchez-Vives, & Slater, 2012; Slater & Sanchez-Vives, 2016; Sanchez-Vives et al., 2010). It also enables high-dose and high-intensity practice, facilitating unsupervised and home-based sessions that enhance the continuity of the treatment also in chronic stages (Faria et al., 2018; Laver et al., 2025; Tieri et al., 2018). In addition, through adaptive adjustments of task difficulty and continuous feedback, it ensures that interventions remain optimally challenging and tailored to individual performance (Calderone et al., 2024; Riva et al., 2020; Senadheera et al., 2024). Furthermore, by simulating realistic contexts, iVR may increase the successful transfer of attentional improvements to daily functioning (Salatino et al., 2023; Serino et al., 2022). Finally, iVR can be more easily integrated with sensors to enable the collection of parameters known to be biomarkers of attentional processing, such as heart rate (HR), heart rate variability (HRV) and oculomotor metrics. HR and HRV are closely linked to cognitive workload (Castaldo et al., 2017; Delliaux et al., 2019; Luft, Takase, & Darby, 2009; Luque-Casado et al., 2016; Thayer et al., 2009), which in turn reflects an individual's capacity of alertness and sustained attention (Unsworth & Miller, 2021). According to the Neurovisceral Integration Theory, HR and HRV mirror the dynamic balance between sympathetic and parasympathetic activity under prefrontal cortical control (Thayer et al., 2009; Thayer & Lane, 2009). In this line, high HRV indicates efficient prefrontal inhibition of subcortical circuits and adaptive attention regulation, whereas low HRV reflects reduced cortical regulation, sympathetic dominance, and excessive cognitive effort (LeDoux, 1996; Thayer et al., 2009; Thayer & Lane, 2009; Wei et al., 2024). Therefore, HR and HRV provide peripheral markers of the efficiency of prefrontal-autonomic integration during cognitively demanding, making them valuable indicators for monitoring cognitive workload in neuropsychological settings. Oculomotor control and attentional network closely overlap (Corbetta et al., 1998; Rizzolatti et al., 1987) with several eye movements demonstrated to be linked with specific component of attentional processing. Pupil diameter, blink rate and fixation stability are modulated by changes in alertness and vigilance as a function of locus coeruleus-norepinephrine system (LC-NE) (Aston-Jones & Cohen, 2005; Joshi, Kalwani, & Gold, 2016; Unsworth & Robertson, 2017) and dopaminergic systems (Demiral et al., 2023; Demiral & Volkow, 2024). The analysis of first fixation direction, fixation asymmetry in count and duration between the two hemifields has been associated with alteration in spatial exploration strategies and slower reaction time in reaching lateralized targets (Kaufmann et al., 2020; Nardo et al., 2019; Paladini et al., 2019). Similarly, higher number of fixations, longer time to fix the target along with the higher number of re-fixations reveal lower top-down abilities and difficulties in selective attention (Stefani & Sauter, 2023). This evidence highlights the strength of using both cardiac and eye movement as more objective, real-time measures of attention functioning with potential application in rehabilitation and assessment protocol. The integration of these measures in iVR protocols can leverage the reliability of data acquired, thereby increasing their potential as reliable biomarkers of everyday functioning and rehabilitation outcomes. Therefore, the present work aims to develop and validate an iVR software for the assessment and rehabilitation of attentional processes, integrating cardiac and eye-tracking measures as objective biomarkers of cognitive performance. By collecting these physiological and oculomotor indicators during iVR-based tasks, the project seeks to identify reliable and sensitive markers of attentional abilities in both healthy individuals and patients with brain lesions. These biomarkers are expected to provide continuous and quantitative measures of attentional functioning, offering valuable information to be translated for both diagnostic and prognostic purposes in clinical practices. The use of iVR allows attention to be evaluated and trained within realistic and controlled environments, facilitating more ecological and personalized management strategies. Consistently, this work aims to provide empirical evidence supporting the integration of immersive technology combined with physiological biomarkers to enhance the accuracy of assessment and the effectiveness of rehabilitation in the current clinical practices for attentional disorders.

In more detail, chapter 2 provides a review of both historical and more recent conceptualization of attention, integrating cognitive and neural perspectives. It delineates the principal theoretical frameworks that have shaped the understanding of attentional processes and explores how lesions within the cortical and subcortical attentional networks contribute to specific patterns of functional impairment. Chapter 3 examines current neuropsychological tools for the assessment and rehabilitation of attentional deficits, highlighting their still present limitations and challenges to be faced. It presents then how the integrate features of immersive virtual reality tools can help in facing these challenges. In Chapter 4, a collection of evidence is presented to outline the key role of biomarkers in neuropsychology, with a specific focus on how heart rate variability (HRV) and oculomotor parameters have been empirically demonstrated to be closely linked to attentional processes. Importantly, Chapter 5 presents the results of an experimental study designed to investigate how HR and HRV are modulated during immersive virtual reality cognitive activities. The study further tests the hypothesis that in complex and realistic virtual scenarios, cardiac measures are influenced not only by cognitive workload but also by additional factors such as physical load. Chapter 6 reports the results of a large-scale study conducted in a healthy adult population, aimed at examining whether the analysis of multiple eye-tracking parameters recorded during immersive virtual reality attention assessment tasks can reliably predict individual attentional capacities across alertness, spatial, and selective attention domains. Notably, Chapter 7 extends this investigation to a clinical population, in which the same eye-tracking parameters identified as biomarkers of attentional capacities in healthy participants are examined in patients with clinically diagnosed attentional deficits. This chapter tests the sensitivity and specificity of combined eye metrics in detecting impairments within specific attention subcomponents, providing valuable insights into the possible application of these new tools for neuropsychological assessment. Furthermore, the study explores the associated cortical and white matter correlates underlying the disrupted oculomotor patterns. Finally, Chapter 8 presents the results of a feasibility study evaluating a newly developed immersive virtual reality rehabilitation protocol aimed at improving attentional performance in brain-lesioned patients. Furthermore, it investigates whether pre-intervention eye-tracking patterns can be used as predictive indicators of individual improvement trajectories, providing valuable insights into the personalization and optimization of neuropsychological interventions.

Chapter 2
Cognitive and Neural Architecture of Attention in healthy and lesioned brain

2.1. Taxonomies of Attentional Process

2.1.1. From the conceptualization of Attention as unitary process

We are constantly immersed in environments that generate a continuous stream of potentially meaningful information, including objects, people, sounds, and places. From this perspective, cognition can be seen as an *"integrated operation of fundamental processing mechanism which act upon, and are themselves acted upon, by the flow of information through the system"* (Williams et al., 1988, p.14). This definition captures the dynamic interaction between the cognitive system and the ongoing flow of information. However, even if information is continuously available, not all of it can be processed simultaneously. The brain, much like any other information-processing system, operates under limited resource capacities (Atkinson & Shiffrin, 1968) and only a subset of the available input can reach conscious awareness and guide our behavior. It is therefore essential to have a cognitive mechanism that allows resources allocation to relevant information while filtering out all the irrelevant input, thereby facilitating the managing of everyday task performance, but also flexible enough to detect other potentially meaningful signals within the continuous flow of information (Bartolomeo, Thiebaut de Schotten, & Chica, 2012). This foundational cognitive mechanism is attention that was defined by Posner, Snyder and Davidson (1980) as an *internal spotlight*.

<u>The Early-Selection Filter Theory and Stimulus-Driven Selection</u>

The first theorizations of attentional mechanisms proposed two main stages of information processing (Broadbent, 1958; Treisman & Gelade, 1980). The first stage allows the stream to be broken down into perceptual units based on a "pre-attentive" analysis. Following this first stage, a second, limited-capacity stage leads to more detailed processing of certain stimuli or locations through focused attention (Neisser, 1968). In 1958, Broadbent provided a unified framework in his Filter Theory of Attention positing that all stimuli presented at any time enters an "unlimited" capacity *sensory buffer* where information is processed based on their physical features (e.g., color, pitch, orientation, and intensity) and stored temporarily in immediate memory. The analysis of these physical features allows filtering out irrelevant information, so that the processing of semantic features (those based on the meaning of an object, such as the identity of a word; Neisser, 1968, p 209) is allowed only for the relevant ones which are then stored in long-term memory or used to formulate an appropriate response to the current tasks (Lachter, Forster, & Ruthruff, 2004). However, an early filtering selection was challenged by studies showing that unattended information can still be processed to some degree. For instance, in dichotic listening tasks, participants can notice when their own name was presented in the unattended ear (Moray, 1959) or followed the meaning of a sentence when it switched from the attended to the unattended channel (Treisman, 1960, 1964). Similarly, conditioned words presented in the unattended stream elicited changes in skin conductance (Corteen & Dunn, 1974), and ignored images slowed responses when they shared semantic properties with attended ones (Driver & Tipper, 1989; Dawson & Schell, 1982). These findings suggested that unattended inputs are not completely filtered out but may be attenuated.

Filter-attenuating Models and The Feature Integration Theory

Treisman (1964) addressed these issues with the attenuation theory, in which attention functions by enhancing relevant stimuli while reducing, rather than eliminating, irrelevant ones. Stimuli with low detection thresholds, such as one's own name, could still break through into awareness. This model is based on the Feature Integration Theory (FIT; Treisman & Gelade, 1980). According to FIT, features such as color, orientation, and motion are coded automatically, pre-attentively, and in parallel in distinct "feature maps" that are inaccessible to consciousness. In the second stage of processing, features are integrated ("bound") into meaningful objects that can be consciously perceived. Focused attention is then required to integrate these features into unified percepts. Evidence for this pre-attentive and later processing model came from visual search tasks: detecting a target defined by a single feature (e.g., a red letter among green letters) results in a rapid and parallel search meaning that reaction times are independent of the number of distractors and the target "pops out". In contrast, the detection of a conjunction target (e.g., a red "X" among green "T"s and red "O"s) is slower and increases linearly with the number of distractors, reflecting the need for attentional binding (Treisman & Gelade, 1980). In this model, although a predominant influence of bottom-up (i.e., stimulus-driven) factors in attention allocation were posited, top-down factors (i.e., goal-driven or knowledge-driven) influence which information will be under the spotlight and those attenuated.

Synergies of Bottom-Up and Top-Down Selection Mechanisms

The conceptualization of attention as an enhancement mechanism was further supported by visual paradigms. By presenting spatial cues that indicated where a target was likely to appear, Posner and colleagues showed that participants could proactively set an attentional template, shifting attention in advance to the expected location. Reaction times were faster for validly cued targets compared to invalidly cued ones, demonstrating that attention can be guided by internal goals and expectations (Posner, Snyder, & Davidson,1980). In the same setting, it was also demonstrated that unexpected, salient stimuli at uncued locations could capture attention exogenously, forcing reorientation and slowing responses. This balance between endogenous (goal-driven or top-down) and exogenous (stimulus-driven or bottom-up) orienting captured the dual nature of attentional control. The psychological models proposed by Treisman and Posner were later supported and refined by neurophysiological evidence. Moran and Desimone (1985) recorded from neurons in area V4 of macaque while two stimuli were presented within a single receptive field. They found that when attention was directed to the preferred stimulus, neuronal responses were strong, but when attention was directed to a non-preferred stimulus, responses to the preferred stimulus were suppressed. This showed that attention can act as a gain-control mechanism, enhancing neural processing of attended stimuli while reducing responses to unattended ones, even within the same receptive field. Building on these findings, Desimone and Duncan (1995) proposed the *biased competition model* of attention. According to this framework, multiple stimuli in the visual field compete for limited neural representation, and attention biases this competition in favor of behaviorally relevant items. This model accounts for spatial, feature-based, and object-based attention: in all cases, top-down signals amplify the neural representation of selected stimuli, allowing them to dominate over competitors (Wu, 2024). Finally, neuroimaging studies in humans have confirmed that attention selectively modulates activity in category-specific cortical areas. In a seminal fMRI experiment, O'Craven, Downing, & Kanwisher (1999) presented participants with superimposed images of faces and places and instructed them to attend selectively to one category while ignoring the other. They found that attending to faces reliably increased activation in the fusiform face area (FFA), whereas attending to places enhanced responses in the parahippocampal place area (PPA), even though the visual input was identical across conditions. This result demonstrated that attention does not simply enhance perception globally but can bias processing toward task-relevant categories by modulating activity in specialized cortical regions.

2.1.2. Toward a multidimensional model of attention processes

Although classical models effectively describe the filtering or spotlight role, they primarily capture one subcomponent of attentional processing: the selection. However, attentional phenomena cannot be subsumed under a single concept, while are better characterized as a set of distinct, though interacting, neurocognitive mechanisms (Bartolomeo, Thiebaut de Schotten, & Chica, 2012; Leclercq & Zimmermann, 2002; Lindsay, 2020; Loetscher et al., 2019; Parasuraman, 1998; Posner & Petersen, 1990; Spaccavento et al., 2019). In accordance with multidimensional frameworks of Posner & Boies (1971), Posner & Rafal (1987) and Van Zomeren & Brouwer (1994), attention can be better divided into two broad subsystems. The first concerns the intensity aspects, encompassing processes one such as alertness, vigilance and sustained attention. The second involves the *selection aspects,* which include selective and divided processes. Building on Shallice's (1982) model of the *Supervisory Attentional System*, strategy and flexibility have been integrated into this conceptualization, as high-order components of attentional control (Leclercq & Zimmermann, 2002; Zimmermann & Fimm, 1994).

Intensity Aspects

Intensity refers to how much attention is allocated to a given task, corresponding to the attentional effort (Kahneman, 1973, p.4) and it is consistent with the conceptualization of mental effort and cognitive workload (Matthews & Reinerman-Jones, 2017; Unsworth & Miller, 2021). *Alertness,* being conceptualized as a basal function of arousal, represents the more basic intensity aspect of attention, and therefore a prerequisite for every attention performance (Sturm et al., 1997; Sturm et al., 2004). Posner and Boies model (1971) describe firstly a tonic component of alertness, representing the general state of wakefulness with a characteristic circadian variation. Tonic alertness' levels can be controlled by top-down processes (i.e., endogenous factors) in self-initiated preparation for an incoming, expected stimulus and it is typically assessed by simple reaction times to visual or auditory stimuli without warning signal (Sturm et al., 2003; Weis et al., 2000). On the other hand, alertness can physically increase efficiency for a short period of time in response to a cue, a warning stimulus in the same or different sensory modality, which closely precedes the target stimulus (i.e., bottom-up processes or exogenous factors; e.g., see Leclercq & Zimmermann, 2002; Posner & Boies, 1971; Sturm et al., 2001; Sturm et al., 2004). This optimization constitutes a voluntary, sudden and transitory change, representing a function of a central mechanism allowing the programming of a response to the information. In addition, it was shown that this increased capacity occurs from 100 milliseconds after the signal beginning and being maximal between 500 and 1'000 milliseconds corresponding to faster reaction times across this time window (Posner and Boies, 1971).

Maintaining a certain level of alertness over a long period of time determines what is known as sustained attention or vigilance. Although the two terms are frequently used as synonyms, they capture two different as well as important aspect of attention processes. In this line, the difference between these two attentional processes lies in the frequency with which target stimuli are presented and must be responded to. Under vigilance conditions, critical conditions have a very low frequency of occurrence, thus resulting in monotonous situations which pose the need for higher top-down regulation to maintain adequate levels of alertness through the whole task duration (Sturm et al., 1999; Spaccavento et al., 2019). In contrast, performing long-lasting tasks with a considerably higher frequency of targets occurrence requires sustained attention. Accordingly, a signal detection analysis of standard vigilance tasks in comparison to more cognitively demanding tasks exhibited that the decrement in the vigilance task is due to a criterion shift, that is, the subject is no longer responsive, while the reduced performance in tasks with more frequent critical signals and higher cognitive load is due to a decline in perceptual efficiency, that is, a loss of sensitivity due to fatigue leading to the so call time-on-task effect or the higher missed and false alarm with time (Mangin et al., 2022; Krämer et al., 2023). The dissociation between vigilance and sustained attention was also revealed from studies in brain-injured patients. The results highlight how patients performing the Sustained Attention to Response Task (SART), in which the subjects have to respond as quickly as possible to targets presented with a high frequency, but has to inhibit the response to rare uncritical stimuli have an impaired performance compared to healthy participants (Robertson et al., 1997). While the performance remains comparable to healthy subjects in case of long, but monotonous tasks (see Leclercq & Zimmermann, 2002). Therefore, it can be concluded that brain-injured patients have frequently been observed to do well when the flow of information is slow and the targets are rare (i.e., vigilance tasks) and poorly when there is much information to process in a continuous stream (i.e., sustained attention tasks).

<u>*Selection Aspects*</u>

The selection aspect broadly reflects which stimuli, spatial locations, or tasks should receive attentional focus and which instead should be inhibited (Zimmermann & Fimm, 1994). The selection process could be location-based, whereby attention focus is direct toward a specific portion of space which is behaviorally relevant compared to its surroundings, a process known as *spatial attention* (Bartolomeo, Thiebaut de Schotten, & Chica, 2012; Corbetta & Shulman, 2011; Petersen & Posner, 2012; Posner, Snyder, & Davidson, 1980; Wolfe, 2018). In the classical Posner cueing paradigm, a central cue biases participants to expect a target on the left or right side of the visual field. Such cueing facilitates behavioral performance and is accompanied by stronger activation in visual cortex corresponding to the attended location, with retinotopic precision. Consistently, Gandhi, Heeger, and Boynton (1999) directing attention to a cued position in the visual field selectively increased responses in the corresponding region of V1, while activity in non-matching cortical sectors remained unchanged. This demonstrates that spatial attention enhances neural processing at relevant locations while leaving unattended regions unaffected (Ghandi, Heeger, & Boynton, 1999).

In addition, selection process can be also feature-based, prioritizing specific attributes of objects that are relevant for the current task, defining what is commonly known as *selective attention*. Neuroimaging studies by Corbetta and colleagues (1990, 1993) provided the first evidence that feature-based attention modulates specialized extrastriate regions: attending selectivity for color, increased the activity within ventral occipitotemporal cortex (V4), attending to motion enhanced responses in dorsal areas (MT/V5), and attending to shape engaged lateral occipital cortex, even though the visual input was unchanged. Electrophysiological recordings in macaques extended this principle, showing that directing attention to a motion direction increased the gain of MT neurons tuned to that direction, while responses to non-preferred directions were suppressed (Treue & Martínez-Trujillo, 1999). More recently, Duecker and colleagues (2025) used magnetoencephalography combined with frequency tagging to show that target-defining features such as color boost neural excitability in early visual cortex, while irrelevant features are actively suppressed even before the target appears.

The way by which this selection process is deployed, can be either covertly, without direct motor actions, or overtly, when it is accompanied by motor responses such as eye or body movements (Corbetta, 1998; Posner & Petersen, 2012; Rizzolatti et al., 1987). According to the premotor theory of attention (Rizzolatti et al., 1987), orienting toward an object or spatial location reflects the preparation of an action directed at that target, even if no movement is ultimately carried out. In everyday life, this mechanism is expressed not only through eye movements, which serve to foveate behaviorally relevant sources of information where visual processing is most precise (Pasqualette & Kulke, 2024), but also through the preparation of motor acts such as reaching, grasping, or manipulating objects. In this sense, attentional selection reallocates resources in anticipation of appropriate behavioral responses, thereby linking perceptual processes with goal-directed action (Allport, 2016). Finally, the decision regarding toward which or where allocating these resources can be biased either by top-down control (i.e., selection based on prior knowledge and current goals), or by bottom-up capture (i.e., salient or unexpected stimuli attract attention regardless of task relevance), supported by partially segregated neural systems (Corbetta & Shulman, 2002; Posner, Snyder, & Davidson, 1980). As widely discussed in the previous section (see section 2.1.1. "*From the conceptualization of Attention as a unitary process*"), selective attention has traditionally been regarded as the defining feature of attentional function. While indispensable for adaptive behavior, it constitutes one functional domain of attention, tightly interconnected with the other components operating in synergy to support attentional processes.

Going higher across the selection aspect of attention, Van Zomeren & Brouwer model (1994) describe the capacity of selecting tasks. In this perspective, *divided attention* represents the ability to perform two tasks simultaneously, either within the same sensory modality or across different modalities (Spaccavento et al., 2019). Two of the most influential theoretical accounts of this capacity are the central capacity theory and the multiple resource theory (Leclercq & Zimmermann, 2002).

The central or single capacity theory postulates the existence of a single, limited pool of general attentional resources that can be flexibly distributed across tasks. The availability of this pool varies as a function of arousal, motivation, and effort. As long as the combined demands of concurrent tasks remain within this global capacity, performance can be maintained; however, when requirements exceed it, interference emerges, and performance deteriorates. Classic dual-task paradigms support this view: for example, when participants were required to perform a continuous tracking task while simultaneously engaging in mental arithmetic, performance in one task declined as the difficulty of the other increased (Kahneman, 1973). More recent neuroimaging evidence confirms the idea of a shared limitation, showing that under dual-task conditions, prefrontal control regions exhibit capacity-related overload consistent with a central bottleneck (Marois & Ivanoff, 2005; Hashemirad Vaziri-Pashkam, & Abbaszadeh, 2025).

By contrast, the multiple resource theory (Wickens, 2008) argues that attentional resources are not unitary but are instead organized into distinct pools specialized for different modalities (e.g., visual vs. auditory, spatial vs. verbal). Interference therefore arises only when two tasks compete for the same pool. Allport, Antonis, and Reynolds (1972) demonstrated that participants could shadow spoken words while simultaneously recognizing visually presented words with little cost, whereas performance deteriorated when both tasks relied on auditory-verbal processing. More recent work has updated this account, showing that interference patterns are best predicted by the degree of resource overlap, with dual tasks across modalities producing less conflict than tasks within the same modality (Wickens, 2008; Wickens, 2024).

A further refinement was introduced by Hirst (1986), who replaced the concept of resources with that of skills, suggesting that the ability to perform multiple tasks depends on the degree of automatization acquired through practice. Spelke, Hirst, and Neisser (1976), for example, demonstrated that after extensive training participants could take dictation while reading aloud unrelated texts, two tasks that initially interfered heavily with each other. More recent studies confirm this principle, showing that training reduces reliance on prefrontal control and reallocates processing to domain-specific cortical networks, thereby reducing attentional costs (Chein & Schneider, 2012; Patelaki et al., 2023).

As an additional adaptive mechanism, the concept of time-sharing has been proposed. Time-sharing refers to the rapid alternation of attention between tasks rather than true parallel processing. Hirst (1986) emphasized that time-sharing should not be considered genuine divided attention but rather a manifestation of the flexibility of the attentional system in adapting to complex situations. In this view, attention is not literally split across tasks, but is instead repeatedly shifted from one to another, with each receiving brief intervals of focused processing.

To conclude, the model of van Zomeren & Brouwer (1994) emphasizes the variety of attentional processes and highlights the importance of adopting a multidimensional approach to studying these phenomena. Correspondingly, at the neural level, evidence shows that different brain networks support the distinct subcomponents of attention. In this perspective, attentional processes arise both from the specialized functions of these regions and from their complex interplay (Corbetta & Shulman, 2002, 2011; Doricchi et al., 2008).

2.2. Neural Correlates of Attention

2.2.1 Cortical Networks of Attention

Firstly in 1990 and later revised in 2012, Posner and Peterseen proposed an influential framework accounting for the cortical correlates of the different attention components. In this line, they describe three networks of the attention systems.

The *Alerting System* is closely linked to brain regions and pathways responsible for generating surges of arousal that is the base of producing and maintaining optimal alertness and vigilance level, ultimately being linked with the intensity aspects of attention. The conceptualization is grounded in earlier evidence showing that several central arousal systems arise from brainstem nuclei (Moruzzi & Magoun, 1949), among them the locus coeruleus-norepinephrine (LC-NE) system is responsible for most of the NE released in the brain (Aston-Jones & Cohen, 2005). The LC projects widely across the neocortex, including areas within the fronto-parietal and saliency networks, and it also receives substantial input from the prefrontal cortex (Unsworth & Robison, 2017). Particularly, through a coeruleo-cortical pathway involving the superior colliculus and thalamus, LC modulates attentional function (Wang & Munoz, 2015). Additionally, the LC receives afferent projections from ventral prefrontal regions such as the ventro-medial prefrontal cortex (vmPFC), the anterior cingulate cortex (ACC), amygdala, hypothalamus, and neighboring brainstem structures, which can drive LC-NE upregulation linked to increases in subjective value (Bast, Poustka & Freitag, 2017).

LC-NE neurons operate in two distinct firing modes, closely resemble the concept of tonic and phasic alertness describing in van Zomeren and Brouwer model of attention (1994). Tonic firing of LC-NE neurons fluctuates with circadian rhythms and reflects an individual's general cortical arousal state, conversely absent during sleep (Aston-Jones & Cohen, 2005; Joshi, Kalwani & Gold, 2016). Phasic firing of LC-NE neurons occurs during processes that involve attention, such as those required to perform voluntary behavior. Particularly, a warning signal is accompanied by activity in LC-NE (Aston-Jones & Cohen, 2005; Petersen & Posner, 2012), while this phasic activation can be blocked by drugs, such as guanfacine and clonidine, which contrast NE release (Petersen & Posner, 2012; Posner & Petersen, 1990). Electrophysiological studies show that P300, a positive wave component occurring 300 msec post stimulus presentation, is related to LC-NE system and linked to cortical updating (Nieuwenhuis, Aston-Jones & Cohen, 2005). The balanced activation between tonic and phasic firing has been shown to enhance signal to noise ratio in target neurons by decreasing spontaneous firing and by potentially increasing firing for salient events (Howells, Stein & Russel, 2012). There is an inverted-U relationship between LC tonic activity and performance on various cognitive tasks consistent with the Yerkes-Dodson curve (Yerkes & Dodson, 1908). Specifically, it is assumed that when tonic LC activity is low (hypoarousal), individuals are inattentive, non-alert, and disengaged from the current task leading to poor behavioral performance and little to no phasic LC activity in response to task-relevant stimuli. As tonic LC activity increases to an intermediate range (phasic mode), attention becomes more focused, LC phasic activity increases for target stimuli, and behavioral performance is optimal. The LC-NE system seems particularly sensitive to salient task-related stimuli that results in increased phasic activity to those stimuli when tonic activity is at intermediate levels (Aston-Jones & Cohen, 2005). However, as tonic LC activity increases further, the individual experiences a more distractible attentional state (hyperarousal and stress), leading to task disengagement, lowered LC phasic activity, and a reduction in behavioral performance (Unsworth & Robinson, 2017).

While the alerting system is closely thought to support the intensity aspects of attention, the second system conceptualized by Petersen and Posner (1990, 2012) seems to be linked to the selection aspects: *the Orienting System*. Based on the evidence of a series of imaging experiments using cuing paradigms in combination with event-related fMRI, Corbetta & Shulman (2002) proposed that orienting (i.e., the decision on which stimuli, spatial locations, or tasks toward which focused attention) is controlled in humans by two interacting networks. A bilateral Dorsal Attention Network (DAN) involving primarily the Frontal Eye Field (FEF) and the Intraparietal sulcus/Superior Parietal Lobule (IPs/SPL) and a mostly right-lateralized Ventral Attention Network entails such as the TPJ, temporoparietal junction (IPL/STG, inferior parietal lobule/superior temporal gyrus) and VFC, the ventral frontal cortex (IFg/MFg, inferior frontal gyrus/middle frontal gyrus) supports both the features-based and spatial-based selective attention (Corbetta & Shulman, 2002, 2011).

Neuroimaging studies described that brain regions across the DAN show a bilaterally sustained activation after the presentation of symbolic cues to shift attention voluntarily to a location. This pattern of sustained activation is thought to be involved in the maintenance of the attentional set, a mental representation spatial location or features that are relevant for the ongoing task performance (i.e., top-down regulation). These results emphasized the role of DAN in preparatory aspects of stimulus selection (Corbetta & Shulman, 2002, 2011). However, this network is also involved in the response or action selection process. Evidence in this direction shows that eye- and arm-related activity increased the activation of DAN regions. According to the premotor theory of attention (Rizzolatti et al., 1987), this overlap between regions responsible for orienting attention and those involved in action planning reflects the intrinsic link between attending to an object and preparing to act upon it. Neurophysiological studies indicate that the dorsal frontoparietal network, which is predominantly recruited for top-down selection, is also modulated by the bottom-up distinctiveness of objects in a visual scene (Corbetta & Shulman, 2011). In this line, it was shown that FEF is involved in generating the salience (activation) maps, which combine bottom-up with top-down information to represent visual objects of interest.

On the other hand, VAN are recruited when sensory stimuli of potentially high behavioral significance, particularly for unattended or low-frequency events, are presented in the scene with the consequence that the ongoing cognitive activity is interrupted. Corbetta & Shulman (2002) defined the VAN as a "circuit-breaking" that has the main role of directing attention towards stimuli that are outside the focus of processing. In cuing paradigms, it was shown that TPJ-VFC link activation is right-lateralized enhanced whether a stimulus appears in a spatial location different from the one previously indicated by the informative cue.

While both networks exhibit distinct proprieties, current theory suggests that attentional capacities originate from their mutual interaction rather than their functional independence. One of the main hypotheses is that encoding processing priorities may take place in the DAN based on both top-down and bottom-up factors (i.e., Priority Maps; Ptak, 2012), while the detection of distinctive events could be initially implemented in the VAN (Corbetta & Shulman, 2011). These detection signals would then contribute to updating Priority Maps in the DAN via inter regional communication (Doricchi et al., 2008) that ultimately allocate attention resources and planned the better action to be implemented towards the stimuli.

The final network was originally defined as a target detection network (Posner & Petersen, 1990) and subsequently defined as *Executive Control System* (Petersen & Posner, 2012). The executive control network results essential for monitoring and managing conflicts between different brain regions, regulates functions such as planning, decision-making, error detection, handling novel or non-routine responses, emotion regulation, and the inhibition of habitual behaviors (Raz & Buhle, 2006). Crucial nodes of this network are identified in the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC). The ACC is primarily responsible for managing cognitive conflicts, such as those arising from incongruent cues, whereas the DLPFC plays a fundamental role in heteromodal decision-making processes, including the resolution of cognitive conflicts. Specifically, the dorsal portion of the ACC (dACC) is activated during tasks involving motor response conflicts rather than stimulus-related conflicts, while the rostral portion (rACC) becomes engaged following error detection (Raz & Buhle, 2006). The original executive network system, known as the cingulo-opercular system (comprising the medial frontal cortex, anterior cingulate cortex, and bilateral anterior insula), is associated with maintaining task parameters and exerting top-down control. Alongside it, a second circuit has been identified, involving the lateral prefrontal cortex and the parietal cortex: the frontoparietal system. This network is thought to play a role in task switching, initiation of activity, and real-time trial-by-trial adjustments (Petersen & Posner, 2012). Finally, the mesocortical dopaminergic system, through its projections to the ACC and DLPFC, plays a key role in supporting the functions of the executive network (Raz & Buhle, 2006).

While cortical regions play a fundamental role in the control of attention, these processes also rely on the integrity of underlying white matter pathways. These tracts provide structural connectivity that allows distributed attentional networks to operate as a coordinated system (Doricchi et al., 2008).

2.2.2. White Matter Tracts Underlying Attention

Most of the evidence that allows the construction of the previously described cortical structural correlates of attention processes came from neuroimaging and neurophysiological studies on healthy participants and monkeys. However, an important contribution on the understanding of the underlined neural substrate of attention also came from studying patients with specific attention disorders. Particularly, extensive research has been conducted on Unilateral Spatial Neglect (USN), a syndrome in which patients fail to orient and respond to stimuli presented in the space contralateral to the lesion (Heilman, Valenstein, & Watson, 2000; Cox & Davies, 2020; Kaiser et al., 2022; Serino et al., 2007). Along with a core spatial and selective attention deficits referred to the impairments of DAN and VAN brain regions (Corbetta & Shulmann, 2002, 2011), USN patients often show non-spatial related impairments as a general reduction in alertness and vigilance (Heilman, Valenstein, & Watson, 2000). These symptoms are largely associated with characteristic right-hemisphere lesions within the VAN. Supporting this view, neuroimaging studies of vigilance consistently demonstrate stronger activation in right-hemisphere regions such as the lateral prefrontal cortex, insula/frontal operculum, and TPJ.

More recently, the study of USN has moved toward a more disconnectionist approach, emphasizing that attentional deficits often arise not only from damage to a single cortical node, but also from disruption of the white matter pathways linking distributed regions (Alves et al., 2022; Doricchi et al., 2008; Hattori et al., 2018; Thiebaut de Schotten et al., 2014; Umarova et al., 2014). Specifically, within the DAN, the superior parietal lobule (SPL)/intraparietal sulcus (IPS) is connected to the superior frontal gyrus (SFG)/frontal eye fields (FEF) via the Superior Longitudinal Fasciculus (SLF I). Within the VAN, the inferior parietal lobule (IPL)/TPJ/superior temporal gyrus (STG) are connected to the middle and inferior frontal gyri (MFG/IFG) through the SLF III and the Arcuate

Fasciculus (AF). Furthermore, the MFG/IFG maintain connections with posterior temporal regions via the Inferior Fronto-Occipital Fasciculus (IFOF), while the Extreme Capsule (EmC) links the STG with the ventral frontal cortex and the Inferior Longitudinal Fasciculus (ILF) connects parahippocampal gyrus with the angular gyrus of the parietal lobe (Karnath et al., 2011; Urbanski et al., 2008; Umarova et al., 2010). In addition, as the connection between the DAN and the VAN, it is suggested that SLF II links the temporoparietal cortex including the angular gyrus with SFG/FEF, and IFOF connects MFG/IFG with SPL/IPS (Hattori et al., 2018). Converging evidence from lesion–symptom mapping studies indicates that attentional deficits in USN often result from damage to white matter tracts rather than isolated cortical regions (Doricchi et al., 2008; Karnath et al., 2011; Urbanski et al., 2008; Umarova et al., 2010). This has led to a shift toward a 'disconnectionist' framework, in which USN and other attentional disorders are understood as arising from disruptions in large-scale network connectivity rather than from the dysfunction of single brain areas (Alves et al., 2022; Doricchi et al., 2008; Thiebaut de Schotten et al., 2014). Consistently, patients with traumatic brain injury (TBI) often present with persistent vigilance and sustained attention deficits, which have been linked to diffused axonal injury and white matter disconnection within fronto-parietal and subcortical pathways (Bonnelle et al., 2011). From this perspective, the study of white matter integrity provides a powerful framework for understanding how attentional processes emerge from the communication across distributed brain networks.

Given this widespread and complex distribution of attention-related brain regions, attention impairments are frequently reported after an acquired brain injury.

2.3. Attention-related impairments in lesioned brain

An acquired brain injury (ABI) refers to damage to the brain that occurs after birth not caused by hereditary factors, congenital conditions, degenerative processes, or birth trauma. ABI can arise from traumatic and non-traumatic causes. (Feigin et al., 2014). Traumatic brain injury (TBI) occurs when the brain is harmed by an external mechanical force. (Feigin et al., 2014). On the other hand, non-traumatic brain injury is caused by illnesses or diseases of the brain, rather than physical trauma. Examples of non-traumatic causes of ABI include cerebrovascular diseases like strokes (Watson et al., 2020). A stroke is an interruption of blood flow to the brain caused by a blockage or by a rupture of blood vessels leading to brain damage (Kuriakose & Xiao, 2020). Other non-traumatic causes include tumors, vascular malformations, and cerebral infections. (Watson et al., 2020).

ABI exerts a profound impact on an individuals' lives, affecting cognitive, behavioral, psychosocial, and physical domains (Barman, Chatterjee, & Bhide, 2016). Among these disabilities, cognitive disorders are one of the most impacting and distressing for the patients (Peeters et al., 2015; Rabinowitz & Levin, 2014; Watson et al., 2020), with attention impairments being some of the most commonly reported. In this line, clinical studies report that attentional difficulties occur in 46% to 92% (Barker-Collo et al., 2009; Spaccavento et al., 2019), up to 60% of patients with TBI (Tsai et al., 2021) and approximately 80% of those diagnosed with brain tumors (Tucha et al.,2000) demonstrate difficulties in focusing on tasks for an extended period (i.e., alertness and vigilance), selecting relevant information without distractions (i.e., spatial and selective attention), and performing two tasks simultaneously (i.e., divided attention). In addition, around 30% of ABI patients experience USN (Esposito, Shekhtman, & Chen, 2021). From a clinical perspective, attention deficits are especially critical because attention functioning represents the foundation for higher-order cognitive functions, such as memory, executive control, decision-making, and planning (Leclercq & Zimmermann, 2002). Consequently, impairments in attention often lead to pervasive disruptions in everyday functioning, including difficulties in learning, managing daily activities, and achieving independence (Barker-Collo, 2009; Hyndman et al., 2008). Consistently, have been shown that these deficits are associated with poorer rehabilitation outcomes, reduced return to work and education, limited social participation, and lower quality of life (Ponsford et al., 2014).

Crucially, these difficulties are not confined to the acute or sub-acute phase of recovery. A growing body of evidence shows that they often persist in the long term, with many patients experiencing enduring cognitive impairments for months, even years post-injury (Mellon et al., 2015; Ponsford et al., 2014). Such persistent deficits, together with psychological distress, contribute to poor quality of life and reduced functional outcomes well beyond the initial recovery phase (Rabinowitz & Levin, 2014; Mavroudis et al., 2024). The long-term impact of ABI is particularly severe in younger patients, for whom the injury disrupts key developmental milestones such as completing education and entering the workforce, thereby reducing socioeconomic opportunities compared to older patients (Gilmore, Katz, & Kiran, 2021). Beyond direct neurological damage, it is also recognized that psychological and emotional factors play a key role in recovery trajectories. Anxiety, depression, and subjective cognitive complaints can exacerbate attentional difficulties and worsen the quality of life and functional outcomes. For instance, strong correlations have been reported between Beck Anxiety Inventory scores, subjective cognitive impairment ratings, and the Neurobehavioral Symptom Inventory, suggesting that emotional distress and symptom perception may exacerbate the functional sequalae of attention impairments (Byrne et al., 2017).

With the proportion of individuals aged over sixty (Gimigliano & Negrini, 2017) and the number of ABI-related hospitalizations among young adults steadily increasing8, epidemiological projections indicate that the number of individuals affected by ABIs will continue to grow in the coming years (Gimigliano & Negrini, 2017; Wafa et al., 2020)

This rising burden places substantial challenges on healthcare systems posing the need to foster a reflection on the potential limitations of currently available assessment and rehabilitation procedures and to identify potential strategies and tools that can overcome such limitations. Identifying and applying such strategies is crucial to equip healthcare systems with the resources necessary to effectively meet patients' and families' needs, while mitigating the escalating socio-economic impact of these deficits.

Chapter 3[1]

Neuropsychological Assessment and Rehabilitation: current challenges and Immersive Virtual Reality solutions

The pervasive impact of attention impairments following acquired brain injuries (ABIs) underscores the need for sensitive assessment procedures as well as rehabilitation protocols able to attentional performance but also functional outcomes in everyday life.

3.1. State of the art in neuropsychology: limitations and challenges

3.1.1. Current neuropsychological assessment and rehabilitation protocols

Neuropsychological assessment, defined as the "normatively informed application of performance-based assessments of various cognitive skills" (Harvey, 2012; Pieri, Tosi, & Romano, 2023), plays a central role in the clinical management of patients with ABI. It provides a comprehensive characterization of cognitive functioning that not only supports diagnostic clarification but also constitutes the starting point for patients' access to rehabilitation pathways. By identifying both impaired and preserved cognitive domains, assessment establishes the baseline profile necessary for planning individualized rehabilitation programs. In addition, it contributes to the prediction of long-term outcomes, offering valuable prognostic information regarding recovery trajectories and everyday functioning, while also enabling clinicians to evaluate treatment effects and monitor both therapeutic benefits and possible adverse consequences of interventions (Casaletto et al., 2017; Donders, 2020; Harvey, 2012; Zucchella et al., 2018). The currently available assessment tools are founded on validated standardized psychometric tests that have proved reliability and validity in detecting attention deficits following ABIs.

Taking back the van Zomeren and Brouwer (1994) multicomponent model of attention (see Chapter 2, section 2.1.2: *"Toward a multidimensional model of attention"*), a wide range of neuropsychological tests are available to assess each attentional subcomponent. Starting with the intensity aspect of attention, alertness capacities are commonly evaluated using computerized paradigms based on a Simple Visual Reaction Time paradigm (SVRT; Barbarotto et al., 1998), in

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Part was also used to construct a Point of view (POV) in "Catinari, L., Crottaz-Herbette, S., Zeugin, D., Defferrard, L.., Perez-Marcos, D., Bertini, C., & Serino, A. (2025). Breaking Barriers in Neurorehabilitation: Exploiting the potential of Immersive Virtual Reality Solutions", currently submitted and under revision in Neurorehabilitation and Neural Repair.

which participants should respond as fast as possible to the appearance of a target stimulus. To assess the phasic component of alertness, a warning cue is typically presented before the target stimulus.
The *Symbol Digit Test* (SDT; Amodio et al., 2002) and *the Digit Symbol Test* (DST; Amodio et al., 2002) are frequently to measure what is generally referred to as speed of processing, though they are also employed as indicators of vigilance and sustained attention. These are two mirror versions in which the participant must associate each symbol with its corresponding number. The test consists of five rows, each containing 25 boxes, for a total of 125 boxes. At the top of the sheet, there are nine symbols, each linked to a specific number. Below, there are boxes containing symbols, and the participant's task is to write the correct number corresponding to each symbol by referring to the key at the top.
The examiner fills in the first three boxes, and the participant completes the next seven boxes as a practice trial. Starting from the eleventh box, the number of correctly matched items is counted within 90 seconds. Other well-established examples of tests used for the evaluation of vigilance and sustained attention capacities are the *Concentration Endurance Test* (d2 Test; Brickenkamp, 1998), *the Ruff 2 and 7 Selective Attention Test* (Ruff et al., 1992), and the *Sustained Attention to Response Test* (Robertson et al., 1997).
Regarding the selection aspect of attention, spatial attention is commonly assessed using the *Behavioral Inattention Test* (Wilson, Cockburn, & Halligan, 1987). BIT is divided into two subtests: Conventional and Behavioral. The BIT Conventional subtest consists of 6 items: line crossing, letter cancelation, star cancellation, figure and shape copying, line bisection, and representational drawing. The BIT Behavioral subtest consists of 9 items: pre-scanning, phone dialing, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation, and card sorting. For selective attention, the *Stroop Color Word Test* (Stroop, 1935) is among the most frequently employed tools. It comprises three subtests requiring participants to focus on task-relevant but less automatic responses (i.e., naming the ink color of words rather than reading the words themselves). Another widely used measure is the *Attentive Matrices test*, in which participants are asked to find targeted numbers among distractors (Spinnler & Tognoni, 1987).
The *Trail Making Test A and B (TMT-A and TMT-B;* Amodio et al., 2002; Giovagnoli et al., 1996) are often used in clinical settings to assess both selective attention and divided attention abilities. In TMT-A, participants are asked to connect a series of numbered circles in ascending order, assessing visuospatial detection, numerical recognition, sequencing, visuomotor coordination, and processing speed. In TMT-B, participants alternate between numbers and letters in ascending order, a task that additionally measures mental flexibility, as it requires managing multiple stimuli and shifting between

two cognitive sets. This variant often results in rule violations, errors, or slower performance (Vallar et al., 2012).

The *dual-task paradigm* is the most common method for assessing divided attention. In this approach, participants perform a primary and a secondary task simultaneously, allowing for the evaluation of attentional resource allocation. The *Paced Auditory Serial Addition Task* (PASAT; Gronwall, 1977) is also frequently employed to assess divided attention as well as working memory abilities. During the PASAT, auditory stimuli consisting of a list of 60 numbers (ranging from 1 to 9) are presented, and participants must add each number to the one that immediately follows, responding aloud. In addition to traditional paper-and-pencil tests, computerized test batteries have been developed to evaluate the different subcomponents of attention along with other cognitive domains. Two well-established examples include the Test of Everyday Attention (TEA; Robertson et al., 1996) and the Test of Attentional Performance (TAP; Zimmermann & Fimm, 2002). The TAP, in particular, includes fourteen subtests covering the full spectrum of attentional components (https://www.psytest.net/en/test-batteries/tap/subtests).

Neuropsychological rehabilitation, on the other hand, is recognized as one of the most significant health strategies for managing ABIs (Gimigliano & Negrini, 2017). It is generally defined as a set of multidisciplinary interventions aimed at minimizing disability and optimizing functional outcomes in individuals with health conditions, while taking into account the interaction between cognitive deficits, personal resources, and environmental demands. In this sense, rehabilitation aims to provide structured activities, based on well-established theories about cognitive functioning, with adequate quantity and quality to facilitate neuroplasticity and recovery (Gunduz, Bucak, & Keser, 2023).

Several rehabilitation protocols are currently available for the remediation of attention deficits. Among these, the Attention Process Training (APT; Sohlberg & Mateer, 1987, 2001) represents one of the most established approaches. The program is based on a hierarchical, multilevel system designed to rehabilitate attention deficits in patients with brain injuries. According to the authors, attention is hierarchically organized into five components: alertness, sustained attention, selective attention, alternating attention, and divided attention. Based on this hierarchy, functions requiring lower cognitive demand should be addressed before those that involve more complex processing; in other words, lower-level attentional processes must be trained prior to higher-level ones.

The APT also follows hierarchical progression within each attentional component: tasks begin with simple exercises and gradually increase in complexity. To progress to a higher level, participants must demonstrate a 35% reduction in task execution time compared to their initial attempt and achieve at least 85% accuracy.

A similar, yet computerized attention rehabilitation protocol was developed by Sturm and colleagues (2003), known as AIXTENT. In addition to direct attention training programs like APT and AIXTENT, other rehabilitation protocols are based on the hypothesis that generalized cognitive training, particularly targeting working memory, can produce broader improvements in attentional functioning. Examples include the rehabilitation version of the Paced Auditory Serial Addition Test (PASAT; Ciaramelli et al., 2006) and computerized interventions such as Cogmed Working Memory Training (Pearson Education Inc., Stockholm, Sweden) and RehaCom (Hasomed GmbH, Berlin, Germany).

Cogmed QM, designed for adolescents and adults, offers online, auto-adaptive serious games targeting visuospatial and verbal working memory. Each program consists of a set of standardized training games delivered in daily sessions of approximately 30-45 minutes, five days per week, over a 5-10 week period. Similarly, RehaCom is a comprehensive software system comprising over 30 adaptive modules designed to assist therapists in rehabilitating specific cognitive impairments across various domains, including attention, memory, perception, and activities of daily living. Previous studies have shown that RehaCom benefits stroke patients by improving working memory, processing speed, executive functions, and autonomy in daily activities (Amiri et al., 2023). Likewise, Cogmed has demonstrated effectiveness in enhancing working memory, attentional capacity, executive functions, and daily life functioning (Westerberg et al., 2007; Åkerlund et al., 2013).

Despite the increasing number of available assessments and rehabilitation protocols, and growing evidence supporting their capacity to ameliorate deficits and enhance detection sensitivity, their overall effectiveness remains variable (Cicerone et al., 2019; Loetscher et al., 2019). Furthermore, both assessment and rehabilitation procedures continue to face several significant methodological and practical limitations (Cicerone et al., 2019; Pieri, Tosi, & Romano, 2023).

3.1.2. Limitation and challenges in current practices

One major limitation relates to the overall small effect sizes often exhibited in current rehabilitation training outcomes (Goikoetxea-Sotelo & van Hedel, 2023), with benefits inconsistently observed across patients with similar neurological diagnoses (Kleim & Jones, 2008; Loetscher et al., 2019). In addition, improvements are not always maintained at follow-ups (Kleim & Jones, 2008). A plausible explanation for these limited outcomes can be found in the current discrepancies between experimental paradigms and routine clinical practice. In this line, in-clinic therapies often result in sub-optimal intensity and dosage, with guidelines strongly suggesting including additional hours in current rehabilitation protocols (Donnellan-Fernandez et al., 2023). The total number of training hours (dose) and the frequency of sessions per week (intensity) have been demonstrated as crucial factors for cognitive rehabilitation (Akerlund et al., 2013; Brady et al., 2022; Cicerone et al., 2019; Weicker et al., 2020). As part of the Rehabilitation and Recovery of peopLE with Aphasia after StrokE (RELEASE) project (Brady et al., 2022), the effect of dose and the intensity of speech therapy was studied in people with aphasia after a stroke. Overall, the results of the meta-analysis indicated that the best language recovery was associated with a higher dose (greater than 20 and up to 50 hours), increased intensity (3 to 5 days or more per week), and personalized speech therapy, compared with the typical clinical services reported internationally (Brady et al., 2022). Furthermore, a study conducted by Weicker et al. (2020) reports a significant dose effect in working memory (WM) rehabilitation. Indeed, they compared the effects of 10 versus 20 sessions of an intensive computerized training program targeting the different components of WM (*WOME, Working Memory; RehaCom®,* Hasomed GmbH, Berlin, Germany) in addition to conventional interdisciplinary neurorehabilitation. They observed a significant improvement in working memory with generalization to daily activities, but only after 20 sessions (self-measured with the Cognitive Failure Questionnaire 'CFQ'; Broadbent et al., 1982) (Weicker et al., 2020). Similar results were found by Akerlund and colleagues (2013) using *Cogmed Working Memory Training* (Pearson Education Inc., Stockholm, Sweden) in addition to standard rehabilitation. The high-intensive intervention group (30-45 minutes per day, 5 days a week, over 5-10 weeks) showed a significant post-intervention and 3-months follow-up improvements in Digit Span (forward and backwards), at the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS), at the Hospital Anxiety and Depression Scale (HADS) and at the Working Memory sub-scale of WAIS-III (Akerlund et al., 2013).

Another limitation often reported in the literature concerns the poor generalization of rehabilitation effects to daily functioning. Even when patients improve on targeted cognitive tests, these gains frequently fail to translate into meaningful changes in everyday life (i.e., generalization; Bogner et al., 2019; Mancuso et al., 2025). Generalization is closely linked to the possibility of experiencing meaningful and personally tailored contents, that align with individual's profile and mastery, within enriched environments (Cicerone et al., 2019; Gilmore, Katz, & Kiran, 2021; Mancuso et al., 2025). Such environments, which incorporate complex multisensory and spatial stimulation11, can maximize functional recovery by promoting synaptic plasticity through the synthesis of neurotrophic factors (Esposito, Shekhtman, & Chen, 2021). In this line, Bogner and colleagues (2019) found that increasing the time spent in contextualized treatment activities improved measures of community participation after discharge in TBI patients. Nevertheless, such ecologically valid contexts remain far removed from the traditional paper-and-pencil or computerized tasks that dominate current clinical practice.

Although existing evidence emphasizes the importance of appropriate dose, high-intensity, and ecologically valid treatments for recovery after ABI, their implementation remains limited. Barriers include restricted access to therapy centers, regional disparities in the availability of rehabilitation services, patients' limited adherence to prescribed treatment plans, and structural constraints such as insufficient financial resources and a shortage of qualified professionals (Cramer et al., 2019; Krakauer et al., 2021). Consequently, delivering high-dose, high-intensity, and individualized rehabilitation continues to be a major challenge in both sub-acute and chronic phases of ABI recovery.

Comparable limitations are also observed in the field of neuropsychological assessment. The major concern relates with its low level of ecological validity in predicting real-world performance (Chayton & Schmitter-Edgecombe, 2003; Negut et al., 2015; Tupper & Cicerone, 1990). Ecological validity comprises two dimensions: veridicality, referring to the extent to which test results predict everyday functioning, and verisimilitude, concerning the naturalness of the assessment and its capacity to reproduce the cognitive demands of real tasks (Negut et al., 2015). Conventional assessment tools, predominantly paper-and-pencil or computerized tests, are typically administered in highly controlled laboratory environments that fail to reflect the multisensory, dynamic, and contextually rich nature of daily life. Consequently, patients' cognitive behavior may not be fully captured during testing, as there is often a significant mismatch between test conditions and real-world demands (Chayton & Schmitter-Edgecombe, 2003). This incongruence may help explain the heterogeneity frequently reported in the prevalence of attention deficits (Kaufmann et al., 2020) and why subtle, yet clinically meaningful attention difficulties can go undetected by traditional methods (Hougaard et al., 2021). Further challenges arise from the potential for subjectivity in administration and scoring procedures, as these can vary between clinicians, introducing bias and reducing comparability across assessments (Spreij et al., 2022). Similarly, among the clinical practices, the same tests can be administered at different times (e.g., pre- and post-rehabilitation) with the risk of a learning effect that can confound outcome interpretation (Pieri, Tosi, & Romano, 2023; Serino et al., 2022).

In line with this evidence, the current challenge in neuropsychological assessment procedures lies in enhancing ecological validity, guaranteeing, at the same time, high control over stimuli administration and scoring procedures, ultimately augmenting the reliability of acquired cognitive measures.

Considering these limitations, neurotechnology and digital therapies might offer promising solutions for enhancing the integration of these features into the current standard assessment and rehabilitation interventions for ABIs management.

3.2. Immersive Virtual Reality for enhancing neuropsychological assessment and rehabilitation

Digital therapeutics (DTx) are defined as evidenced-based, clinically evaluated software designed to treat, manage and prevent a broad spectrum of medical conditions (Phan, Mitragotri, & Zhao, 2023). Examples of DTx include self-care apps for tailored treatments of mental health disorders and behavioral programs to treat drug addictions (Doumas et al., 2021; Tosto-Mancuso et al., 2022). Thereby, the specific characteristics of DTx activities vary based on the rehabilitation objectives and the technical specifications of the systems on which they are implemented (Riva et al., 2020). Among these different systems, virtual reality (VR) has emerged as a powerful tool for delivering DTx in the field of neurorehabilitation (Tosto-Mancuso et al., 2022). VR involves using a combination of hardware and software solutions creating a simulated environment where the user can interact in real time with artificial objects and agents. In neurorehabilitation, with the generic terms of "virtual reality", trails, meta-analyses and reviews often refer to any digital solution, including non-healthcare commercial digital tools. While such applications align with the technological definition of virtual reality (Amiri et al., 2023), they cannot be categorized as DTx, since they typically refer to games and platforms originally designed for entertainment purposes and then adopted for neurorehabilitation training. Using commercially available gaming consoles (e.g., PlayStation EyeToy, Nintendo Wii or Microsoft Xbox-Kinect) can lead to certain improvements, like any kind of generic stimulation. However, they lack the rehabilitation principles and guidelines that characterize DTx solutions, and thus their real effectiveness is questionable. Depending on the extent to which users perceive themselves as being immersed in the virtual environment rather than in the real world, three main types of VR-solutions have been defined: non-immersive, semi-immersive and immersive.

In non-immersive VR-solutions, users remain fully aware of the real-world surroundings, as these solutions are commonly accessed via computers or gaming consoles using 2D interface devices (e.g., mouse or keyboard).

Semi-immersive VR-solutions enhance the sense of immersion by projecting the virtual environment onto a computer screen. Although users still perceive the real world, the experience is augmented through advanced interface devices (e.g., cameras, cybergloves or haptic feedback devices) that enable dynamic interaction within the virtual environment. Both non-immersive (Akerlund et al., 2013; Amiri et al., 2023; Rozevink et al., 2021) and semi-immersive (Faria et al., 2018; Serino, A., et al., 2022; Serino, S., et al., 2017) VR-solutions, implemented in experimental paradigms, have proven to be effective either in promoting cognitive benefits or in detecting cognitive deficits post ABIs. Indeed, these first two classes of VR-solutions offer foundational features like the delivery of high-dose, high-intensity treatments, higher engagement in clinical procedures by using gamified activities, personalized activities and higher experimental control in administration procedure. These features provide the groundwork for the third type of VR-solutions, the fully immersive (iVR-solutions). IVR-solutions incorporate the core features of non-immersive and semi-immersive tools, while introducing unique attributes encompassing a heightened sense of flow, greater engagement and motivation, larger multisensory and spatial stimulation, and enriched environments enhancing ecological validity. Exploiting all together, iVR-solutions (Figure 1) may be a powerful tool for advancing rehabilitation and assessment, with the potential to address some of the above highlighted challenges currently faced in the field (Phan, Mitragotri, & Zhao, 2023; Pieri, Tosi, & Romano, 2023; Serino et al., 2022).

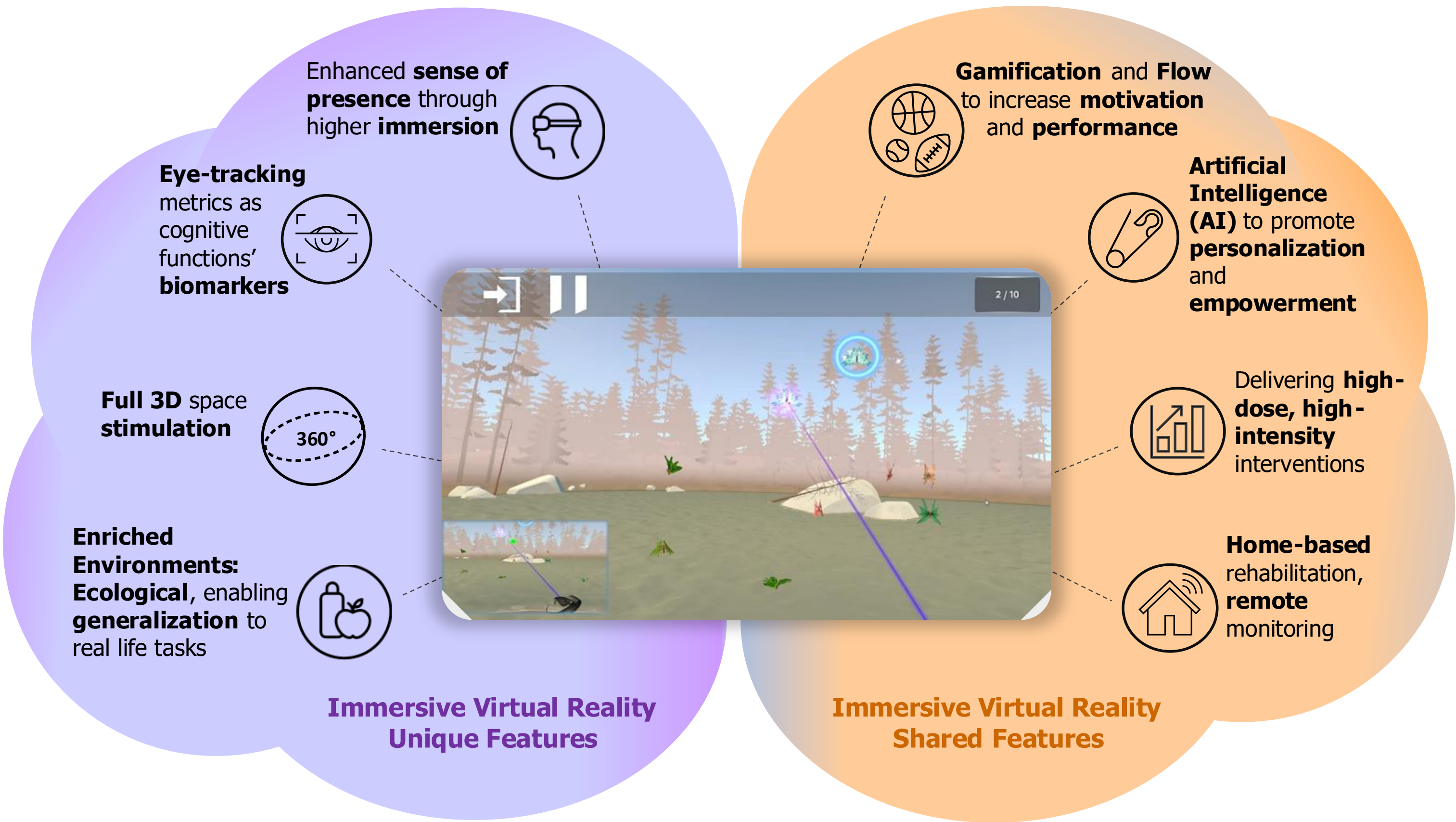


Figure 1. ***Description of the integrated features that characterized Immersive Virtual Reality (iVR) solutions****. On the left (in purple), the unique features introduced by iVR-solutions are highlighted. On the right (in orange), the elements shared across non-immersive, semi-immersive and iVR-solutions are outlined. In the center, an immersive virtual environment taken from MindFocus, an in development iVR-solutions for cognitive rehabilitation after ABIs (MindMaze, SA).*

3.2.1. Immersion and "sense of presence": increased flow state and intrinsic motivation

iVR-solutions delivered via Head-Mounted Displays (HMDs), provide multimodal (mostly visual and auditory) digital stimuli replacing those from the real world. Motion trackers detect the user's movements and position in order to update the virtual environment in near real-time based on user actions (Ma & Zheng, 2011; Rizzo, 2019). This way, key multisensory and sensory-motor integration mechanisms, which normally underline subjective experience in real world, can be manipulated to create a sense of embodiment in the virtual environment (Blanke, Slater, & Serino, 2015; Kilteni, Groten & Slater, 2012). In the context of iVR, visuo-motor congruence, where the movements of the tracked real body are reproduced in real-time by the movement of the virtual body (i.e., multisensory integration within the PPS; Blake, Slater, & Serino, 2015; Serino, 2019), the observation that one's own intention to move correspond to specific and predicted consequences in iVR, combined with the first-person perspective in which the user acts, generate ownership of the virtual body (i.e., sense of ownership / self-identification), the experience of being located at the virtual body's position (self-location) (Arzy et al., 2006; Kilteni, Groten, & Slater, 2012) and the feeling of controlling the virtual body (sense of agency) (Cornelio et al., 2022). These cognitive mechanisms together lead the brain to corroborate the hypothesis that the subjects of the virtual experience are actually ourselves, minimizing all the sensory information that contradicts this prediction (e.g., visual inputs that signal the seen body does not look like the real one) (Perez-Marcos, Sanchez-Vives, & Slater, 2012; Slater & Sanchez-Vives, 2016; Sanchez-Vives et al., 2010). That enhanced sense of presence in iVR can explain the higher psychophysiological activation, as evidenced by changes in skin conductance (GSR) response and heart rate variability (HRV) measures during the completion of tasks in immersive setup compared to the same tasks using non-immersive hardware (Chirico et al., 2017; Lo Priore et al., 2003).

Engaging in environment that changes in a flexible and real-time way based on one's own body movement and actions (e.g., closed sensorimotor loop) along with multimodal feedback (e.g., vibro-tactile, audio-visuo-spatial) enhances the likelihood of achieving a higher level of flow through a greater sense of presence (Khoshnoud et al., 2020). The *state of flow* is an optimal state of consciousness characterized by intense focus, deep absorption, and enjoyment, alongside an effortless ease of processing (Csikszentmihalyi, 2014). This positive psychological state is linked to increased goal-oriented attention, underpinned by reduced Default Mode Network (DMN) activity as users become more engaged in interacting with the (virtual) environment (Ju & Wallraven, 2018) Flow also promotes moderate increase in arousal and performance, consistent with the inverted U-shape curve of Yerkes-Dodson Law (Khoshnoud et al., 2020; Yerkes & Dodson, 1908). Flow is especially facilitated in the context of game-like applications, which is a prominent feature of VR-solutions. The incorporation of serious games, defined as games that do not have entertainment as their primary goal (Michael & Chen, 2005), has a well-established history in education and healthcare. Similarly, gamification, described as "the use of game design in non-game contexts" (Deterding et al., 2011), is emerging as major trend in clinical practices. By integrating the motivating and multimedia aspects of computer-generated environments, game-like applications can significantly increase engagement, motivation, and performance (Catania et al., 2024; Tolks, Schmidt, & Kuhn, 2024; Tosto-Mancuso et al., 2022); thereby, addressing the frequently reported lack of motivation and engagement of patients in conventional therapy. Although the flow state and gamification are features shared with non-immersive and semi-immersive solutions, their effects are amplified in iVR-solution due to its greater immersion and enhanced sense of presence. Supporting this, Montoya and colleagues (2020) demonstrated that an iVR-solution for upper-limb training induced high levels of flow, enhanced performance, and reduced fatigue compared to non-immersive set-up. In the same way, assessing the level of motivation in a group of stroke patients enrolled in an iVR motor training (Virtual Reality Kitchen, VRK), Epure & Holte (2017) found that the mean level of motivation was higher in iVR group than in the control group.

3.2.2. Ecologically valid and highly controlled environments

While reproducing the complexities that patients face in real-life situations is hard in standard clinical settings, iVR offers the possibility to create meaningful scenarios that resemble daily situations, allowing for more accurate observation of behaviors, closely resembling those in real life. Making the bridge between clinical environments and everyday functioning, this aspect ensures assessing and training cognitive functions in complex, multisensory, dynamic, three-dimensional scenarios. As a result, the acquired measures present higher reliability, allowing for more accurate observation of behaviors, closely resembling those of real-life situations. This can potentially help detect mild deficits and monitor patients' progress in greater detail than traditional methods (Pieri, Tosi, & Romano, 2023). iVR-based cognitive assessments have already been successfully implemented to evaluate attention, working memory capacities, and executive functions. Climent and collaborators (2021) developed "the Aquarium" to evaluate attention and working memory in individuals over 16 years old (Climent et al., 2021). Similarly, Serino and colleagues (2017) explored the use of a 360° version of the Picture Interpretation Test (PIT) to assess executive functions (S. Serino et al., 2017). Thanks to its capacity to use the full 3D space, iVR-solutions seem particularly well-suited for testing visuo-spatial disorders like unilateral spatial neglect (USN). Allowing the presentation of multisensory three-dimensional stimuli within a 360° field of view, distributed in multiple sectors of space, iVR-solutions can overcome the current limitations in the USN assessment. In this context, Belger and colleagues (2024) utilized an HMD to create a realistic and safe street-crossing environment (the "immersive virtual road-crossing task", iVRoad) to detect and quantify discrete neglect signs in chronic stroke patients (Belger et al., 2024). Recently, Perez-Marcos and colleagues (2023) developed an iVR-based USN assessment using ecological tasks in multimodal, realistic environments, allowing the concurrent stimulation and evaluation of different sectors of a 3D (potentially 360°) space, i.e., peripersonal and extrapersonal space. The application of these iVR tasks in a group of ABIs patients revealed that about 30% of patients, with no clear sign of USN from standard paper-and-pencil tests, performed below the normal range in the iVR-based tasks, highlighting how iVR-based solutions can detect subtle signs of extra-personal space USN that may go unnoticed with traditional tools (Thomasson et al., 2024). The collection of more ecological measures of cognitive functioning can not only help in detecting subtle but clinically relevant deficits, often underrated in standard clinical practices, but it can also result in better prognostic indices (Parson, 2016; Pieri, Tosi, & Romano, 2023).

In the context of rehabilitation, several studies have shown that activities with a relevant context can enhance patients' engagement in therapeutic exercises, allowing for a better transfer of the skills acquired during training to real-life situations (Catania et al., 2024; Martino Cinnera et al., 2022; Salatino et al., 2023; Serino et al., 2022). Gamito and colleagues (2017) developed a cognitive training program based on VR, including tasks simulating daily life activities and targeting different cognitive functions such as working memory and subcomponents of attention. The tasks in the study, integrated into an iVR environment, included activities such as navigating a virtual supermarket to memorize and retrieve a list of items, memorizing routes to move from one point to another, and locating specific objects based on visual cues. Other activities involved solving puzzles that required organizing objects in a three-dimensional space, as well as attention exercises where participants had to respond to visual or auditory stimuli while ignoring distractions.

The results showed improvements in sustained attention and working memory in a group of 20 patients, included four to six weeks after a stroke, following a semi-intensive training program (2–3 sessions per week) for four to six weeks, compared to a passive control group (waiting list) (Gamito et al., 2017).

Another training program using iVR, the VIRTUE system (VIRTUal reality for strokE) developed by Chatterjee and collaborators (2022), engages patients in various immersive environments to perform daily life activities, testing cognitive processes such as attention, planning, sequencing, problemsolving, and memory. In a group of 40 patients, included between one day and three weeks after the onset of a stroke, improvements in overall cognitive functioning were observed after the training. The results showed a significant increase in MoCA (Montreal Cognitive Assessment) scores in the group with severe cognitive impairment at inclusion (MoCA < 15), with a median increase of 8 points (range: 3–17 points). For patients with moderate cognitive impairment at inclusion (MoCA 15–24), the improvement was more limited (median increase of 3 points). In contrast, in the control group (who received non-immersive VR sessions unrelated to the therapeutic goals, environments, or scenarios used in the iVR group), improvement was minimal (median: 0 points). Finally, an important result concerned the duration of hospitalization, which was significantly shorter for patients who received iVR training compared to the control group (Chatterjee et al., 2022).

Furthermore, regarding the rehabilitation of unilateral spatial neglect (USN), Choi and colleagues (2021) evaluated the effect of an iVR program including 10 different applications in a group of 24 patients enrolled between one and six months after a stroke. All patients received thirty-minute training sessions, three times per week for four weeks, and were evenly divided between a group that underwent the iVR-based rehabilitation program and a control group that received conventional neuropsychological care. The results showed a significantly greater improvement in neglect symptoms in the iVR group, as measured notably through a line bisection test and a visuospatial perception test (performance on the left and right sides, processing time). Moreover, compared with the control group, the iVR group showed a trend (with a significance threshold of $p = 0.052$) toward transfer of training benefits to daily life activities, as indicated by fewer deficits in a test assessing activities of daily living (Catherine Bergego Scale, CBS). Finally, compared to the control group who received standard rehabilitation training, the iVR group also showed an increase in both the degree and speed of head rotation, which may be related to positive effects on attention and alertness toward the contralesional side of space (Choi, Shin, & Bang, 2021).

In addition to enabling more immersive and ecologically valid scenarios, iVR-solutions have the potential to maintain a high level of experimental control over stimuli administration (Pieri, Tosi, & Romano, 2023). Directly processed by the iVR software, classic performance indexes (i.e., accuracy, errors, reaction times) can be easily and objectively collected and exploited in more powerful post-process analyses. This saves time and minimizes errors associated with manual scoring and inter-operator variability (Pieri, Tosi, & Romano, 2023; Spreij et al., 2022).

3.2.3. Personalized high-dose, high-intensity and home-based delivery

As in non-immersive and semi-immersive VR-solutions, in iVR the collection and analysis of these large amounts of data occur automatically, in real-time, even in the absence of direct therapist supervision (Tieri et al., 2018). From the clinician's perspective, the possibility to quantify and monitor performance-based outcomes online and remotely is a valuable tool to fine-tune therapy delivery and provide feedback to the patients, both in-clinic and home-based rehabilitation settings (Hao et al., 2024). For users, having constant, real-time feedback and the ability to track their progress over time can induce augmented feeling of involvement and control in the rehabilitation process (Kern et al., 2019). Moreover, in contrast to other VR-solutions, which typically require multiple devices for implementation (e.g., PC, keyboard, mouse, haptic gloves, cameras), iVR-solutions generally consist of an HMD and two controllers. This simplified setup allows for easier deployment directly at the hospital bedside or in home-based settings, making them suitable for autonomous patient use. Overall, with the possibility of acquiring data avoiding the common 1 to 1 relationship required by standardized clinical procedures, along with the simplified set-ups, iVR-solutions enable the possibility of following more patients simultaneously, guaranteeing home-based, unsupervised sessions, iVR-solutions can increase the number of patients who can receive the treatments, promote long-lasting rehabilitation, and increase the amount of training currently provided by the healthcare system, while reducing economic, organizational and logistical barriers for accessing clinical services and alleviating constraints on professional operators. In this line, Cochrane meta-analyses by Laver and colleagues (2015, 2017, 2025) have compared intervention delivered by different VR technologies to conventional therapy for upper limb rehabilitation. Their findings indicate that VR-solutions alone do not outperform conventional approaches. However, when combined with usual care in order to increase therapy dose, intensity and the integration of ecological valid activities, VR-solutions can achieve greater improvements and facilitate generalization to daily activities (Laver et al., 2025). Similar conclusions emerge in cognitive rehabilitation, where integrating with traditional rehabilitation has demonstrated superior outcomes in overall cognition, attention, executive function, and mood improvement (Manuli et al., 2020; Faria et al., 2018; De Luca et al., 2018; Kim et al., 2011).

Moreover, currently, thanks to new Artificial Intelligence (AI) methods, the implementation of gamified VR-solutions is becoming more flexible (Tieri et al., 2018). AI-driven algorithms can dynamically adjust gamified activities' levels, scenarios, and difficulty, creating highly personalized and adaptive experiences (Tolks, Schmidt, & Kuhn, 2024). In clinical practices, this adaptability represents a significant step toward personalized and tailored protocols that fulfil the neuroplasticity principles of salience and specificity (Kleim & Jones, 2008). However, these activities must be integrated within a rehabilitation program grounded in well-established theoretical models of cognitive functioning, such as the hierarchical multicomponent model of attention proposed by Leclercq and Zimmermann (2002) and by Zomeren and Brouwer (1994). This model postulates the priority of rehabilitating attention components related to intensity before addressing those related to selectivity (see also Sturm et al., 2003). By integrating these theoretical principles and quickly adapting to patients' performance, these algorithms enable the development of personalized and validated training protocols, marking a significant advancement in neurorehabilitation (Calderone et al., 2024; Senadheera et al., 2024).

By allowing patients to engage in activities suited to their skill level and providing clear and immediate feedback on their actions, their sense of empowerment in the therapeutic process is significantly enhanced (Riva et al., 2020). In positive psychology, empowerment refers to the psychological state of feeling competent, in control, and capable of internalizing activity goals and it is a vehicle to strength intrinsic motivation and engagement (Menon, 1999; Ryan & Deci, 2000). According to Ryan and Deci's Self-Determination theory (2000), competence and autonomy are two of the universal basic psychological needs that drive human action, yielding positive effects on behavior and its outcomes (Sailer et al., 2017). The possibility of increased intrinsic motivation is commonly associated with improved outcomes, acquiring reliable measures of cognitive performance, and reducing dropout rates encouraging consistent participation in clinical practices (Catania et al., 2024; Maggio et al., 2025).

Thus, based on the above-described evidence and features, iVR-solutions can boost rehabilitation and assessment procedures and provide clinicians with several features to deliver and implement protocols with the key components proven essential for optimal outcomes and for the acquisition of more reliable measurements on cognitive functioning. However, iVR-solution should not be conceived as to replace conventional therapy, but rather as a tool to significantly improve it. Moreover, despite clear clinical evidence supporting iVR-solutions for both diagnosis and rehabilitation, its adoption remains limited. One major issue is the relatively small number of randomized clinical trials and Class I studies supporting the effectiveness of iVR-solution protocols, which reduces the overall reliability of these applications in the standard management of motor-cognitive disorders in ABI patients. A recent systematic review of VR-solutions for rehabilitating USN (Salatino et al., 2023) found that among nine studies on iVR-solutions, only two were classified as Class I. Moreover, even structured studies often have small sample sizes and exhibit heterogeneity in terms of protocols used, of motor and cognitive disorders, of patient's clinical profile, further limiting the generalizability of available findings. Additionally, the frequent lack of follow-up assessments as well as the limited measures on the generalizability of rehabilitation outcomes raise relevant questions regarding the long-term maintenance of observed improvements and their impact on daily-life activities. Finally, adoption of iVR-solutions requires structural adaptation of the current neurorehabilitation system, mainly based on 1-therapist 1-patient model, in terms of organization and finance.

Establishing strong clinical relevance and evidence-based credibility for iVR-solutions in both assessing and rehabilitating motor-cognitive disorders after ABIs is essential to advancing towards the widespread adoption of iVR-solutions as an adjunct to standard clinical care. However, providing evidence is not sufficient to guarantee adoption. The integration process of iVR-solutions within the current clinical management must be associated with a clear implementation plan, with an adaptation of the current care system to innovation, and with proper education and training of professionals.

One final and important aspect to highlight regarding the potential of iVR in neurorehabilitation assessment and rehabilitation protocols is its compatibility with sensor technologies capable of capturing meaningful indicators of cognitive functioning. By integrating sensors within iVR environments, it becomes possible to collect biomarkers of cognitive processes (e.g., behavioral, physiological, or neurophysiological data) in highly controlled yet ecologically valid contexts. This integration enhances the objectivity and precision of the measurements obtained and strengthens their reliability for both diagnostic and prognostic purposes. Moreover, these physiological and behavioral measures can be associated with conventional performance indices, offering a more comprehensive understanding of the patient’s cognitive functioning. In particular, indices derived from motion tracking, eye-tracking, and heart rate variability appear especially promising for inclusion in iVR protocols, as they provide sensitive and dynamic markers of attention, cognitive load, and engagement during cognitive tasks.

Chapter 4

Integrating oculomotor and cardiac measures as biomarkers of attention in Immersive Virtual Reality

4.1. The role of biomarkers in clinical practices

Cognitive operations result from the coordinated activity of distributed neural systems that are embedded within, and continuously interact with, peripheral physiological networks. Neural regulation of autonomic, endocrine, and motor systems enables adaptive responses to environmental and internal demands, while afferent bodily signals reciprocally influence cortical and subcortical activity (Critchley & Harrison, 2013; Thayer & Lane, 2009). This bidirectional communication forms the basis of an integrated brain-body system in which cognitive, emotional, and physiological processes are functionally interdependent. Converging neuroimaging and psychophysiological evidence indicates that regions such as the prefrontal cortex, insula, anterior cingulate cortex, and brainstem nuclei mediate top-down and bottom-up interactions between neural activity and peripheral physiology (Beissner et al., 2013; Craig, 2002; Barrett & Simmons, 2015). Within this neurovisceral framework, cognitive states are accompanied by systematic and quantifiable modifications in physiological and behavioral responses that reflect underlying neural dynamics (Allen et al., 2022).

The concept of a biomarker originated in biomedical sciences, where the National Institutes of Health Biomarkers Definitions Working Group defined it as: "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (National Institutes of Health Biomarkers Definitions Working Group, 2001). In cognitive neuroscience, this concept has been extended to encompass molecular, neurophysiological, and behavioral indices that provide quantifiable correlates of brain function (Woo et al., 2017). Empirical evidence demonstrates that patterns of neural activation, autonomic modulation, and behavioral measures can reliably index specific cognitive operations, supporting the use of multimodal biomarkers to characterize both healthy and impaired functioning (Criscuolo, Schwartze & Kotz, 2022). Accordingly, the integration of biological and behavioral biomarkers provides a valuable framework for investigating the organization, efficiency, and adaptability of cognitive systems in health and disease. An increasingly recognized aspect of biomarker research lies in its translational potential. The characterization of individual cognitive capacities through multimodal biomarkers represents a promising tool for diagnostic, prognostic, and personalized interventions (Criscuolo, Schwartze & Kotz, 2022). Combining behavioral and cognitive assessments with measures of brain, respiratory, and cardiac activity may elucidate critical links between cognitive dysfunction (e.g., attention deficits after acquired brain injuries) and altered brain-body coupling. In this context, Kim and colleagues (2022) described the benefits that biomarkers can have in clinical practices. They offer benefits for patients, caregivers, and clinicians by: (a) informing clinical pathway planning and goal setting, and (b) identifying which individuals to target, when, and at what level of intervention to promote optimal recovery. The clinical application of these biomarkers can improve risk stratification and thereby guide the implementation of tailored treatment strategies (Kim, Shin, & Chang, 2022).

Starting from this framework, heart rate variability (HRV) and eye-tracking measures have been linked to individual attentional capacities. Particularly HRV reflects the dynamic balance of autonomic regulation associated with both the amount of attention that should be allocated to a task (i.e., alertness) and the capacities for maintaining attention for a long period of time (i.e., sustained attention), together with defining what is known as cognitive workload (Thayer & Lane, 2009). Furthermore, eye-movement patterns can be modulated by alertness levels and exploration strategies, providing insight into how attentional resources are distributed across the spatial environment (Corbetta & Shulman, 2002; Nobre & Kastner, 2014). When integrated within immersive Virtual Reality (iVR) paradigms, these cardiac and oculomotor indices can exhibit enhanced sensitivity to fluctuations in attentional engagement (Clay, König & König, 2019; Kaiser et al., 2022). The immersive, interactive, and multisensory properties of iVR elicit ecologically valid cognitive and perceptual demands while preserving experimental control (Parson, 2016; Pieri, Tosi, & Romano, 2023), thereby amplifying the coupling between physiological regulation, gaze dynamics, and task-related cognitive states (Castillo-Escamilla et al., 2024; Chirico et al., 2017; Kaiser et al., 2022). This integration offers powerful tools for translation into neuropsychological assessment and rehabilitation protocols, enhancing diagnostic precision, prognostic prediction, and the personalization of intervention strategies. In the next paragraphs, the interplay between HRV and eye movements with attentional abilities will be discussed in greater detail, demonstrating their potential as biomarkers for detecting attention impairments following acquired brain injuries, and particularly how immersive Virtual Reality (iVR) scenarios can enhance their reliability

4.2. Heart Rate Variability: a cognitive workload biomarker

4.2.1. Cognitive workload and the link with the intensity aspect of attention

The framework of attention processes proposed by van Zomeren and Brouwer (1994) posits that the intensity aspect of attention (i.e., alertness, sustained attention, and vigilance) refers to the degree of attentional resources allocated to a given task. The intensity of attention partly determines how effective control processes are implemented to achieve current goals (Unsworth & Miller, 2021). From this perspective, the conceptualization of attention intensity has been closely linked to that of cognitive or mental workload (Unsworth & Miller, 2021).

In applied ergonomics, Cognitive Workload (CWL) is regarded as a multidimensional construct influenced by task characteristics (e.g., demands, performance requirements), individual factors (e.g., skill, attention capacity), and, to some extent, the environmental context in which performance occurs. In this sense, CWL has been defined as “the level of attentional resources required to meet both objective and subjective performance criteria, which may be mediated by task demands, external support, and past experience” (Young et al., 2015).

To illustrate the reasoning that links cognitive workload to the intensity aspect of attention, imagine two individuals performing the same task. Although the task is identical, they may perceive and report different levels of difficulty and workload. These differences largely stem from interindividual variations in attentional resources, particularly in how effectively each individual can increase and sustain alertness over time (i.e., sustained attention and vigilance). Thus, subjective differences in attentional intensity capacities lead individuals to perceive the same task as differing in cognitive workload, which in turn contributes to differences in performance outcomes.

CWL has been recognized as a key component of various cognitive-energetic models of performance becoming critical for variation in overall task engagement and efficiency. One influence framework in this sense is the flow-channel model (Csikszentmihalyi & Csikszentmihalyi, 1992; Engeser & Rheinberg, 2008; Fong et al., 2015; Keller & Blomann, 2008; Khoshnoud, Igarzabel & Wittman, 2022). According to this model, when task demands exceed an individual’s available attentional resources, frustration, anxiety, and disengagement arise. Conversely, when cognitive demands fall below the individual’s skill level, boredom and apathy ensue. In both cases, when demands are either too high or too low relative to skill, concentration diminishes, leading to reduced performance (Perone, Weybright, & Anderson, 2019).This dynamic aligns with the inverted U-shape relationship between arousal and performance, first described by Yerkes-Dadson law where at both high and low levels of alert state corresponds a decreasing in performance (Landhäußer & Keller, 2012; Khoshnoud, Igarzábal, & Wittman, 2020; Yerkes & Dodson,1908). Accordingly, optimal performance emerges when arousal is balanced, sufficient to meet cognitive demands without exceeding individual attentional capacity. Under these conditions, when alertness is appropriately elevated but regulated, cognitive workload remains balanced, performance improves, and the individual enters a flow state. Flow state has been conceptualized as an optimal state of consciousness with high degree of concentration which leads to absolute absorption in an activity, sense of enjoyment and ease of processing (Csikszentmihalyi, 2014). This state is associated with strong attentional focus implying the inhibition of task-irrelevant stimuli or thoughts. Neuroimaging studies agreed in sustaining that this flow-related focus is linked to the higher activation within the executive control network, which underpins higher-order cognitive functions such as working memory, attentional control, and inhibition (van der Linden, Tops, & Bakker, 2021). Concurrently, reduced self-referential and off-task thinking during flow is associated with decreased activity in the Default Mode Network (DMN), alongside enhanced activation in both reward-related regions (e.g., amygdala, hippocampus, nucleus accumbens, dorsolateral prefrontal cortex, cingulate cortices, and insula) and attention-related networks (e.g., orienting and alerting systems; Petersen & Posner, 2012) (Alameda, Sanabria, & Ciria, 2022; Gold & Ciorciari, 2021; Ju & Wallraven, 2019; see van der Linden et al., 2021, for a review). Along with these cortical mechanisms, it has recently proposed a primary role of the locus coeruleus-norepinephrine (LC-NE) system in regulating cognitive workload and attentional engagement. Aston-Jones and Cohen (2005) proposed that the LC-NE system modulates arousal levels dynamically, governing the balance between task engagement and disengagement through cost–benefit trade-offs. The LC-NE system essentially determines when and how much attentional intensity should be deployed for a given task (van der Linden et al., 2021). Neuroimaging and psychophysiological studies suggest that the tonic and phasic modes of LC-NE activity underline both the flow-channel and the inverted U-shaped relationship between CWL and performance. Specifically, at intermediate tonic NE levels, phasic NE responses to task-related stimulus are strong, leading to optimal task engagement, known as the exploitation mode of the LC-NE system. When tonic NE levels are high, phasic responses become less specific and more broadly tuned, reflecting an exploration mode characterized by distractibility and environmental scanning. Conversely, low tonic NE and weak phasic responses correspond to disengagement, associated with fatigue and boredom (Hopstaken et al., 2015). The tonic level of LC-NE activity, which parallels an individual's baseline alertness, determines the responsiveness of phasic reactions and thus underpins interindividual differences in attentional intensity and perceived cognitive workload when facing specific task demands.

Given the close link between the intensity aspect of attention (i.e., alertness and sustained attention) and the cognitive workload (CWL) experienced by individuals and the established relationship between CWL, engagement, and performance, it becomes crucial to assess CWL in neuropsychological practice. Following acquired brain injury, patients frequently experience impairments in attentional processing (see Chapter 2, section 2.3, "*Attention-related Impairment in Lesioned Brain*", for a detailed discussion), with approximately 31% exhibiting difficulties related to the intensity aspect of attention (Spaccavento et al., 2019).

During both assessment and rehabilitation, it is therefore essential to modulate task demands based on each patient's attentional resources, avoiding excessive cognitive workload while maintaining engagement within the flow state to enhance performance, motivation, and adherence. Maintaining patient motivation is particularly critical for reducing drop-out rates, sustaining engagement, and optimizing functional recovery (Catania et al., 2024; Serino et al., 2022). Currently, the most common approach for evaluating CWL relies on self-report measures, with NASA's Task Load Index (NASA-TLX; Hart & Staveland, 1988) being the most widely used. This multidimensional tool assesses six facets of workload: mental, physical, and temporal demand, along with performance, effort, and frustration. It provides a direct, person-centered estimation of perceived workload (Longo et al., 2018) and has been successfully applied across a variety of high-demand contexts, including surgery (Zheng et al., 2012), laboratory paradigms such as the N-back task (Luque-Casado et al., 2016; Muth et al., 2012), and neurorehabilitation settings involving both motor (La Bara et al., 2021) and cognitive training (Wu et al., 2023). In addition to self-reports, performance metrics such as error rates and hit scores are often used as indirect indicators of CWL.

However, self-report measures are inherently subjective and prone to bias (Cavedoni et al., 2020; Solhjoo et al., 2019). They rely on post hoc self-reflection and retrospective recall, often introducing a temporal delay between the performance event and the completion of the questionnaire (Bishop, McNeil, & Izzetoglu, 2021). Similarly, performance metrics require tasks with frequent measurements of performance (Ahmadi et al., 2023). Therefore, while these tools provide valuable insight into subjective workload perception, they should be complemented by objective, real-time measures of CWL able of capturing fluctuations in attentional and mental effort during task performance, rather than solely before or after sessions (Luque-Casado et al., 2016).

Physiological measures, on the other hand, provide continuous, non-intrusive monitoring of CWL. Previous research indicates associations between CWL and oculomotor metrics such as pupil dilation and fixation patterns (e.g., fixation count and duration; Soler-Dominguez et al., 2017; Souchet et al., 2022; Tao et al., 2020), electrodermal activity (EDA; Babaei et al., 2021) and electroencephalography (EEG; Brouwer et al., 2012). In addition, a substantial body of studies has linked cardiac measures with CWL, particularly focused on heart rate (HR) and heart rate variability (HRV).

4.2.2. Heart Rate (HR) and Heart Rate Variability (HRV): The Neurovisceral Integration Model

HR refers to the number of heart contractions per unit of time, typically expressed in beats per minute (bpm) (Weisdorf & Spodick, 1976). HRV quantifies the variability in intervals between consecutive heartbeats (interbeat intervals, IBIs) and can be computed using time-domain or frequency-domain indices (e.g., low-frequency bands: 0.04–0.15 Hz; high-frequency bands: 0.15–0.40 Hz; Thayer et al., 2009). Among these classic HRV measures have been recently reported the need to explore different metrics (e.g., non-linear or multivariate; Delliaux et al., 2019). Both HR and HRV serve as objective indicators of autonomic nervous system (ANS) modulation linked to the arousal level (Khoshnoud, Igarzabel & Wittman, 2022). The two branches of the ANS, the sympathetic nervous system (SNS, responsible for "fight-or-flight" responses) and the parasympathetic nervous system (PNS, responsible for "rest-and-digest" responses) operate as excitatory and inhibitory physiological mechanisms, respectively (Cacioppo et al., 2007). A large body of evidence shows that increased level of arousal, closely linked with higher CWL, is typically associated with enhanced HR (sympathetic activation) and lowered HRV (linked to parasympathetic withdrawal) (Hughes et al., 2019). This imbalance between the ANS branches is reflected in HR and HRV measures and correlates with declines in attention and cognitive performance (Castaldo et al., 2017; Delliaux et al., 2019; Luft, Takase, & Darby, 2009; Luque-Casado et al., 2016; Thayer et al., 2009). Consistently, Luft and colleagues (2009) demonstrated that participants underwent five different tasks (e.g., simple reaction time, choice reaction time, working memory, short-term memory and sustained attention) which required different levels of attention impacted differently on HR and HRV measures. Particularly, tasks with higher level of CWL were the one that resulted in stronger reduction in registered HRV (Luft, Takase, & Darby, 2009). A comprehensive framework to explain the observed relation between ANS and CWL lies on the Neurovisceral Integration Model (Thayer et al., 2009; Thayer & Lane, 2009). Within this model, the prefrontal cortex (PFC), particularly the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC), serve as a central inhibitory node within the Central Autonomic Network (CAN). Through descending projections to the amygdala, hypothalamus, periaqueductal gray (PAG), and medullary nuclei such as the nucleus tractus solitarius (NTS) and ventrolateral medulla, the PFC exerts top-down inhibitory control over subcortical sympathoexcitatory centers. This inhibition stabilizes the balance between sympathetic and parasympathetic activity, ensuring adaptive modulation of arousal and attentional resources according to task demands. Under conditions of balanced CWL, efficient PFC functioning maintains parasympathetic predominance, high HRV, and moderate arousal, which facilitate optimal attentional focus and performance. However, as CWL increases and the system approaches its regulatory limits, prefrontal efficiency declines, leading to reduced inhibitory signaling toward subcortical structures. This disinhibition results in sympathetic dominance, expressed as elevated HR and decreased HRV, indicative of overarousal and reduced attentional stability (LeDoux, 1996; Thayer et al., 2009; Thayer & Lane, 2009; Wei et al., 2024). The locus coeruleus norepinephrine (LC-NE) system contributes to this regulation by modulating PFC excitability and attentional gain. Moderate LC tonic activity enhances PFC function and inhibitory control, whereas excessive LC activation under high CWL saturates cortical norepinephrine levels, impairing prefrontal regulation and promoting sympathetic overactivation (Aston-Jones & Cohen, 2005). HR and HRV thus provide peripheral markers of the efficiency of prefrontal autonomic integration. High HRV reflects strong inhibitory coupling and flexible adaptation to cognitive demands, while low HRV indicates prefrontal disinhibition, sympathetic predominance, and impaired attention regulation under excessive workload.

Although the association between CWL and HR and HRV is well established in laboratory settings, understanding how these parameters behave in ecologically complex contexts remains a significant challenge. Real-life situations rarely impose purely cognitive demands; rather, they combine physical effort, multimodal stimulation, and emotional engagement. These concurrent sources of load jointly influence autonomic regulation, making it difficult to isolate the specific contribution of CWL to HR and HRV changes.

4.2.3. HRV in Immersive Virtual Reality: a valuable perspective in neuropsychology

Immersive virtual reality (iVR) provides a powerful methodological tool to simulate life-like scenarios in which it can be better understood how the interplay between different sources of load can be reflected in HRV and HR measures. Consistently, experimental studies have shown that higher sense presence provided by immersive environment is frequently associated with greater sympathetic activation, expressed as increased HR and decreased HRV compared to non-immersive or two-dimensional conditions (Chirico et al., 2017; Lo Priore et al., 2003; Slater et al., 2006, 2009). This pattern indicates that the subjective sense of “being there” in a vivid and behaviorally engaging environment recruits physiological resources similar to those mobilized in real-world high-arousal or high-demand situations (Marín-Morales et al., 2021). In addition, physical activity and enjoyment strongly modulate HR and HRV responses in iVR. In physically engaging immersive tasks (e.g., exergames), the combination of movement-related metabolic demand and affective arousal produces additive sympathetic activation, leading to larger HR increases and HRV reductions than those predicted by cognitive load alone (Rubio-Arias et al., 2024; Villafaina et al., 2020). Interestingly, higher enjoyment and motivation along with flow experience moderate this relationship: individuals reporting higher enjoyment maintain performance with more stable HRV, suggesting efficient prefrontal–autonomic coupling despite high workload (Peifer et al., 2014). Thus, while HR and HRV reflect physiological arousal, their interpretation in iVR must account for affective engagement and motor effort, not only cognitive demands.

Collectively, these findings indicate that HR and HRV are differentially modulated in immersive virtual environments compared with conventional laboratory tasks. In iVR, autonomic responses reflect not only the cognitive workload imposed by the task but also the integrated effects of sensory immersion, emotional engagement, motor activity, and flow. Higher immersion and presence amplify sympathetic activation, while enjoyment and flow can mitigate perceived effort, enabling sustained performance. Therefore, collecting HR and HRV measures within iVR paradigms could provide a more ecologically valid framework for assessing CWL, offering potential clinical applications as real-time physiological biomarkers to monitor and adapt neurorehabilitation protocols, helping maintain an optimal balance between attentional resources and task demands.

Given this evidence, future research should examine how HR and HRV are modulated within immersive environments to clarify how these parameters reflect and adapt to different types of loads. In particular, studies should aim to disentangle the effects of cognitive workload from those of physical load typically present in iVR, more realistic contexts, and to determine how HR and HRV can be used to track subjective workload perception and predict changes in performance in immersive settings, supporting their potential translational application in iVR protocols as biomarker of cognitive workload.

4.3. Oculomotor metrics indexes attention abilities

4.3.1. Neural overlapping between oculomotor control and attention networks

Attention processed is often described as operating in two modes, bottom-up or top-down, and two types, covert and overt. The first distinction reflects the way in which attention is engaged, either by the unattended or salient stimuli in a reflexive manner (i.e., bottom-up capture) or by internal goal, expectations and prior knowledge in a voluntary manner (i.e., top-down control; Posner, Snyder, & Davidson, 1980; for a detailed description see Chapter 2, sections 2.1.1 and 2.1.2). The second distinction reflects the way in which either of these two modes may be reflected. In this line, it has been highlighted that we can focus our attention resources on a specific object or portion of space covertly, without moving our eyes directly toward the relevant information. For instance, attending a stimulus or spatial location improves the detection and discrimination of that target even when eye movements are not allowed. Conversely, during overt attention, a specific action toward the stimulus is effectively executed such as fixation (Corbetta et al., 1998; Posner, Snyder, & Davidson, 1980). Using function magnetic resonance (fMRI) (Beauchamp et al., 2001; de Haan et al., 2008) and EEG (Kulke et al., 2021, Kulke et al., 2016) has been suggested that similar brain regions are activated during overt and covert attention. Specifically, a fronto-parietal network including overlapping areas among the attentional networks (e.g., Dorsal and Ventral Attentional Networks, DAN and VAN) and those related to oculomotor control, seems to be reliably activated by both covert and overt shifts of attention (Beauchamp et al., 2001; de Haan et al., 2008; Corbetta et al., 1998; Rizzolatti et al., 1987), with a greater neural activation that covert attentional shift (Pasqualette & Kulke, 2024). One of the most influential attempts to explain the relationship between attention and eye movements was proposed by Rizzolatti and colleagues (1987) through the Premotor Theory of Attention. According to this theory, orienting attention toward an object or a spatial location reflects the preparation or intention to act upon it, even in the absence of an actual movement. In other words, attention shifts are considered to arise from the activation of motor plans that are not necessarily executed. This framework suggests that the neural overlap observed between attentional and motor regions, particularly those involved in eye movement control, reflects an underlying process of action planning directed toward the attended stimulus (Rizzolatti et al., 1987). Within this perspective, attention can originate from any effector system capable of goal-directed action, such as the eyes, hands, or head. However, the oculomotor system holds a privileged role in selective spatial attention, as eye movements represent the most frequent and efficient means of exploring the visual environment. Consistently, Corbetta and colleagues (1998) through fMRI and surface-based representation of functional brain activity in task in which attention was shifted to visual stimuli with or without concurrent eye movements, showed that there is a greater overlap in all tasks between attention networks and whose controlled eye-movement. So that not only the two processes are functionally related, but share functional anatomic areas (Corbetta et al., 1998). The major nodes involved in oculomotor control are supplementary and frontal eye field (SES/FEF) and parietal eye field (PEF) in the posterior intraparietal sulcus, along with the superior colliculus (SC) and cerebellum (Cb). Brain stem nuclei in the pons mediate between cerebellar and cerebral system, and reticular nuclei represent the final efferent motor pathway. The major input comes from the dorsolateral prefrontal cortex (dlPFC) for spatial memory, response selection e.g., goals, reward, decision making) and motor planning. The posterior parietal cortex (PPC) influences the oculomotor pathway, brings information regarding visuospatial attention, spatial orientation, and multisensory integration. The dorsal visual stream (occipito-parietal and middle temporal regions) serves information related to vision for action and motor perception. Besides these circuits, the motor processes outside the oculomotor system affect oculomotor processes through efference copy signals (i.e., internally) and through motor action that move the origin of the gaze (e.g., locomotion, head and body movements) (Lappi et al., 2016).

Most of these regions involved in the oculomotor control are widely described as part of the DAN and VAN for control attention intensity and selection processes (see Chapter 2, section 2.2 "*Neural Correlates of Attention*").

From this evidence, it can be posited that eye movements can be conceptualized as a biomarker of attention processes.

4.3.2. Different eye parameters for detecting attention components

Several different types of eye movements have been described and studied in relation to attention abilities.

*Fixation*s are described as instances where the eyes cease the scanning process of the environment and hold the central fovea vision in a position (i.e., area of interest, AOI) to allow the subject to process the visual target. The typical fixation duration is 100-300 msec (Salvucci & Goldberg, 2000). Fixation may seem to be static and stationary, but involves small imperceptible movement of the eyeballs, which can be classified into: microsaccades or involuntary saccadic-like movements during fixations, but with lower amplitudes compared with saccades. Microtremors or fast fixations eye movements observable in the frequency range of 50-100 Hz, with a high speed of 1.5°/s, and drifts defined as slow motions with speed of about <50'/a (Marandi & Gazerani, 2019). The most used fixation metrics used are the mean number of fixations, total number of fixations, fixation duration, total fixation duration i.e. the cumulative duration of all of the fixations on a particular AOI, time to first fixation on target, fixation density, re-fixation and the direction of the first fixation (Skaramagkas et al., 2023). Quick and simultaneous eye movements between fixations are termed *saccades.* During saccades, vision is temporarily suppressed to prevent visual distortions caused by eye movements. These shifts are essential for exploring new areas of the visual field and can be driven either by external stimuli (reflexive saccades) or by internal cognitive processes, such as memory recall or action planning. When viewing a scene, fixations tend to concentrate on visually salient areas, while saccades vary in amplitude and direction to cover the most relevant parts of the stimulus. The size and duration of saccades depend on the task being performed: during reading, saccades are small and last approximately 30 milliseconds, whereas during scene viewing they are larger and last between 40 and 50 milliseconds (Carter & Luke, 2020; Lappi et al., 2016). The most used saccadic movement features are the number of saccades, saccadic velocity/amplitude, saccade rate and duration (Skaramagkas et al., 2023). Compared to saccades, *smooth pursuit* eye movements allow the gaze to be maintained on selected objects regardless of whether the subject or the objects are stationary or moving. Smooth pursuit eye movements have a maximum velocity of about 100◦/s and latency 100-130 ms (Skaramagkas et al., 2023).

Eye blinking a short period (usually 100 - 400 ms) in which the eyes are covered simultaneously by the eyelids during wakefulness. It is a semi-autonomic action similar to breathing where one can do it voluntarily (voluntary blink), or it can occur as a reflex to light or a mechanical touch (reflex blink) or occurring involuntarily with no external trigger (spontaneous blink). In addition to cleaning and lubrication of the surface of the cornea and the conjunctiva, measures such as blink rate and blink duration are associated with cognitive and neural processing. The pupils are also important source of cognitive neural processing. The dilatation and constrictions of the pupils are called pupillary responses (Marandi & Gazerani, 2019). In the past years, experts have used pupil dilatation data to reveal the subjective difficulty of cognitive tasks and their intensity (cognitive workload). Statistical features (e.g., mean, range) of pupil diameter, latency and peak of task-evoked pupil dilations were used as index of cognitive activity.

Given the multicomponential nature of attention (Leclercq & Zimmermann, 2002; van Zomeren & Browuer, 1994), research has shown that different eye metrics can be linked to a specific subcomponent of attention processes.

In this perspective, pupil diameter has been widely used as an indicator of the intensity of attentional engagement and alertness levels, as well as of sustained attention, the capacity to maintain a stable level of alertness over extended periods of time. Sustained attention is supported by a right-lateralized cortical network involving the fronto-parietal, salience, and default mode networks (Petersen & Posner, 2012; Posner & Petersen, 1990; Sadaghiani & D'Esposito, 2015; Sturm & Willmes, 2001). This system plays a crucial role in maintaining arousal, focusing on task-relevant stimuli, and reorienting attention following errors or lapses. Reduced responsiveness within this network has been linked to attentional lapses, which correspond to decreased activation in sustained attention regions and increased activity in default mode areas, ultimately leading to impairments in goal-directed behavior. In addition to cortical regions, the locus coeruleus-norepinephrine (LC-NE) system plays a central role in regulating sustained attention and alertness (Aston-Jones & Cohen, 2005; Petersen & Posner, 2012; Posner & Petersen, 1990). The LC-NE system modulates prefrontal cortical representations according to attentional control demands (Cohen, Aston-Jones, & Gilzenrat, 2004), and its activity has been shown to correlate pupil dynamics (Aston-Jones & Cohen, 2005; Joshi, Kalwani, & Gold, 2016). Specifically, baseline pupil diameter provides an indirect index of LC activity modes: in the hypoactive mode, baseline pupil size is small; in the tonic mode, it is relatively large; and in the phasic mode, it falls at intermediate levels (Aston-Jones & Cohen, 2005; Joshi, Kalwani, & Gold, 2016).

Behavioral evidence further supports this relationship. Murphy and collaborators (2011) observed an inverted-U relationship between baseline pupil size and performance in an auditory oddball task:

performance deteriorated when baseline pupil diameter was either very small or very large but was optimal at intermediate levels. This finding suggests that pupil diameter indexes both tonic and phasic modes of LC activity, reflecting fluctuations in alertness and arousal across the entire LC-NE activation curve. Consistently, studies have shown that under conditions of fatigue or low alertness, baseline pupil diameter becomes smaller and more variable (van den Brink, Murphy, & Nieuwenhuis, 2016), and that greater variability in both baseline and phasic pupil responses is associated with decreased attentional control and increased reaction time variability (Unsworth & Robison, 2017). Along with modulation of pupilar diameter as function of alertness levels, blink parameters also emerged as important markers of individual differences in alertness abilities. Recent works have shown that blink events correlated with momentary surges in arousal networks as measured by BOLD variations in various brainstem nuclei (e.g., cerebellum, insula, lateral geniculate nucleus, and visual cortex) in drowsy state and are interpreted as transient surges of arousal aimed at maintaining wakefulness and alertness. As a result, in low level of alertness state, these events manifest as longer and more frequent (Demiral et al., 2023; Demiral & Volkow, 2024) and they are associated with dopaminergic signaling (Jongkees & Colzato, 2016). Evidence from clinical populations further supports this link: prolonged blink duration has been reported in Parkinson's disease in association with reduced levels of alertness and reduced level of dopamine (Vasudevan et al., 2025), whereas schizophrenia, often characterized by hyperalert states, is associated with elevated blink rates and higher level of dopamine (Nielsen, Dietz, & Jefsen, 2025). Finally, longer and frequent blinks during a vigilance task are associated with performance declined and correspond to right cerebral blood flow velocity declined (McIntire et al., 2014). Similarly, fixation stability (i.e., the ability to maintain fixation on a stimulus for a brief amount of time) has been thought to reflect the efficiency of neural processes in maintaining attention and controlling eye tracking. This highlights that higher fixation stability relates to more effective top-down control mechanisms (Zhou et al., 2024). In this line, Unsworth and colleagues (2020) reported that participants who showed higher fixation stability on fixation cross prior to the appearance of the target stimulus show faster reaction time (RT, msec), conversely higher instability of fixation lead to slower reaction time (RT, msec).

In a similar way to how previous research has demonstrated links between various oculomotor measures, like pupil diameter, eye blink and fixation stability, and the intensity aspect of attention a growing body of evidence has revealed a strong association between eye movements and the selection component of attention. Empirical studies indicate that individuals with reduced selective attention capacities exhibit a higher number of fixations compared to those with stronger attentional control (Geerlings et al., 2014; Skaramagkas et al., 2023). This finding has been interpreted as reflecting difficulties in suppressing visual distractors, making individuals more vulnerable to bottom-up capture by salient but task-irrelevant stimuli and less efficient at applying top-down filtering mechanisms (Ridderinkhof & Wijnen, 2011).

Geerligs and colleagues (2014) further suggested that in older adults, these difficulties may be partially compensated by an increased reliance on top-down attentional resources, manifesting as more effortful and extensive visual exploration strategies. Accordingly, the increased fixation count observed may reflect both greater distractibility and a compensatory attempt to maintain task performance through more exhaustive search behavior (Goller, Mitrovic, & Leder, 2019; Schmidt et al., 2018). Supporting this interpretation, other eye-tracking measures, such as a higher number of refixations, longer latency to first fixate the target, and greater dwell time on distractors, have also been shown to predict deficits in selective attention, indicating challenges in filtering irrelevant information and a tendency toward inefficient or erratic visual exploration (Stefani & Sauter, 2023).

Regarding spatial attention, the direction of the first fixation provides a key index of how attentional resources are allocated toward salient visual content. Studies in healthy participants consistently show a natural leftward bias during visual exploration, known as pseudoneglect (Bowers & Heilman, 1980). This phenomenon has been attributed to a hemispheric imbalance, whereby the right hemisphere plays a dominant role in directing spatial attention (Heilman & Van Den Abell, 1980). More recent evidence suggests that pseudoneglect primarily arises from the interaction between the dorsal (DAN) and ventral (VAN) attention networks. When no explicit task rules guide exploration, spatial attention depends on the dynamic interplay between these two systems (Nardo et al., 2019). The VAN detects relevant stimuli in the environment and transmits this information to the DAN, which then plans and executes the attentional shift toward that location (Nardo et al., 2019). When multiple relevant stimuli are present, the VAN signals their co-occurrence to the DAN, which resolves this attentional competition by initiating a strategic exploration pattern that, in healthy individuals, typically begins toward the left side of space, manifesting as pseudoneglect. This interpretation is supported by neurostimulation evidence. Using a cortico-cortical paired associative stimulation (ccPAS) protocol targeting the frontal–parietal connection, Guidali and colleagues (2023) demonstrated that stimulating the right frontal eye field (rFEF) followed by the right inferior parietal lobule (rIPL) enhanced the leftward shift of the first fixation, thereby increasing the pseudoneglect bias in healthy participants. Overall, these findings indicate that the direction of the first fixation serves as a reliable marker of exploration efficiency and reflects the effectiveness of spatial attention allocation and response readiness to lateralized stimuli (Bagattini et al., 2022; Chiffi et al., 2021; Guidali et al., 2023; Nardo et al., 2019; Strauch et al., 2024). The disruption of these efficient spatial exploration patterns are frequently reported in patients with unilateral spatial neglect (USN), following mostly right-lateralized lesion within the VAN and DAN. A large body of studies show that using the dislocation of fixation along the x-axis (i.e., gaze-index and gaze-laterality) can be used as a reliable biomarker for the detecting and diagnosis of USN (Franceschiello; Nardo et al., 2019) with higher reliability compared to standard clinical assessment tools (Kaufmann et al., 2020). Similarly, a fixation pattern imbalanced on the right hemifield is frequently observed in USN patients compared to healthy subjects (Paladini et al., 2019). Higher number of refixation and preservative refixation on the right side of the visual scene is thought to reflect the frequently reported *productive or positive symptoms* reported in USN patients derived from an hyper-attraction toward the ipsilesional (right) hemifield (Rusconi et al., 2002).

4.3.3. Sampling rate requirements for oculomotor measures

The sampling rate of an eye-tracking system is a critical methodological parameter, as different oculomotor measures place distinct demands on temporal resolution (Holmqvist et al., 2011; Duchowski, 2017). *Pupil-based measures*, including pupil diameter and task-evoked pupillary responses, are characterized by relatively slow temporal dynamics, with meaningful changes typically occurring over hundreds of milliseconds. Consequently, previous work has shown that sampling rates in the range of approximately 50-100 Hz are generally sufficient for reliable pupillometry (Beatty & Lucero-Wagoner, 2000; Mathôt et al., 2018). *Blink-related metrics*, such as blink rate and blink duration, similarly do not require very high sampling frequencies, as blinks constitute relatively long-lasting periods of signal loss rather than brief, high-frequency events. Methodological studies indicate that sampling rates around 60-100 Hz are adequate for reliably detecting and quantifying blink frequency and duration, although higher sampling rates may improve the temporal precision of blink onset and offset estimation (Stern et al., 1984; Holmqvist et al., 2011). *Fixation-related measures*, including fixation duration, fixation count, refixations, fixation stability, and spatially derived gaze metrics such as gaze dispersion or gaze index, primarily rely on the spatial clustering of gaze samples over time. Previous research has demonstrated that sampling rates between approximately 60 and 120 Hz are sufficient for reliable fixation detection and characterization in attentional and visual exploration studies, particularly in applied and ecological settings (Salvucci & Goldberg, 2000; Nyström & Holmqvist, 2010; Holmqvist et al., 2011). At these frequencies, fixation-based metrics can be estimated with adequate temporal and spatial accuracy for most cognitive and behavioral analyses. The sampling rate requirements for *saccade-related measures* depend strongly on the specific parameters of interest. Spatial characteristics such as saccade direction, amplitude, and the side of the first saccade are primarily determined by gaze displacement and can be reliably estimated at moderate sampling rates (approximately 60-120 Hz) (Duchowski, 2017; Holmqvist et al., 2011). In contrast, saccadic metrics that depend on fine-grained temporal dynamics, such as peak velocity, acceleration profiles, microsaccades, or detailed velocity-based analyses, require substantially higher sampling rates, typically in the range of 250-500 Hz or higher, to ensure accurate measurement (Engbert & Kliegl, 2003; Nyström & Holmqvist, 2010).

Overall, these methodological considerations indicate that the selection of an appropriate eye-tracking sampling rate should be guided by the specific oculomotor indices under investigation, distinguishing between measures driven primarily by spatial gaze distribution and those relying on rapid temporal dynamics.

4.3.4. Leverage eye parameters with Immersive Virtual Reality: a potential application in neuropsychology

Given the strong evidence for a close relationship between eye movements and attentional processes, oculomotor metrics ca n be considered reliable and objective biomarkers for use in clinical settings, both as diagnostic and prognostic indicators. The collection of these measures does not rely on verbal or motor responses, which are often impaired in patients with acquired brain injuries and may confound performance on standardized neuropsychological tests. As such, eye-tracking measures provide a more objective and real-time assessment of attentional functioning, offering valuable insights into the underlying cognitive mechanisms of attention.

However, the acquisition of such data is still rarely implemented in clinical settings, mainly due to the need for multiple instruments and complex setup procedures. Moreover, collecting eye-tracking data during commonly used paper-and-pencil or computerized tests does not fully capture the underlying mechanisms of attention, as these assessments often suffer from low ecological validity and may not reflect attentional processes as they occur in real-world contexts.

In this regard, immersive virtual reality (iVR) represents a valuable and promising tool. Modern head-mounted displays (HMDs) are now equipped with integrated eye-tracking systems, which greatly simplify data acquisition and improve the reliability and sensitivity of oculomotor measures by providing highly ecological, interactive environments (Clay, König & König, 2019; Kaiser et al., 2022). Recent applications have shown that combining eye-metrics with iVR can enhance diagnostic procedures, allowing for the detection of clinically relevant attentional deficits that often remain unnoticed by standardized protocols, while also providing prognostic indicators useful for defining personalized rehabilitation pathways (Hougaard et al., 2021; Thomasson et al., 2024). Within rehabilitation contexts, real-time eye-tracking feedback can be used to adapt stimuli and scenarios dynamically based on patient performance, enabling a more personalized, engaging, and potential effective training experience (Martino Cinnera et al., 2024). Finally, most of the study used single eye metrics to predict attention abilities, while, as we described in detailed in this paragraph, several eye parameters can be used as a biomarker of each of the different attentional subcomponents. Using a one-to-one analysis can lead to an underestimation of the predictive power (Daley et al., 2020).

Given this evidence, future research should implement iVR-based attentional paradigms that simultaneously acquire multiple eye parameters and analyze them through a multimodal approach to better define the relationship between eye movements and attentional processes in healthy populations. Furthermore, applying this methodology to patients with acquired brain injuries could provide sensitive and specific diagnostic and prognostic biomarkers of attentional deficits, thereby supporting both clinical assessment and the design of individualized rehabilitation strategies.

Summary of Theoretical Background and Objectives of the Present Thesis

Overall, the literature reviewed highlights several unresolved issues in the assessment and rehabilitation of attentional deficits following acquired brain injury. Despite growing evidence supporting the value of physiological or oculomotor metrics as biomarkers of attentional functioning, limited research has systematically examined their behavior in more realistic, life-like scenarios, such as those offered by iVR, which may enhance the reliability of the attention related measures. In particular, it remains unclear how cardiac indices such as heart rate and heart rate variability reflect cognitive workload when cognitive demands are intertwined with physical load and affective engagement, as typically occurs in immersive scenarios. Moreover, although individual eye-tracking metrics have been associated with specific attentional components, their combined predictive value across multiple attentional domains has rarely been investigated, especially within ecologically valid immersive settings. Crucially, the translational relevance of these iVR-based oculomotor framework for clinical populations with attentional impairments, as well as their potential prognostic value for rehabilitation outcomes, remains largely unexplored.

The empirical studies presented in this thesis are designed to address these gaps by developing and testing iVR cognitive tasks integrating cardiac and eye-tracking measures as objective biomarkers of attentional functioning. Chapter 5 investigates autonomic modulation during iVR cognitive tasks, disentangling the contributions of cognitive workload and physical load on cardiac measures. Chapter 6 examines whether a multidimensional combination of eye-tracking parameters acquired during iVR attention tasks can reliably predict distinct attentional capacities in healthy adults. Chapter 7 extends this framework to a clinical population, testing the sensitivity and specificity of combined oculomotor measures in detecting attentional deficits and exploring their cortical and white matter correlates. Finally, Chapter 8 evaluates the feasibility of an iVR-based attention rehabilitation protocol and explores whether pre-intervention eye-tracking patterns can serve as predictors of individual rehabilitation trajectories, supporting the development of personalized neuropsychological interventions.

Chapter 5

Decoupling the contribution of Physical and Cognitive Workload on HRV in Immersive Virtual Reality

5.1. Introduction

It is well established that successful task performance depends on the balance between an individual's cognitive skills and the level of challenge (i.e., cognitive workload, CWL) posed by the activity (Csikszentmihalyi & Csikszentmihalyi, 1992; Engeser and Rheinberg, 2008; Fong et al., 2015; Keller and Blomann, 2008; Khoshnoud, Igarzabel & Wittman, 2022). According to the flow-channel model, this optimal combination leads to the so-called *flow* state, conceptualized as an optimal state of consciousness with high degree of concentration which leads to absolute absorption in an activity, sense of enjoyment and ease of processing (Csikszentmihalyi, 2014). This positive psychological state is associated with increased goal-oriented attention, underpinned by reduced activity in the Default Mode Network (DMN) along with increasing activation within both the reward system (e.g., amygdala, hippocampus, nucleus accumbens, dorsolateral prefrontal cortex, cingulate cortices, and insula) and attention-related networks (e.g., orienting and alerting network; see Petersen & Posner, 2012 for a review) (Alameda, Sanadria & Ciria, 2022; Gold & Ciorciari, 2021; Ju & Wallraven, 2019; see van der Linden, Tops, & Bakker, 2021, for a review). Moreover, it leads to a moderate increase in arousal and performance, in line with the inverted U-shape relationship described by Yerkes-Dodson Law (Landhäußer & Keller, 2012; Khoshnoud, Igarzábal, & Wittman, 2020; Yerkes & Dodson,1908). Conversely, when CWL exceeds skill level, individuals often experience frustration and anxiety, leading to diminished concentration and, consequently, poor performance (Longo et al., 2018; Luque-Casado et al., 2016; Lucchese, Padovano, & Facchini, 2025; Perone, Weybright, & Anderson, 2019; Solhjoo et al., 2019). Accurate CWL assessment is therefore essential, especially in neurorehabilitation settings where cognitive resources are already compromised by brain lesions. Maintaining patients' motivation is also critical to reduce drop-out rate, sustain engagement and optimize functional recovery (Catania et al., 2024; Serino et al., 2022). Currently, the common approach for evaluating CWL is self-report measures, with NASA's Task Load Index (NASA-TLX; Hart, & Staveland, 1988) being the most widely used. This tool provides a direct, person-centered estimation (Longo et al., 2018) and it has been successfully applied in high-demand contexts such as surgery (Zheng et al., 2012), laboratory paradigms (N-back task: Luque-Casado et al., 2016; Muth et al., 2012) as well as in neurorehabilitation (motor-training: La Bara et al., 2021; cognitive-training: Wu et al., 2023). However, self-reports are inherently subjective and prone to bias (Cavedoni et al., 2020; Solhjoo et al., 2019). In healthy populations, distortions such as the *better-than-average* effect, (i.e., overestimation of one's own abilities) are well documented (Guenther & Alicke, 2010). In clinical population, self-assessment can be even more problematic due to anosognosia (i.e., a lack of awareness or an underestimation of their specific deficits) following brain lesion (Heilman, Barrett, & Adair, 1998; Orfei et al., 2007). As an alternative, psychophysiological measures are increasingly recognized as objective, sensitive and real-time biomarkers of cognitive processes (see Charles and Nixon, 2019, for a review). Among these, heart rate (HR) and heart rate variability (HRV) have been consistently associated with CWL. A large body of evidence shows that increasing CWL is typically associated with elevated HR and reduced HRV, reflecting autonomic nervous system (ANS) imbalance and corresponding declines in attention and cognitive performance (Castaldo et al., 2017; Delliaux et al., 2019; Luft, Takase, & Darby, 2009; Luque-Casado et al., 2016; Thayer et al., 2009). These cardiac measures therefore provide reliable indicators of workload (Hughes et al., 2019). The link between ANS and CWL is conceptually framed within the Neurovisceral Integration Model (Thayer et al., 2009; Thayer & Lane, 2009), which posits that HR and HRV index the dynamic adjustments of a neural network coordinating autonomic and cognitive control. Within this model, prefrontal cortex (PFC) functions as key hub of the central autonomic network, exerting top-down inhibitory control over subcortical sympathoexcitatory structures (e.g., amygdala, caudal and ventrolateral medulla) to maintain balance between sympathetic and parasympathetic outflow (Thayer et al., 2009). In *default mode* or under balanced task engagement, such regulation sustains adaptive performance. By contrast, when CWL exceeds, hypoactivation of PFC leads to reduced inhibitory control and disinhibition of sympathoexcitatory circuits (i.e., "flight or fight" response; LeDoux, 1996), corresponding to HR increasing and HRV decreasing (Forte & Casagrande, 2025; Thayer et al., 2009; Thayer & Lane, 2009; Wei et al., 2024). These changes are thought to be partially mediated by the baroreflex system, i.e., the negative feedback loop adjusting heart activity to blood pressure fluctuations, which itself can be modulated by behavioral manipulations of CWL (e.g., Delliaux et al., 2019; Duschek, Werner, & Reyes del Paso, 2013; Lusque-Casado et al., 2016). Most of the above cited evidence supporting HRV as biomarkers of CWL derives from controlled laboratory paradigms (e.g., N-back, mental arithmetic, Stroop task). Although such tasks allow precise modulation of cognitive demands, their ecological validity remains limited. Real-world cognitive challenges are dynamic and multimodal, requiring simultaneous integration of motor, perceptual and executive processes (Marucci et al., 2021). It is therefore crucial to investigate HRV modulation under naturalistic conditions, interactive contexts that better approximate everyday demands. Immersive virtual reality (iVR) offers a powerful framework in this direction. iVR enables the creation of simulated environments that closely mimic the complexity of daily life activities, while maintaining a high degree of experimental control (Parsons, 2016; Pieri, Tosi, & Romano, 2023; Serino et al., 2022). Evidence suggests that acting within immersive environments elicits stronger physiological responses than traditional 2D conditions (Chirico et al., 2017; Lo Priore et al., 2003; Slater et al., 2006, 2009). This increased modulation is thought to be driven by the *sense of presence* (i.e., the sense of being the subject of those actions and actively participating in the experience; see Slater and Sanchez-Vives, 2016 for a review) that is higher in iVR settings. Moreover, HRV pattern observe in iVR tend to approximate those elicited by real-life experiences, reinforcing the ecological validity and higher reliability of these measures (Marín-Morales et al., 2021). So far, studies investigating CWL in iVR have been conducted primarily on applied contexts such as aviation and piloting (Reddy et al., 2022), education and training (Hsin et al., 2023), driving simulators (Ju, Williamson, & Wallraven, 2022), and exposure-based clinical interventions (McCall et al., 2015). However, there is currently limited work using HRV as a proxy of CWL in iVR tasks specifically designed for cognitive training. The possibility of having reliable physiological biomarkers of CWL represents a promising tool to be exploited in rehabilitation settings. Integrating such measures with the potential of iVR in rehabilitating cognitive deficits after acquired brain injuries (Chatterjee et al., 2022; Salatino et al., 2023; Serino et al., 2022) could allow the implementation of real-time, adaptive and tailored modulation of task demands, thereby keeping patients within an optimal balance between challenge and skill (i.e., flow state), ultimately facilitating engagement and therapeutic outcomes (Longo et al., 2018; Luque-Casado et al., 2016; Solhjoo et al., 2019). Importantly, it must be emphasized that iVR, much like real-life activities, involves not only CWL, but also physical workload (PWL), as interactions with the environment require motor engagement (Garde et al., 2002; Luft, Takase & Darby, 2009; Srinivasan et al., 2016). The effects of PWL on HRV are well documented: motor activity activates autonomic regulation through central command (i.e., feedforward motor signals) originating in cortical motor areas, as well as through exercise pressor reflexes driven by afferent feedback from working muscles (Michael, Graham, & Davis, 2017; Stanley, Peake, & Buchheit, 2013). These mechanisms increase sympathetic outflow and reduce vagal tone, leading to elevated HR and decreased HRV (Stanley, Peake, & Buchheit, 2013). Even light activities such as walking or object manipulation can measurably reduce vagally mediated HRV (Hautala, Tulppo, & Seppänen, 2009), while more intense or prolonged efforts induce stronger suppression and delayed vagal recovery (Buchheit, 2014). Similarly, in occupational contexts, manual handling or repetitive lifting has been shown to decrease HRV regardless of mental workload, underscoring the unique contribution of motor demands to autonomic modulation (Michael, Graham, & Davis, 2017; Tomes, Schram, & Orr, 2020). Understanding and disentangling these partially independent sources of modulation is therefore essential if HRV is to be used as a valid biomarker of cognitive workload in ecological and clinical contexts.

The present study addresses this gap by examining the relative contributions of CWL and PWL in iVR scenarios. Using a new wearable sensor to continuously record HR and HRV, together with measures of cognitive performance, physical performance, and subjective workload ratings (NASA-TLX), we aim to identify which HRV indices (e.g., across time-, frequency-, and non-linear domains) are sensitive to cognitive demands and/or predominantly reflect motor activity. Crucially, only those HRV parameters that show modulation by workload components (CWL or PWL) and demonstrate consistent correlations with the related objective performance and subjective workload ratings will be considered as candidate biomarkers. Clarifying this distinction will provide the basis for establishing HRV as a robust physiological marker of workload in immersive environments and for informing the development of real-time, adaptive, and patient-centered interventions in cognitive rehabilitation.

5.2. Material and Methods

5.2.1. Participants

A total of 18 healthy adult participants with no history of psychiatric, neurological, and/or epileptic disorders were recruited initially in the current study[2] by e-mail advertising. They all had normal or corrected-to-normal vision. Five participants were excluded from analyses due to inadequate physiological signal acquisition, defined as missing or incomplete data (<50%) in at least one protocol condition. The final sample therefore comprised 13 participants (6 female; mean age = 26.9 years, SD = 2.68 years; mean educational level = 13.85 years, SD = 1.91 years; mean MoCA score = 28.45, SD = 1.23).

All participants were fully informed about the experimental procedure and the objectives of the study and provided written informed consent for participation and the processing of personal data. The experiment was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethical Committee of the Lausanne University Hospital (*Prot. 2017-01588*). A compensation of 20 CHF/hour for their participation was attributed. Data collection has taken place at the Service Universitaire de Neuroréhabilitation (SUN), Lausanne University Hospital.

[2] The present study is part of a wider project conducted in collaboration between the Department of Psychology (University of Bologna), the Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland) and MindMaze SA (Lausanne, Switzerland).

Sample size estimation

The present study was conceived as an exploratory investigation aimed at disentangling the relative contributions of cognitive and physical workload to cardiac autonomic modulation in immersive virtual reality scenarios. At the time of study design, reliable effect size estimates for HRV modulation during interactive iVR tasks combining cognitive and physical demands were not available; therefore, a formal a priori power analysis was not feasible.

Sample size was defined based on methodological feasibility and consistency with previous psychophysiological studies employing immersive virtual reality paradigms and cardiac measures. For instance, Malińska et al. (2015) investigated heart rate variability during virtual reality immersion in a sample of 19 healthy adults, analyzing ECG-derived parameters across repeated temporal segments. Similarly, Hsin et al. (2022) investigated HRV and mental workload during a 360° VR learning task with 28 undergraduate participants, linking autonomic measures to subjective workload indexes. Finally, Özgün et al. (2024) explored the relationship between cognitive performance and HRV using a VR cognitive assessment system in a sample of 16 healthy adult participants. For completeness, a post-hoc sensitivity analysis was conducted to estimate the ability of the present design to detect effects of the magnitude observed in the main analyses. Specifically, the analysis was based on the Cognitive × Physical interaction effect on mean heart rate, which represented the primary effect of interest and showed a large effect size (η^2partial = .19). Assuming an alpha level of .05 and a within-subject design with four repeated conditions, the achieved statistical power was high ($1 - \beta \approx .98$).

5.2.2. Equipment and Devices

To record physiological data, participants wore the Healer R3 wearable device (L.I.F.E.'s Healer Line, https://www.x10x.com/telehealth/)3, an adaptable t-shirt equipped with embedded sensors for multimodal monitoring. The system integrates twelve standard ECG leads (L1, L2, L3, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6) with carbon dry electrodes sampled at 500 Hz, three respiratory band channels (Thoraz, Xiphoid, Abdomen) with a sampling rate of 50 Hz, and ten 9-axis inertial measurement units (3-axis accelerometer, 3-axis gyroscope, 3-axis magnetometer) sampled at 100 Hz. Data were continuously collected and managed through the KoR 1 Logger, a compact unit integrated into the back of the garment which stored locally and transmitted the collecting data via wireless connectivity. Recording sessions were initiated via the Healer R mobile application, which

[3] Healer is certified in Europe (CE) as a class IIa medical device according to the applicable requirements of Directive 93/42/EEC (MDD) and 2007/47/EC

also allowed verification of electrode status, while real-time monitoring and data synchronization were performed through the Healer Desktop application on the same Wi-Fi network.
For the visualization of the activities comprising the experimental protocol, participants were fitted with the HTC Vive Pro Eye head-mounted display (HMD) with a display resolution of 1440 x 1600 pixels per eye, 90 Hz refresh rate and a field of view (FOV) of 110° (HTC Company statements). Patients' position was calibrated via HTC SteamVR 2.0 tracking system to ensure the virtual environments displayed were centered (see Fig.5.1).

5.2.3. Experimental Procedure

Participants were seated at the center of the experimental room, ensuring freedom of arm and hand movements and fitted with both Healer R3 and the HMD. The experimental protocol combined iVR-based activities from MindFocus software (MindMaze SA). The software comprises iVR-based activities designed to train targeted attentional components in patients with ABIs. The activities employed in the current protocol were selected with the aim to manipulate both cognitive and physical demands, resulting in four 10-minutes conditions: low cognitive/low physical load, high cognitive/low physical load, high cognitive/high physical load, and low cognitive/high physical load (see section *"MindFocus iVR-based activities"*). The four experimental conditions were administered in a counterbalanced block-wise order. Specifically, four predefined condition sequences were created, each representing a different ordering of the experimental conditions. Participants were assigned to these sequences following a rotating allocation procedure, ensuring that each condition appeared equally often in each ordinal position across participants.
After each condition, participants completed the NASA-TLX (Hart & Staveland, 1988) to provide subjective ratings of perceived workload (see section: *"NASA Task Load Index, NASA-TLX"*). Before the manipulation protocol, participants completed a 10-minutes resting-state condition while they performed a Free Viewing Exploration task (see section: *"MindFocus Free-Viewing Exploration task, iVR-FVE"*), used to establish baseline physiological activity.
Finally, a 10-minutes recovery phase, which replicated the baseline iVR-FVE condition, allowing a return of physiological parameters toward baseline. The overall duration of the experimental protocol is about 2 and a half hours.
All the immersive virtual reality environments visualized are developed using the Unity game engine (Unity Technologies, www.unity.com) by MindMaze SA (Lausanne, Switzerland) (see Fig.5.1).

<u>*MindFocus Free-Viewing Exploration task (iVR-FVE)*</u>

Both for the baseline and recovery phases, participants performed a 10-minutes version of the Free-Viewing Exploration task (iVR-FVE) included in the Assessment Module of MindFocus software (MindMaze, SA). The iVR-FVE is a 3D adaptation of the task originally developed by Nardo and colleagues (2019) in bidimensional form. The task consists of a series of 1500 ms video clips showing everyday-life scenarios, presented in two possible randomized sequences. Each video displayed a dynamic main event occurring either on the left (Lateral Left), the right (Lateral Right), or bilaterally. In bilateral conditions, the primary event is more prominent either on the left (Bilateral Left) or the right (Bilateral Right). To re-center participants' gaze between trials, a uniform grey screen with a central black cross was displayed for a randomized duration of 3500 to 5000 ms, in increments of 250 ms. The task was fully passive: participants were instructed to observe the videos without performing any motor response and to minimize body and head movements (see Fig.5.1).

<u>*MindFocus iVR-based activities*</u>

The trial session comprised interactive activities selected from the Rehabilitation Modules of MindFocus (MindMaze, SA), which include multiple levels that progressively increase cognitive and physical demands. For each of the four experimental conditions, two activities lasting five minutes each were selected.

In the *low cognitive/low physical load condition (LCLP),* participants performed Butterfly Level 1 and Fencing Level 2. In Butterfly Level 1, they were asked to aim the laser pointer and press the controller trigger (low physical load) toward a single butterfly presented without distractors (low cognitive load). In Fencing Level 2, participants reproduced a sequence of two balls presented in different spatial positions by reaching with the hand (low physical load), following the order of presentation (low cognitive load).

In the *high cognitive/low physical load condition (HCLP)*, Butterfly Level 22 and Fencing Level 14 were included. In Butterfly Level 22, participants identified a target butterfly among multiple distractors (high cognitive load) while using the laser pointer and trigger button (low physical load). In Fencing Level 14, participants reproduced progressively longer sequences of balls appearing in different spatial sectors, either in the same or inverse order as presented (high cognitive load), by reaching with the hand (low physical load).

In the *low cognitive/high physical load condition (LCHP)*, participants performed Tennis Level 3 and Ball Level 10. In Tennis Level 3, they hit balls approaching from different spatial locations (low cognitive load) at high speed and frequency that adapted to performance (high physical load). In Ball

Level 10, participants hit footballs approaching with high speed and frequency (high physical load), without distractors (low cognitive load).

In the *high cognitive/high physical load condition (HCHP)*, Ball Level 12 and Soccer Level 8 were played. In Ball Level 12, participants hit only the footballs while avoiding distractors (high cognitive load) under conditions of high speed and frequency (high physical load). In Soccer Level 8, they responded to balls thrown by specific players, adapting their action based on software instructions (high cognitive load), again under high speed and frequency demands (high physical load, see Fig.5.1)

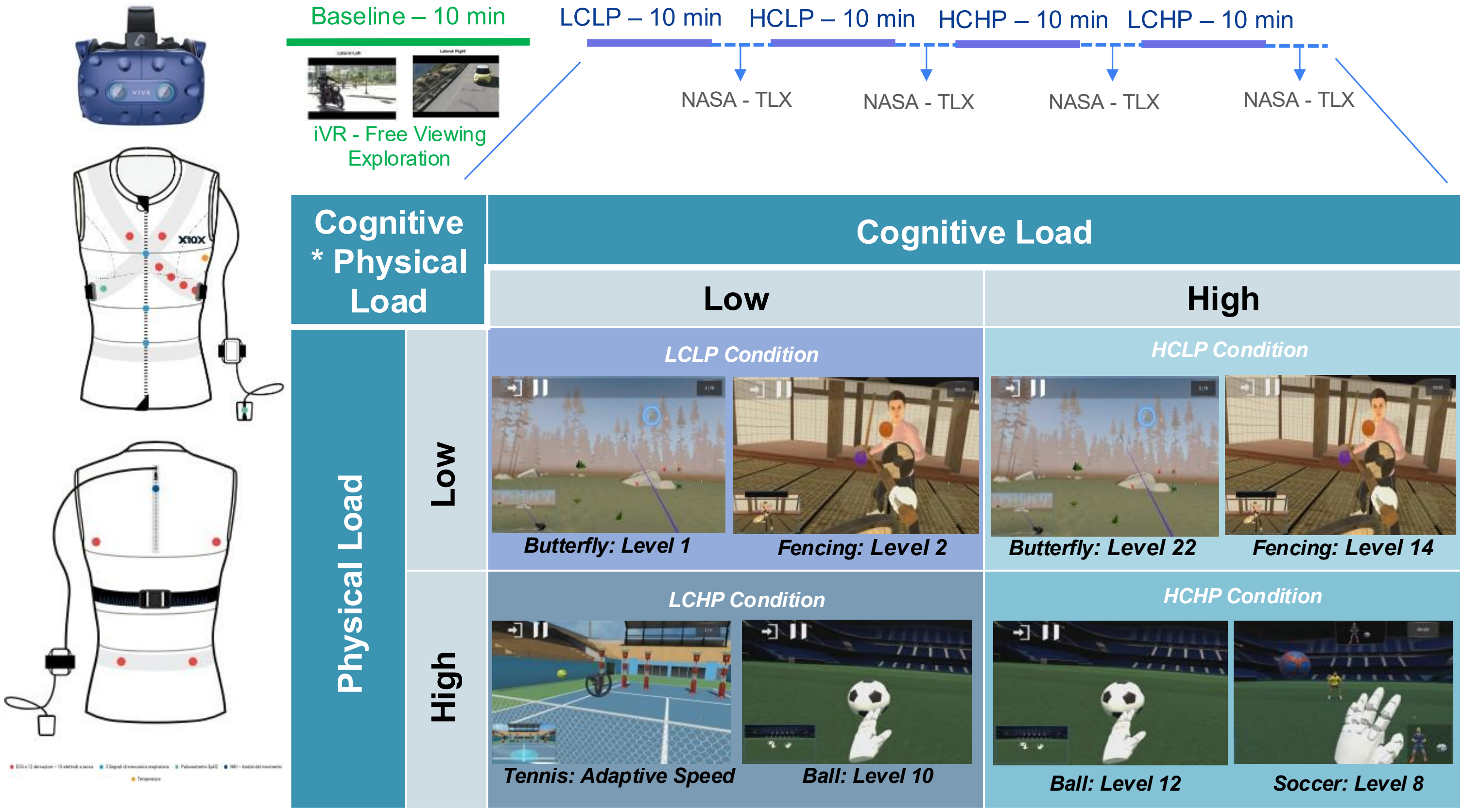


Figure 5.1. Experimental protocol and task design. Participants first completed a 10-minute baseline phase consisting of the Free-Viewing Exploration task (iVR-FVE; MindFocus, MindMaze SA), followed by four 10-minute interactive iVR activities corresponding to the Low Cognitive/Low Physical load (LCLP), High Cognitive/Low Physical load (HCLP), High Cognitive/High Physical load (HCHP), and Low Cognitive/High Physical load (LCHP) conditions. Each condition comprised two gamified tasks selected from the MindFocus Rehabilitation Modules that systematically varied cognitive and physical demands: (i) LCLP: Butterfly Level 1, Fencing Level 2; (ii) HCLP: Butterfly Level 22, Fencing Level 14; (iii) LCHP: Tennis (adaptive speed), Ball Level 10; (iv) HCHP: Ball Level 12, Soccer Level 8. Subjective workload was assessed with the NASA-TLX after each condition.

NASA Task Load Index (NASA-TLX)

Subjective workload was assessed using the NASA Task Load Index (NASA-TLX; Hart & Staveland, 1988). The NASA-TLX comprises six subscales: mental demand, physical demand, temporal demand, performance, effort, and frustration, each rated on a 20-point Likert scale ranging from "*very low*" to "*very high*".

Although participants completed the full NASA-TLX after each experimental condition, in their native tongue (English, Italian or French), for the purposes of this study, analyses focused specifically on the mental demand and physical demand subscales as measures of subjective workload in these two domains (see Fig.2).

5.2.4. Pre-processing of ECG and Respiratory signals: Heart Rate Variability and Respiration Rate Analysis

ECG and respiratory signals recorded with the Healer R3 system were exported in raw format and processed separately for each participant and for each of the four 10-minutes protocol conditions using Kubios HRV Premium software (Kubios Oy, Kuopio, Finland; Tarvainen et al., 2014). The analysis pipeline included automated R-peak detection, followed by visual inspection of the resulting RR interval time series to ensure accuracy. Following recommendations for short-term recordings (Alcantara et al., 2020), artifacts were corrected using the medium threshold (0.25 s), with intervals deviating more than 25% from the local average adjusted via cubic spline interpolation. Cleaned inter-beat interval (IBI) series were then used to compute standard time-domain, frequency-domain, and non-linear heart rate variability (HRV) metrics in accordance with Task Force guidelines (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) (see Table 5.1).

Domain	***Variable***	***Unit***	***Description / Interpretation***
Time-domain	Mean RR (Mean of NN intervals)	ms	Average duration of NN (normal-to-normal) intervals; inverse of mean heart rate. Longer RR intervals generally reflect stronger parasympathetic (vagal) activity.
	Mean HR (Mean Heart Rate)	bpm	Average heart rate (beats per minute). Increased by sympathetic activation, decreased by parasympathetic activation.
	SDNN (Standard Deviation of NN intervals)	ms	Standard deviation of NN intervals reflects overall HRV, influenced by both sympathetic and parasympathetic activity.
	RMSSD (Root Mean Square of Successive Differences)	ms	Root means square of successive differences between NN intervals; robust marker of short-term parasympathetic (vagal) modulation.
	NN50 (Number of interval differences > 50 ms)	counts	Number of successive NN interval pairs differing by >50 ms; reflects parasympathetic (vagal) activity.
	pNN50 (Percentage of interval differences > 50 ms)	%	Percentage of successive NN interval pairs differing by >50 ms; parasympathetic (vagal) index.
	SD HR (Standard Deviation of Heart Rate)	bpm	Standard deviation of mean HR; reflects overall autonomic variability (mixed sympathetic and parasympathetic).
Frequency-domain	VLF (Very Low Frequency power, 0.003–0.04 Hz)	ms^2	Power in very low-frequency band; mechanisms unclear (thermoregulatory, hormonal influences); not a direct marker of autonomic modulation.
	LF (Low Frequency power, 0.04–0.15 Hz)	ms^2	Power in low-frequency band; reflects baroreflex activity and both sympathetic and parasympathetic influences.

	HF (High Frequency power, 0.15–0.40 Hz)	ms^2	Power in high-frequency band; respiration-related fluctuations, considered a reliable marker of parasympathetic (vagal) activity.
	LF/HF ratio (Low Frequency / High Frequency)	ratio	Ratio of LF to HF power; often interpreted as an index of sympatho-vagal balance, though its validity is debated.
	Total Power	ms^2	Total variance of NN intervals across all frequency bands; reflects overall autonomic modulation.
Non-linear	RR Triangular Index (HRV Triangular Index)	unitless	Geometric measure: total number of NN intervals divided by the height of the histogram; reflects global autonomic modulation (mixed).
	TINN (Triangular Interpolation of NN interval histogram)	ms	Baseline width of the triangular interpolation of the NN histogram; measure of overall HRV (mixed sympathetic and parasympathetic).
	SD1 (Poincaré plot short axis)	ms	Reflects short-term variability, primarily parasympathetic (vagal) activity.
	SD2 (Poincaré plot long axis)	ms	Reflects both short- and long-term variability (mixed sympathetic and parasympathetic).
	SD2/SD1 ratio (Poincaré ratio)	ratio	Ratio of long- to short-term variability; often interpreted as sympatho-vagal balance.
Respiratory	Resp (Respiration Frequency)	Hz	Mean respiration frequency; influences HF band power, which reflects parasympathetic modulation.

Table 5.1. Summary of heart rate variability (HRV) parameters across time-domain, frequency-domain, non-linear, and respiratory measures, including their units and physiological interpretations in terms of sympathetic and parasympathetic modulation.

5.2.5. Computing Physical and Cognitive performance variables

<u>*Physical Performance Index (PPI)*</u>

To quantify physical performance during each protocol condition, hand kinematic data registered, from the sensors embedded in the controllers of HMD, were analyzed following a stepwise procedure. First, delta hand position was computed for each timestamp as the difference between consecutive 3D coordinates (x,y,z) of the hand position (HandPosition_{t+1} – HandPosition_{t}). Second, these differences were squares for each axis, and the Euclidean distance between consecutive positions were calculated.

For each of the participants, for each condition a 3D diagram was computed representing the hand kinematic across the overall duration of the iVR activities (Fig.5.2). Third, instantaneous hand speed was obtained by dividing DISTANCE by the elapsed time (Δt). For each timestamp, left and right-hand speeds were summed to obtain an overall measure of motor activity. To summarize motor activity over the entire duration of each 10-minute condition, the Area Under the Curve (AUC) of the speed-time series was extracted. The AUC represents the total movement performed by a participant, reflecting the overall *Physical Performance Index* (PPI) during a condition (Murphy, Willen &

Sunnerhagen, 2013). The AUC was computed using the trapezoidal rule, which approximates the definite integral by partitioning the curve into trapezoids and summing their areas.

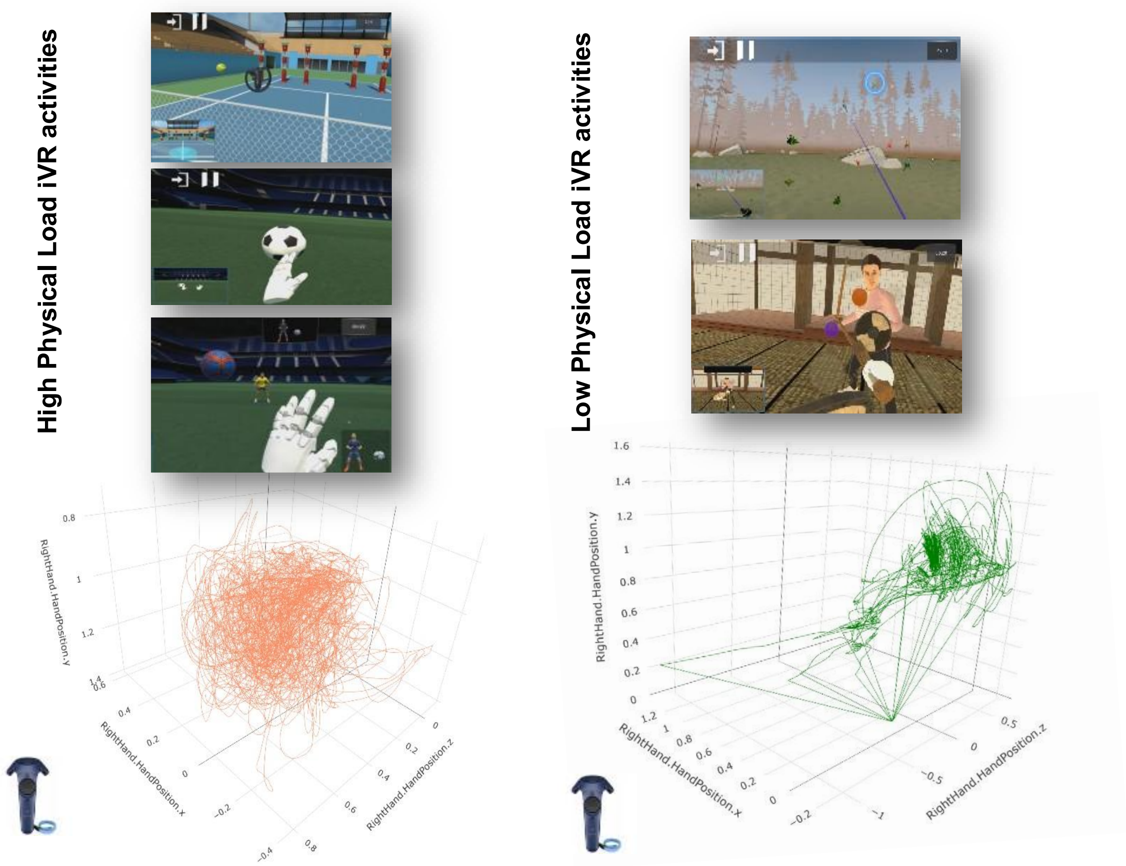


Figure 5.2. Schematic 3D representation of kinematic hand movement extracted for each patient in each experimental condition. A representative trajectory under High Physical Load Condition (on the left) using Tennis, Soccer and Ball iVR activities. On the right, the kinematic hand trajectory registered during the Low Physical Condition (on the right). Hand position data were recorded from HMD controllers and plotted across the entire session duration to quantify motor activity, which was subsequently used to compute the Physical Performance Index (PPI)

Cognitive Performance Index (CPI)

Cognitive performance for each condition was quantified using both trial engagements and task accuracy. For each activity comprising each of the four conditions, the distribution of trial completed across all participants was examined, and the 95th percentile of the distribution was taken as the maximum effective trial count for that activity. Each participant's effective number of completed trials was then divided by this 95th percentile value, yielding a normalized trial engagement index. Accuracy was defined as the proportion of targets successfully hit out of the total number of targets presented. *Cognitive Performance Index* (CPI) was expressed as the product of the normalized trial engagement index and the accuracy score, according to the following formula:

$$CPI = \frac{Trials}{P95(Trials)} \times \frac{TargetsHit}{TotalTargets}$$

5.2.6. Statistical Analysis

All statistical analyses were performed in R (RStudio-2024.12.01.563 for Windows 11, R version 4.3.3 – 2025-02-28 ucrt, Posit team, PBC, Boston, MA) using the packages lme4, lmerTest and emmeans. Statistical significance was set at $p < .05$. For linear mixed-effects models, fixed effects were evaluated using Satterthwaite-approximated p-values from the model summary. When significant interactions were observed, post-hoc pairwise comparisons were performed on estimated marginal means (EMMs), with p-values adjusted for multiple comparisons using the false discovery rate (FDR) method (Benjamini & Hochberg 1995).

Validation of Workload Protocol Manipulation

To assess whether the experimental protocol successfully modulated perceived physical and cognitive workload, a linear mixed-effects model (LMM) was fitted using subjective ratings from the NASA-TLX physical and mental demand subscales as dependent variables. The model included Scale (*Physical vs. Mental demand*) and Condition (*LCLP, LCHP, HCLP, HCHP*) as within-subject factors, with random intercepts for participants. The significance of fixed effects was evaluated using Type III Wald χ^2 tests.

Exploring physiological biomarker of cognitive and physical workload

To examine whether the experimental manipulation modulated autonomic responses, and to determine whether such modulation was specifically related to cognitive demand, physical demand, or their interaction, linear mixed-effects models (LMMs) were fitted for each physiological parameter extracted from ECG and respiratory recordings (see Table 4.1). All physiological measures were baseline-corrected by subtracting the resting-state (Baseline) value from each experimental condition.

Each model followed the structure:

$$\textit{Baseline-corrected physiological}_i \sim \textit{Cognitive} \times \textit{Physical} + (1|\textit{Subject}_i)$$

Where Cognitive (low vs high load) and Physical (low vs high load) were included as fixed effects, and a random intercept accounted for repeated measures within participants.

Correlation Analyses and Biomarker validity

Finally, to evaluate whether the physiological parameters that showed significant modulation in the LMMs could serve as biomarkers of task performance and perceived workload, correlation analyses were performed. The goal was to test whether specific autonomic indices were not only sensitive to the experimental manipulation, but also consistently related to performance and subjective perception within the same workload domain (cognitive or physical). To this end, baseline-corrected physiological indices were correlated with the Physical Performance Index (PPI), the Cognitive

Performance Index (CPI), and the NASA-TLX Mental and Physical demand subscales using Pearson's correlation (two-tailed, $\alpha = .05$).

5.3. Results

5.3.1. Validation of Workload Protocol Manipulation

The LMM highlighted a significant main effect of Condition ($\chi^2_{(3)} = 53.33$, $p < .001$), but no main effect of Scale ($\chi^2_{(1)} = 0.47$, $p = .49$). Importantly, there was a robust Condition × Scale interaction ($\chi^2_{(3)} = 76.93$, $p < .001$), indicating that the manipulation differentially affected mental and physical workload ratings (see Fig.5.3). On the Mental demand scale, ratings were higher in the high cognitive load conditions compared with the low cognitive load conditions. Specifically, HCHP (90.7 ± 4.4) was rated higher than LCLP (76.2 ± 4.4, $p < .001$) and LCHP (53.9 ± 4.4, $p = .013$), while HCLP (74.2 ± 4.4) was rated higher than both LCHP ($p < .001$) and LCLP ($p < .001$, see Fig.4). On the Physical demand scale, ratings were driven by physical load manipulation. HCHP (321.0 ± 26.0) was rated higher than both LCLP (56.3 ± 26.0, $p < .001$) and HCLP (292.4 ± 26.0, $p < .001$), while LCHP (78.2 ± 26.0) was higher than LCLP ($p < .001$, see Fig.5.3). These results confirm that the protocol successfully modulated subjective workload in the expected direction: mental demand increased with cognitive load, and physical demand increased with physical load. Interestingly, the pattern of the data also suggests that in HCHP conditions, the high physical demands tend to attenuate participants' perception of cognitive effort.

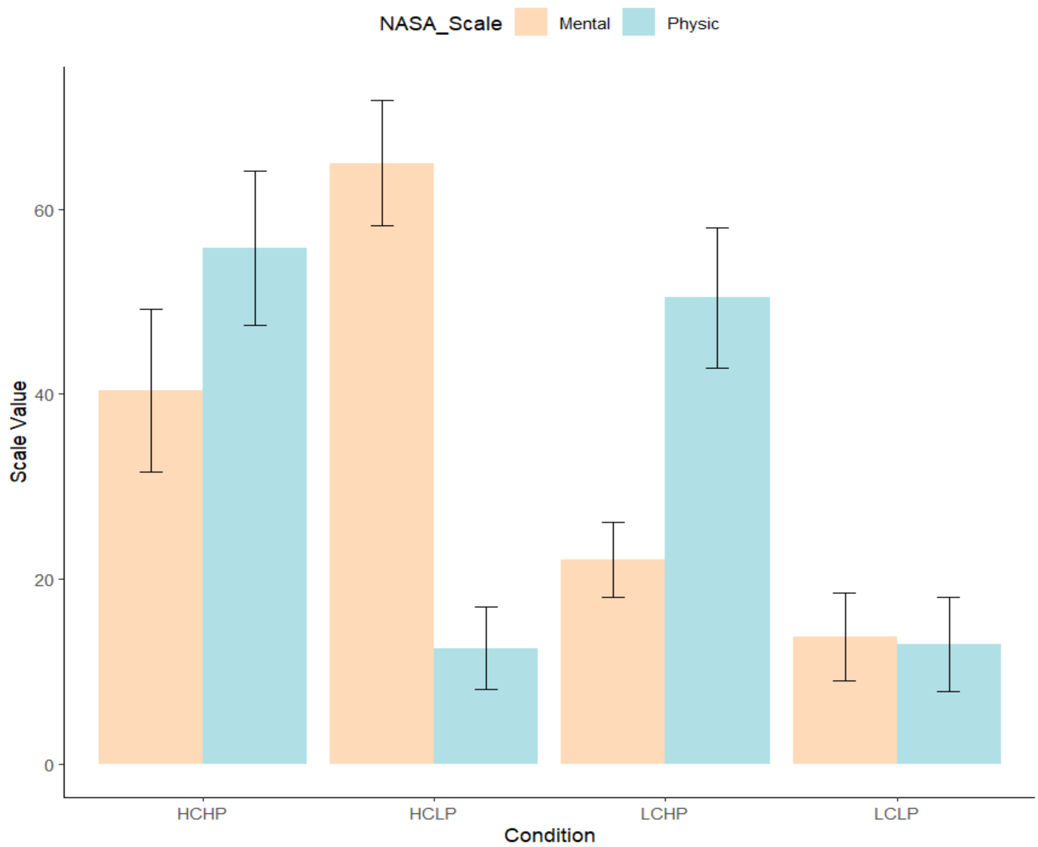


Figure 5.3. Estimated marginal means (± SE) of NASA-TLX Mental and Physical demand ratings across the four experimental conditions (LCLP = Low Cognitive/Low Physical load, LCHP = Low Cognitive/High Physical load, HCLP = High Cognitive/Low Physical load, HCHP = High Cognitive/High Physical load). Mental demand ratings increased selectively with higher cognitive load, whereas physical demand ratings increased selectively with higher physical load, confirming that the protocol effectively manipulated the intended workload dimensions. Bars filled in peach represent Mental demand, and bars filled in light blue represent Physical demand. Error bars represent the standard error of estimated marginal means from the LMM model.

5.3.1. Cognitive and Physical Performances

The LMM underscore a significant main effect of Physical workload (β = 8.695, SE = 2.151, $t_{(33)}$ = 4.041, $p < 0.001$, $\eta^2_{partial}$ = .33), while no significant effect was found for the Cognitive workload condition (β = -1.455, SE = 2.151, $t_{(33)}$ = -0.676, p = 0.50, $\eta^2_{partial}$ = .01). Importantly, the Physical x Cognitive workload interaction was significant (β = 9.687, SE = 2.151, $t_{(33)}$ = 4.503, p = < 0.001, $\eta^2_{partial}$ = .38). The post-host contrast showed that under high cognitive/high physical load participants maintained the higher accuracy performance (HCHP: M = 91%, se = 43.9) compared to LCHP (M = 74%; p = 0.02), HCLP (M = 54%; p < 0.001) and LCLP (M = 76%, p = 0.03; Figure 5.4A). Moreover, in HCLP, participants showed lower performance accuracy compared to the HCLP (p = 0.004) and the LCLP (p = 0.003). While no significant difference was found in cognitive performance between the LCHP and LCLP (p = 0.75; Figure 5.4A).

Concerning the Physical Performance, the LMM showed only a significant main effect of physical load condition (β = 119.734, SE = 11.60, $t_{(33)}$ = 10.32, $p < 0.001$, $\eta^2_{partial}$ = .76; Figure 5.4B), while neither the cognitive load ($\beta = 12.624$, SE = 11.60, $t_{(33)} = 1.088$, $p = 0.28$) nor the interaction physical x cognitive load ($\beta = 1.678$, SE = 11.60, $t_{(33)} = 0.145$, $p = 0.89$) were significant. The main effect of Physical load highlighted that during high physical load condition, the physical performance (M = 306.7, se = 20.2) was high compared with the one achieved during low physical load conditions (M = 67.2, se = 20.2; Figure 5.4B).

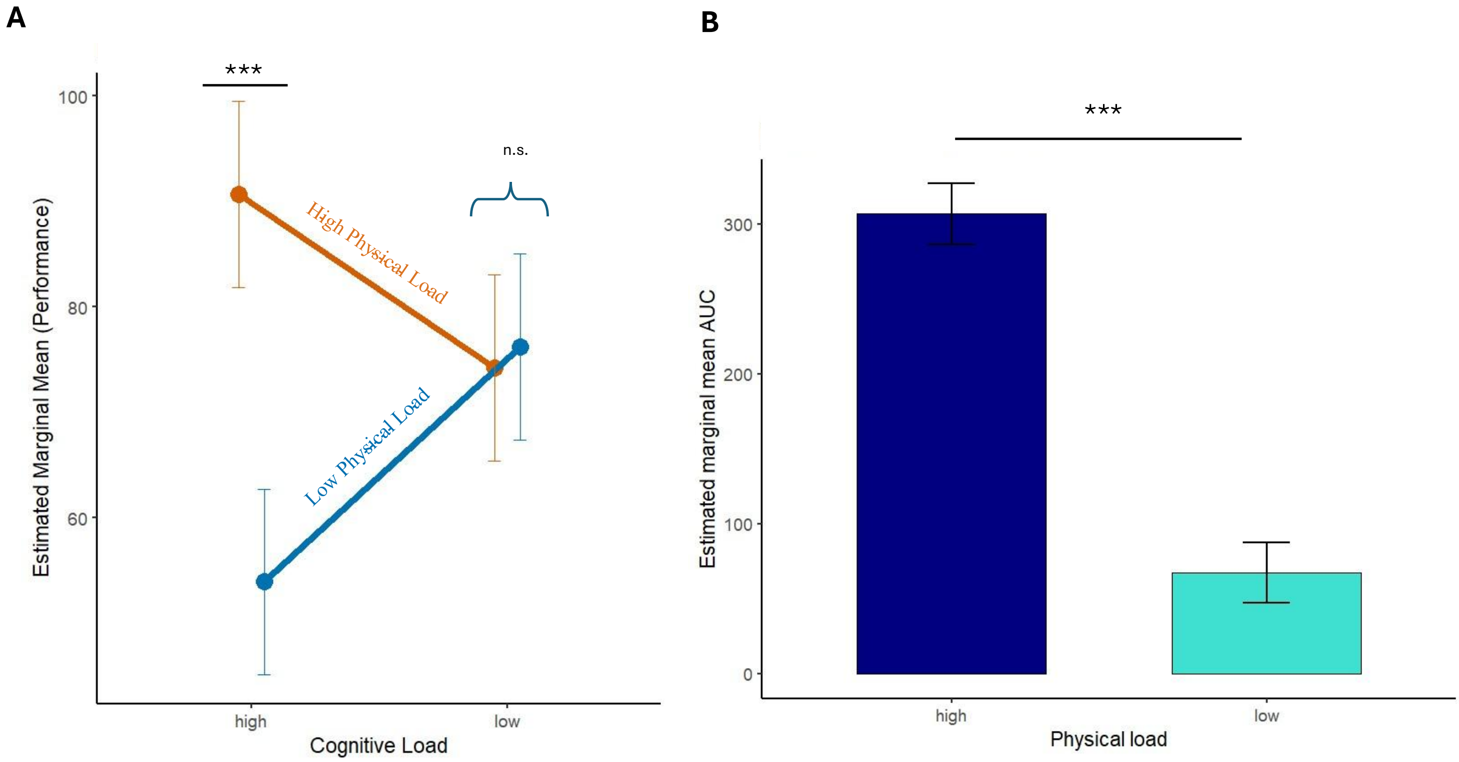


Figure 5.4. Cognitive Performance and Physical Performance responses to cognitive and physical load. A) Estimated marginal means (± SE) from the LMM show that Cognitive Performance increased selectively with high physical (orange line), with a stronger increase under High compared to Low cognitive load. **B)** Estimated marginal means (± SE) from the LMM show that Physical Performance increased selectively with high physical load conditions.

5.3.2. Physiological Biomarkers of Cognitive and Physical Workload

Table 5.2. summarizes the results of the LMMs conducted for each ECG- and respiration-derived variable, along with correlations with subjective NASA-TLX ratings and performance indices. Several measures demonstrated sensitivity to the experimental manipulation of workload conditions, particularly to physical load. Significant associations also emerged primarily between physiological markers, the NASA-TLX physical demand subscale, and the Physical Performance Index (PPI), suggesting a stronger physiological coupling with physical workload compared to cognitive workload. Therefore, only a subset shows potential as candidate biomarkers with systematic associations to subjective ratings and performance. Accordingly, in the following sections, we present detailed results focusing on those biomarkers that consistently relate to specific workload domains.

Variables		Workload Conditions (p-value LMM)			Subjective ratings (p-value Pearson)		Performance (p-value Pearson)	
		Cognitive	Physical	Cognitive* Physical	NASA Mental Scale	NASA Physical Scale	PPI	CPI
Phy	PPI	*0.33*	***<0.01****	*0.90*	*0.76*	***<0.01****	---	***0.04****
Cog	CPI	*0.50*	***<0.01****	***<0.01****	***0.03****	*0.17*	***0.04****	---
Time	**Mean HR (bpm)**	*0.12*	***<0.01****	***<0.01****	*0.88*	***<0.01****	***0.01****	*0.60*
Time	RMSSD (ms)	*0.34*	*0.47*	*0.30*	*0.47*	*0.21*	*0.07*	*0.63*
Time	**Mean RR (ms)**	*0.18*	***<0.01****	***0.01****	*0.93*	***<0.01****	***<0.01****	*0.62*
Time	SDNN (ms)	*0.55*	*0.77*	*0.63*	*0.64*	*0.29*	*0.33*	*0.68*
Time	pNN50 (%)	*0.31*	*0.19*	*0.34*	*0.59*	*0.97*	*0.73*	*0.94*
Time	NN50 (beats)	*0.93*	***<0.01****	*0.93*	*0.25*	***0.02****	*0.16*	*0.63*
Time	**RR tri-index**	*0.05*	***<0.01****	*0.67*	*0.69*	***0.046****	***<0.01****	*0.35*
Time	TINN (ms)	*0.61*	*0.55*	*0.93*	*0.76*	*0.39*	*0.39*	*0.94*
Freq	HF (Hz)	*0.21*	*0.95*	*0.84*	***0.02****	*0.38*	*0.25*	*0.51*
Freq	Resp (Hz)	*0.79*	*0.20*	*0.63*	*0.99*	*0.0*	*0.31*	*0.40*
Freq	LF (Hz)	*0.46*	***<0.01****	*0.19*	*0.56*	*0.16*	***<0.01****	*0.46*
Freq	VLF (Hz)	*0.46*	*0.40*	*0.40*	*0.63*	*0.96*	*0.30*	*0.54*
Freq	Total Power ratio (ms^2)	*0.66*	*0.58*	*0.63*	*0.73*	*0.47*	*0.88*	*0.76*
Freq	LF/HF ratio	*0.34*	*0.81*	*0.95*	*0.25*	*0.08*	*0.11*	*0.38*
NLin	SD HR (bpm)	*0.48*	*0.07*	*0.34*	*0.87*	***<0.01****	*0.10*	*0.95*
NLin	SD1 (ms)	*0.14*	*0.19*	*0.70*	*0.37*	*0.21*	***0.03****	*0.65*
NLin	SD2 (ms)	*0.40*	*0.62*	*0.69*	*0.14*	*0.09*	*0.61*	*0.50*
NLin	SD2/SD1 (ms)	*0.67*	*0.64*	*0.18*	***0.04****	*0.26*	*0.10*	*0.15*

Table 5.2. Summary of linear mixed-effects model (LMM) results testing the effects of cognitive load, physical load, and their interaction (Cognitive × Physical) on physiological parameters derived from ECG and respiratory measures. Baseline-corrected values were analyzed with models including fixed effects of Cognitive and Physical load and a random intercept for subjects. The table also reports Pearson's correlations between each physiological parameter, subjective NASA-TLX ratings (mental and physical demand subscales), and performance indices (Physical Performance Index, PPI; Cognitive Performance Index, CPI). Significant effects and correlations are highlighted in bold ($p < .05$). These results guided the identification of candidate biomarkers with domain-specific associations (e.g., parameters selectively related to physical workload). The first column indicates the measures' domain: Phy = Physical domain; Cog = Cognitive domain; Time = Time domain; Freq = Frequency domain; NLin = non-linear domain.

Mean HR (bpm)

The LMM revealed a significant main effect of Physical load ($\beta = 3.90$, $se = 0.68$, $t_{(33)} = 5.71$, $p < .001$, $\eta^2_{partial} = .50$), indicating that Mean HR increased on average by ~3.9 bpm under high relative to low physical load. The main effect of Cognitive load was not significant ($\beta = -1.09$, $se = 0.68$, $t_{(33)} = -1.60$, $p = .120$, $\eta^2_{partial} = .07$). Importantly, there was a significant Cognitive × Physical interaction ($B = -1.90$, $se = 0.68$, $t_{(33)} = -2.78$, $p = .009$, $\eta^2_{partial} = .19$).

Post-hoc contrasts indicated that under high physical load, Mean HR increased more strongly when Cognitive load was low (LCHP: M = 12.16 bpm, se = 1.68) compared to high cognitive load (HCHP: M = 6.18 bpm, se = 1.68). Under low physical load, HR remained close to baseline (HCLP = 2.18 bpm; LCLP = 0.56 bpm). Post-hoc contrasts confirmed that the largest HR increase occurred in the

LCHP condition (11.6 bpm relative to LCLP, p < .001), while HR increases were attenuated when high physical demands coincided with high cognitive demands (HCHP < LCHP, -5.98 bpm, p = .008). Under low physical load, HR remained close to baseline (HCLP = 2.18 bpm; LCLP = 0.56 bpm), with no significant difference between them (p = .410; Fig.5.5).

Pearson's correlations further confirmed the specificity of this effect. Mean HR change from baseline correlated positively with subjective physical demand ratings (NASA Physical Scale: r = .42, 95% CI [.16, .63], p = .003) and with the Physical Performance Index (PPI/AUC) (r = .57, 95% CI [.33, .73], p < .001), but not with subjective mental demand ratings (NASA Mental Scale: r = -.02, p = .884) nor the Cognitive Performance Index (r = -.08, p = .601; Fig.5.5).

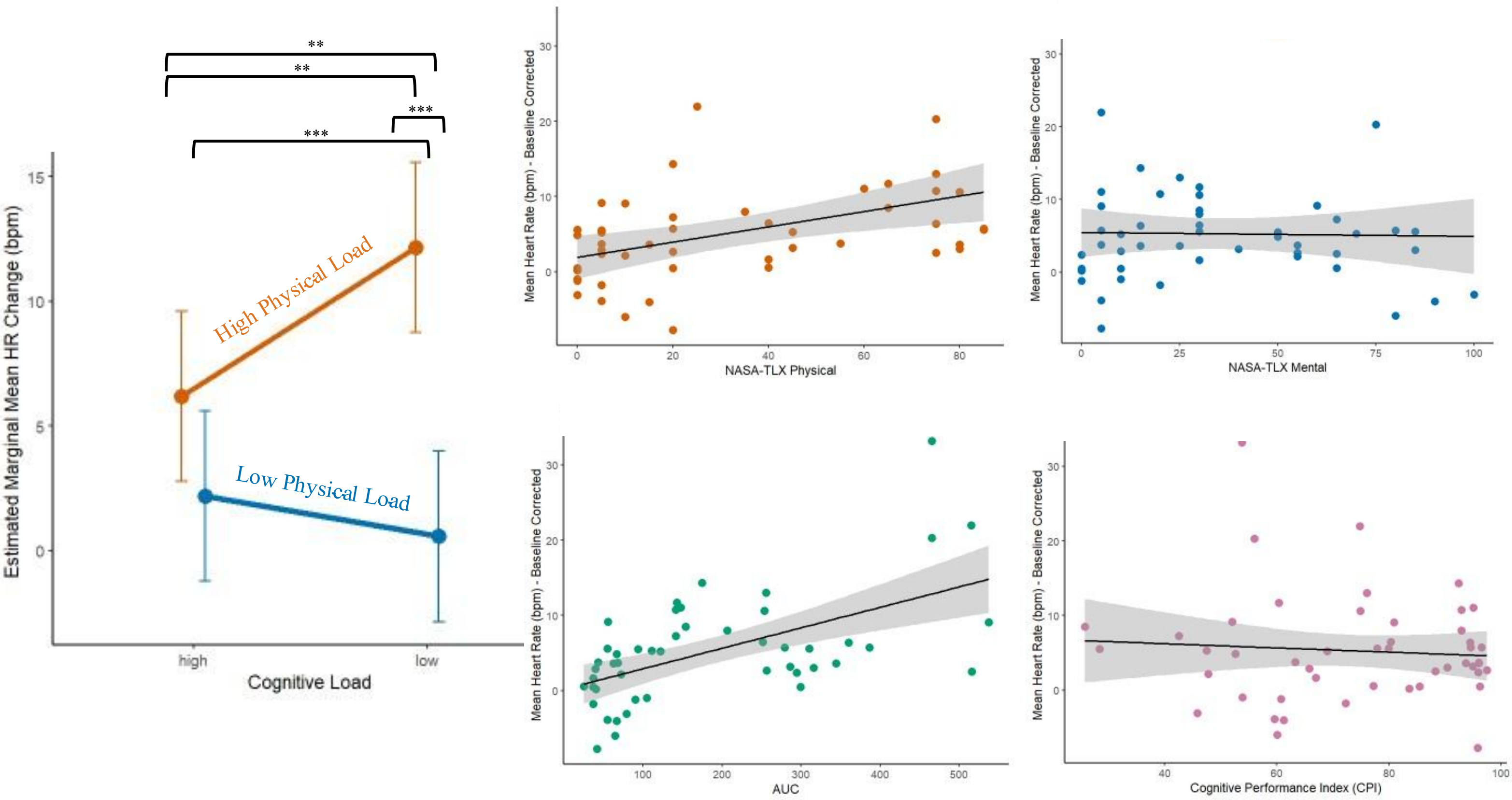


Figure 5.5. Mean heart rate (HR) responses to cognitive and physical load. *Left:* Estimated marginal means (± SE) from the LMM show that Mean HR increased selectively with high physical (orange line), with a stronger increase under low compared to high cognitive load. *Right:* Scatterplots with regression lines (95% CI shaded) illustrate correlations between baseline-corrected mean HR and subjective workload ratings (NASA-TLX Physical and Mental demand subscales) as well as performance indices (Physical Performance Index, PPI/AUC; Cognitive Performance Index, CPI). Mean HR was positively associated with physical demand ratings (r = .42, p = .003) and with PPI (r = .57, p < .001), but not with mental demand ratings or CPI. ** p < 0.05; ** p < 0.01; *** p < 0.001, ns = not significant*

Mean RR (ms)

The LMM revealed a significant main effect of physical load (β = -37.21, se = 6.32, $t_{(33)}$ = -5.89, p < .001, $\eta^2_{partial}$ = .51) indicating shorter RR intervals under high (LCHP and HCHP) compared to low physical load (LCLC, HCLP). The main effect of cognitive load was not significant (β = 8.76, se = 6.32, $t_{(33)}$ = 1.39, p = .176, $\eta^2_{partial}$ = .05). Moreover, the Cognitive × Physical interaction was significant, (β = 17.23, se = 6.32, $t_{(33)}$ = 2.73, p = .010, $\eta^2_{partial}$ = .18; Fig.5.6).

Pairwise comparisons confirmed that RR intervals were shortest in the LCHP condition (M = -116.00 ms), which differed significantly from HCHP (M = -64.03 ms; contrast = -52 ms, p = .010), HCLP (M = -24.06 ms; contrast = -92 ms, $p < .0001$), and LCLP (M = -7.12 ms; contrast = -109 ms, $p < .0001$). RR intervals in the HCHP condition were significantly shorter than in HCLP (p = .039) and LCLP (p = .006), while no significant difference emerged between HCLP and LCLP (p = .351). These results indicate that physical load robustly shortened RR intervals, with the strongest vagal withdrawal observed in LCHP, while concurrent high cognitive demands (HCHP) attenuated this effect. Pearson's correlations further supported this interpretation. Baseline-corrected mean RR was negatively correlated with NASA-TLX Physical demand subscale (r = -.39, 95% CI [-.61, -.12], p = .006) and with the Physical Performance Index (PPI/AUC) (r = -.55, 95% CI [-.72, -.32], $p < .001$), but not with NASA-TLX Mental demand subscale (r = .01, p = .933) or the Cognitive Performance Index (r = .07, p = .622; Fig.5.6).

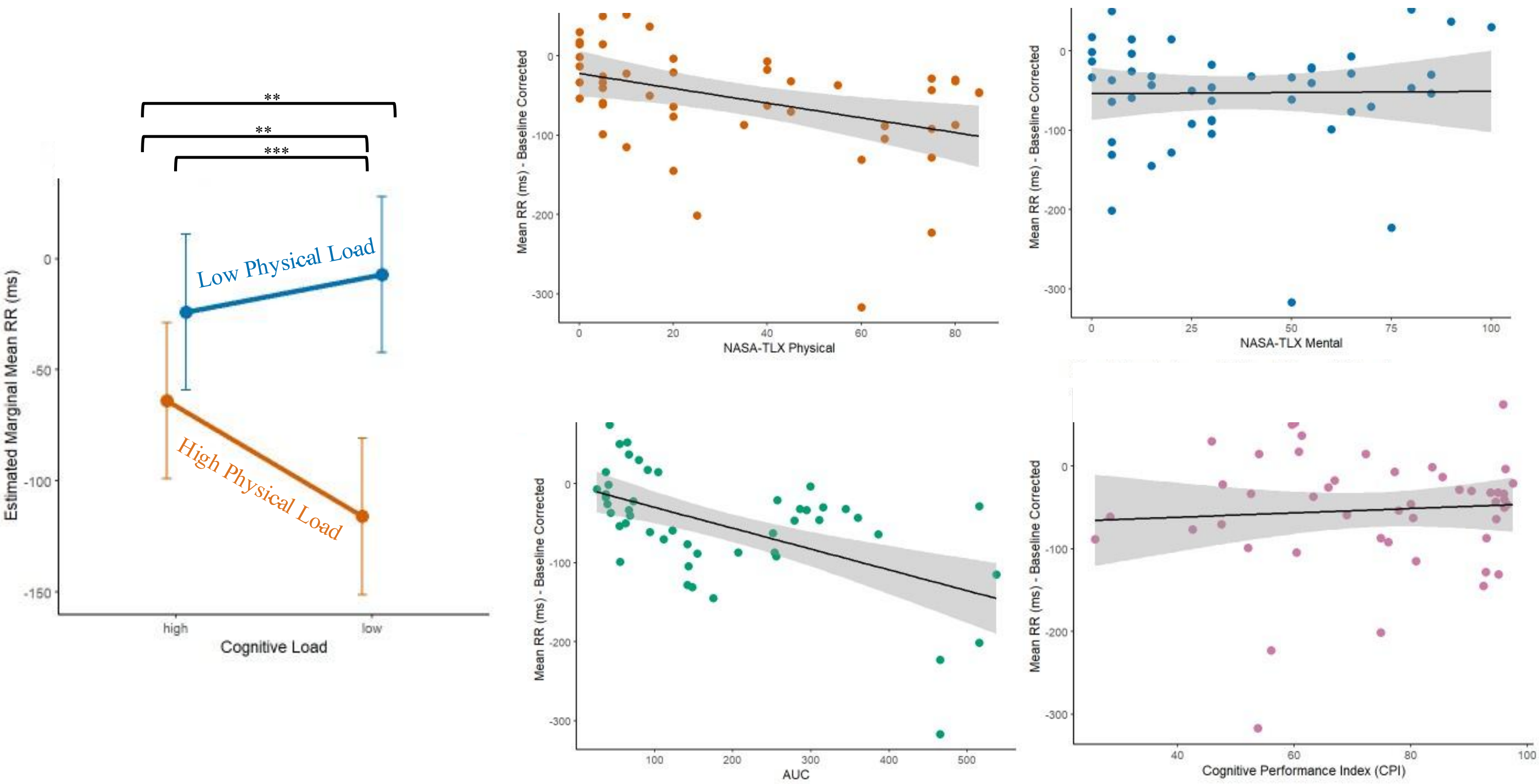


Figure 5.6. Mean RR interval responses to cognitive and physical load. *Left:* Estimated marginal means (± SE) from the LMM show that RR intervals were shortened under HP load (orange line), with the strongest reduction observed in the LCHP condition. *Right:* Scatterplots with regression lines (95% CI shaded) illustrate correlations between baseline-corrected mean RR and subjective workload ratings (NASA-TLX Physical and Mental demand subscales) as well as performance indices (Physical Performance Index, PPI/AUC; Cognitive Performance Index, CPI). RR intervals were negatively associated with physical demand ratings ($r = -.39$, p = .006) and PPI ($r = -.55$, $p < .001$) but showed no relationship with mental demand ratings or CPI.
** p < 0.05; ** p < 0.01; *** p < 0.001, ns = not significant*

RR Triangular Index

The LMM revealed a significant main effect of physical load (β = -1.34, se = 0.19, $t_{(33)} = -7.20$, $p < .001$, $\eta^2_{partial}$ = .61), indicating reduced RRtri values under high (M = -3.244) compared to low physical load (M = -0.564; Fig.5.7). The main effect of cognitive load was marginal ($\beta = 0.37$, se = 0.19, $t_{(33)} = 2.00$, $p = .054$, $\eta^2_{partial} = .11$), while the Cognitive × Physical interaction was not significant ($\beta = 0.08$, se = 0.19, $t_{(33)} = 0.42$, $p = .675$, $\eta^2_{partial} < .01$). Based on Pearsons' correlations RRtri reductions were negatively associated with NASA-TLX physical subscale ratings (r = -.29, 95% CI [-.53, -.01], p = .047) and with the Physical Performance Index (PPI/AUC) (r = -.39, 95% CI [-.61, -.12], $p = .006$). In contrast, no significant correlations emerged with NASA-TLX mental demand ratings (r = .06, $p = .691$) or the Cognitive Performance Index (r = -.14, $p = .351$; Fig.5.7).

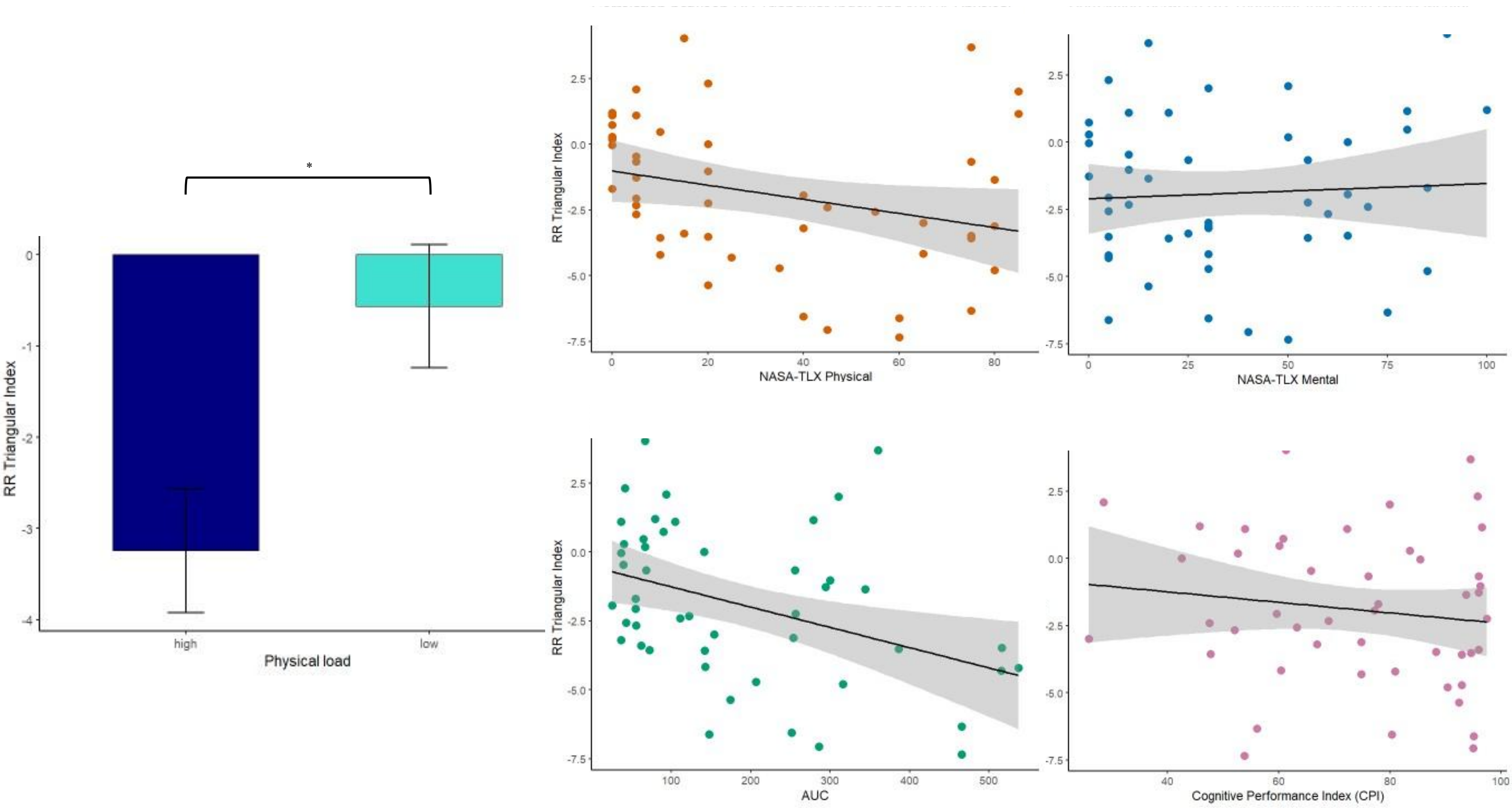


Figure 5.7. RR Triangular Index (RRtri) as a function of workload and its associations with subjective ratings and performance. *Left:* Estimated marginal means (± SE) show that RRtri was significantly lower under high compared to low physical load, independent of cognitive load (p<0.01). *Right:* Scatterplots with regression lines (95% CI shaded) illustrate baseline-corrected RRtri values as a function of NASA-TLX ratings and performance indices. RRtri was negatively correlated with NASA-TLX physical demand ratings ($r = -.29$, $p = .047$) and the Physical Performance Index (PPI/AUC; $r = -.39$, $p = .006$), while no significant associations were observed with NASA-TLX mental demand or the Cognitive Performance Index (CPI). *$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, ns = not significant.*

5.4. Discussion

The aim of this study was to disentangle the relative contributions of cognitive workload (CWL) and physical workload (PWL) to subjective ratings, task performance, heart rate (HR), and heart rate variability (HRV) measures. While HR and HRV are widely used as biomarkers of workload, previous research has primarily examined their association with CWL in controlled laboratory settings. This approach fails to account for the fact that, in ecological settings, mental workload emerges from the synergy of multiple interdependent factors, and that physical effort itself can influence both the perceived workload and HR/HRV measures (Stanley, Peake, & Buchheit, 2013; Buchheit, 2014; Michael, Graham, & Davis, 2017).

To address this gap, we developed a protocol in immersive virtual reality (iVR) that allowed the concurrent manipulation of CWL and PWL within interactive, multimodal and complex scenarios, while recording physiological signals with new-generation wearable sensors.

The results show that our protocol is effective in manipulating the targeted load components, as confirmed by subjective ratings (NASA-TLX). Tasks with high cognitive demands (HC) or high physical demands (HP) were associated with significantly higher reports of CWL or PWL, respectively, compared to their low-load counterparts (LC and LP). Notably, the results from subjective reports also suggest that HP conditions attenuated participants' perception of cognitive demands, especially when cognitive requirements were high (i.e., HC conditions). These findings are consistent with the idea that PWL requires cognitive resources, posing the need of redirecting part of the attentional focus toward body signals and motor control to cope with it, ultimately reducing the salience of the concurrent CWL (Schaefer, 2014; Wickens, 2008). In addition, acute physical activity has been associated with lower subjective mental strain and improved affective state (Dietrich & Audiffren, 2011). From this evidence, PWL may act as distractor or as a competing resource, in line with the dual-task and resource competition frameworks (Schaefer, 2014; Wickens, 2008). These models posit that attentional and perceptual resources are shared between motor and cognitive domains, so, tasks that required simultaneously motor and cognitive activity constrain cortical availability (de Souza et al., 2025; Hogg et al., 2022). The present results further underscore the importance of taking into account the contribution of single workload sub-components when employing subjective ratings from the NASA-TLX (Galy, Paxion, & Berthelon, 2018). A more fine-grained analysis of these components can have a non-negligible effect on understanding overall workload perception (Collet, Averty, & Dittmar, 2009; Galy, Paxion, & Berthelon, 2018; Zenia et al., 2025), particularly in environments that mirror every-day situations, where cognitive and physical demands are often jointly involved (Garde et al., 2002; Luft, Takase & Darby, 2009; Srinivasan et al., 2016). These findings from subjective ratings are further strengthened by the evidence from our cardiac measures analysis. Mean heart rate (HR) and mean RR interval (RR), widely accepted as respectively reflecting sympathetic and parasympathetic activation (Delliaux et al., 2019; Hughes et al., 2019; Thayer et al., 2009; Thayer & Lane, 2009; Wei et al., 2024), were robustly modulated by PWL and consistently linked to subjective ratings (i.e., NASA-TLX Physical demand subscale) and physical performance (Physical Performance Index, PPI). The observation of HR acceleration and corresponding RR shortening under HP conditions, is consistent with the classical autonomic response to motor effort characterized by an increase sympathetic activation (i.e., mean HR) coupled with parasympathetic inhibition (i.e., mean RR). These responses are mediated by two primary mechanisms: a central command, a feedforward drive from cortical and subcortical motor regions that pre-activates autonomic adjustments at exercise onset, and the exercise pressor reflex, a feedback loop driven by mechanoreceptor and metaboreceptor activation in working muscles (Williamson, 2010; Michael, Graham, & Davis, 2017). Together, these mechanisms increase cardiac output and ensure oxygen delivery to active muscles. Crucially, our results highlight that these cardiovascular responses are not uniform but depend on the interaction between PWL and CWL. The increasing in mean HR with the concurrent decreasing in mean RR were most pronounced when high physical demands occurred in the absence of high cognitive requirements, while they were attenuated when high CWL was combined with high PWL. This pattern suggests that cognitive and physical load do not have a linearly addition effect but rather compete for shared attentional and physiological resources. Consistently with the multiple-resource and resource-competition models (Schaefer, 2014; Wickens, 2008), the human system relies on a limited pool of resources that must be flexibly allocated across task domains. When cognitive processing demands are high, a portion of cortical and autonomic resources are diverted toward executive control, thereby constraining the full expression of autonomic adjustments to physical effort and vice versa. The results from correlation analyses further corroborate this primary role of PWL in shaping workload perception and performance-related indices. In this line, mean HR increases were positively correlated with subjective ratings of physical demand and with physical performance index, indicating that greater cardiac acceleration was associated with stronger perceived physical effort required by the task and higher motor output (i.e., AUC of overall speed movements). Accordingly, mean RR intervals were negatively correlated with physical ratings and performance, meaning that shorter beat-to-beat intervals were linked to higher subjective physical demands and increased physical task performance. Importantly, neither mean HR nor mean RR showed significant associations with mental demand or cognitive performance, underscoring their specificity to physical effort.

The same specificity was evident for the RR triangular index (RRtri), a geometric measure of global HRV derived from the distribution of RR intervals (Sztajzel, 2004). RRtri decreasing under high PWL resulted as independent from CWL. Moreover, this greater suppression of the overall autonomic nervous system variability was associated with stronger perceived physical effort and higher motor output. Since RRtri captures the width of the RR distribution, its reduction suggests a global contraction of autonomic flexibility under motor strain, driven primarily by parasympathetic inhibition. The selective link with PWL observed here is consistent with findings from occupational ergonomics, where repetitive lifting or manual handling suppressed HRV independently of cognitive demands (Mehta & Agnew, 2012; Taelman et al., 2011). Extending these results to iVR, our findings highlight RRtri as a reliable and ecological marker of physical workload in interactive, multimodal environments.

Other indices showed significant but less selective associations. pNN50 was negatively correlated with physical ratings, reflecting parasympathetic withdrawal during physical activity (Forte, Favieri, & Casagrande, 2019; Schmitt et al., 2013), but its sensitivity results as less consistent. Low-frequency (LF) power correlated with both mental demand and physical performance, consistent with its hybrid role as an index of sympathetic–parasympathetic modulation (Goldstein et al., 2011; Reyes del Paso et al., 2013). High-frequency (HF) power was positively related to cognitive performance, in line with evidence linking parasympathetic activity to attentional control (Hansen et al., 2003; Thayer et al., 2009), however it was not modulated by CWL in our protocol. Among non-linear measures, SD-HR correlated with physical demand, SD1 with cognitive performance, and SD2/SD1 with mental demand (Delliaux et al., 2019; Laborde et al., 2017), but these effects were less systematic than those observed for HR, RR, and RRtri.

Taken together, our results demonstrate that in complex iVR scenarios, PWL exerts the strongest and most consistent influence on HRV, emerging as the primary driver of cardiac modulation linked to subjective physical effort experienced and motor performance. Conversely, No HRV measures selectively tracked CWL, suggesting that CWL effects are more likely subtle and masked when motor engagement is present. At the same time, the interaction effects, observed for mean HR and mean RR modulation, highlight cognitive effort as modulator of the expression of physical responses. Consistently, these results can be framed within the view that motor and cognitive processes compete for limited neural and physiological resources (Schaefer, 2014; Wickens, 2008). Moreover, it aligns with evidence that physical engagement can increase the sense of enjoyment, motivation and affective state, leading to a reduced focus on the cognitive effort invested in the task (Dietrich & Audiffren, 2011). Compared to the linear relationship between CWL and cardiac modulation typically reported in 2D settings, our results suggest that more complex environments, that more closely simulate the ones experienced in everyday life, require participants to distribute resources across multiple concurrent demands. This interplay revealed specific interactions between cognitive and physical components in shaping subjective effort, cardiac modulation and performance. By leveraging the ecological validity and the higher sense of presence of iVR (Chirico et al., 2017; Lo Priore et al., 2003; Slater et al., 2006, 2009; Slater and Sanchez-Vives, 2016), together with the recording of ECG signals (Marín-Morales et al., 2021), our approach demonstrates the potential of immersive methods for a more reliable multidimensional workload assessment in settings that approximate real-world complexity (Garde et al., 2002; Luft, Takase & Darby, 2009; Srinivasan et al., 2016).

From a practical perspective, this line of research holds promise for clinical applications, particularly in adaptive rehabilitation protocols. Wearable HRV monitoring could support dynamic adjustments of task difficulty to maintain participants within an optimal workload zone (i.e., flow state; Csikszentmihalyi, 2014). The flow state has been linked to enhanced engagement, motivation, and learning, which are crucial for rehabilitation outcomes (Catania et al., 2024; Harmat et al., 2016; Keller & Bless, 2008; Serino et al., 2022).
While our study highlights robust markers of PWL, further work is needed to identify cognitive-specific biomarkers that could complement them, allowing for more precise regulation of both motor and cognitive dimensions of workload in adaptive, patient-centered interventions. Moreover, the relatively small and homogeneous sample restricts generalizability of the present findings. Although the study was designed as an exploratory investigation, future research should include larger and more diverse, including clinical populations, to confirm the robustness of the observed effects and to refine effect size estimates for future a priori power calculations (Mulder, 1992; Fairclough & Houston, 2004). Nevertheless, post-hoc power estimates are intrinsically dependent on the observed effect size and should therefore be interpreted cautiously. Consistent with current methodological recommendations, effect size reporting remains the most informative indicator of the strength and relevance of the reported findings.

Second, our task manipulations, though ecologically richer than standard laboratory tests, capture only a subset of real-world demands. Broader paradigms targeting different cognitive processes (e.g., memory, decision-making under stress) and physical efforts (e.g., endurance activity) may reveal complementary autonomic signatures. Third, while wearable sensors provided reliable recordings, HRV is highly sensitive to breathing, posture and motor-related noise (Quintana & Heathers, 2014). These influences may mask more subtle cognition-related modulations, underscoring the need for multimodal monitoring (e.g., eye-tracking, electroencephalography). Particularly, eye-tracking measures such as pupil diameter, number of fixations, blink rate and dwell time on regions of interest have been shown to be modulated by CWL (Soler-Dominguez et al., 2017; Souchet et al., 2022; Tao et al., 2020), also in iVR protocols (Souchet et al., 2022). Unlike HRV, these measures are less prone to confounding by motor-related noise and they can be easily acquired within iVR environment, as recent head mounted displays are equipped with embedded eye-tracking technology. Future studies should therefore combine cardiac indices with oculomotor metrics in iVR protocols to gain deeper insight into CWL modulation.

In conclusion, by disentangling the relative contributions of CWL and PWL within iVR, our study shows that mean HR, mean RR, and RRtri are reliable markers of PWL, while CWL plays a modulatory but not independently trackable role in autonomic responses in our protocol. These results highlight the importance of multidimensional approaches to workload assessment in ecologically valid environments and point toward the potential of wearable-based monitoring to inform adaptive interventions aimed at sustaining optimal workload states, including flow, in both healthy and clinical populations.

Chapter 6

Eye Movements as Biomarkers of Attentional Components in Immersive Virtual Reality: Insight from a Large Cohort of Healthy Adults

6.1. Introduction

At any given moment, we are immersed in environments reach in multitude of sensory inputs. Since cognitive resources are limited in processing capacity (Atkinson & Shiffrin, 1968), the brain must prioritize certain information over others. Attention serves this function by biasing neural competition in favor of task-relevant material (Desimone & Duncan, 1995; Kastener et al., 2001; Treisman et al., 1960; Reynolds & Heeger, 2009), enabling relevant stimuli to dominate processing while suppressing irrelevant ones. This selective mechanism can be guided either by top–down control (i.e., selection based on prior knowledge and current goals), or by bottom–up capture (i.e., salient or unexpected stimuli attract attention regardless of task relevance), supported by partially segregated neural systems (Corbetta & Shulman, 2002; Posner, Snyder, & Davidson, 1980). Moreover, attention can be deployed covertly, without direct motor actions, or overtly, when it is accompanied by motor responds (e.g., eye-movements; Corbetta, 1998; Posner & Petersen, 2012; Rizzolatti et al., 1987). According to the premotor theory of attention (Rizzolatti et al., 1987), orientation toward an object or spatial location often reflects an intention to act upon it, even if no effective movements occur. In everyday life, eye movements are used to foveate relevant source of information, where visual processing is most precise (Pasqualette & Kulke, 2024), thereby reallocating attentional resources in preparation for an appropriate behavioral response (Allport, 2016; Pasqualette & Kulke, 2024). This close coupling between attention and action is reflected in overlapping neural substrates: a shared dorsal frontoparietal network is consistently engaged during both attentional allocation and preparation of eye movements toward attended targets (Corbetta & Shulman, 2002; Rizzolatti et al., 1987). Evidence from neuroimaging (Beauchamp et al., 2001; de Haan et al., 2008; Corbetta et al., 1998) and electrophysiology studies (Kulke et al., 2016; Kulke et al., 2021) further supports this convergence, highlighting the tight link between attention-related networks and oculomotor metrics (Lappi et al., 2016). Building on this evidence, eye metrics have been increasingly used as proxies for individual differences in attentional capacities (Tao et al., 2020). Given the multicomponential nature of attention (Leclercq & Zimmermann, 2002; Lindsay, 2020), research effort has gone in the direction of revealing whether and which oculomotor indices best capture specific attentional subcomponents. Modulation of pupil diameter has been shown to predict alertness abilities (i.e., the readiness to respond to upcoming stimuli; Petersen & Posner, 2012; Unsworth & Robison, 2016), through their association with the locus coeruleus norepinephrine activity (LC-NE), a system responsible for sleep-wake cycles and arousal regulation (Aston-Jones & Cohen, 2005; Petersen & Posner, 2012; Joshi, Kalwani, & Gold, 2016). Beyond pupil diameter, reduced alertness has been associated with higher fixation instability (Unsworth, Mille & Robison, 2020; Zhou et al., 2024), shorter fixation duration (di Stasi et al., 2013; Friedman & Komogortsev, 2024), increased blink frequency (Demiral et al., 2024) and longer blink duration (McIntire et al., 2014). In spatial attention research, the direction of the first fixation revealed a consistent leftward bias in healthy individual, a spatial exploration strategy known as "pseudoneglect", which reflects right-hemisphere dominance in spatial allocation (Bowers & Heilman, 1980; Heilman & Van Den Abell, 1980). Disruptions of this pattern are characteristic of unilateral spatial neglect (USN), a syndrome in which patients fail to orient and respond to stimuli toward controlesionale space (Heilman, Valenstein, & Watson, 2000; Cox & Davies, 2020; Kaiser et al., 2022; Serino et al., 2007). Complementary indices such as gaze index (i.e., distribution of time across hemifields; Hougaard et al., 2022; Nardo et al., 2019), gaze laterality (i.e., proportion of fixations per hemifield; Cazzoli et al., 2015; Cox & Davies, 2020; Franceschiello et al., 2022; Hougaard et al., 2022; Kaufmann et al., 2020), number of re-fixations, and perseverative eye patterns (Cazzoli et al., 2011; Cox & Davies, 2020; Paladini et al., 2019) have also been identified as markers of spatial attention, distinguishing healthy individuals from USN patients. Regarding selective attention, metrics such as fixation patterns (Geerlings et al., 2014; Skaramagkas et al., 2023), and time spent on distractors versus targets reveal the efficiency of selective filtering (Hollingworth & Bahle, 2019; Ridderinkhof & Wijnen, 2011; Stefani & Sauter, 2023). Alterations in these parameters have been linked to less efficiency of top-down mechanism or attentional set control (Goller, Mitrovic, & Leder, 2019; Schmidt et al., 2018).

Despite the robustness of existing results, most evidence comes from laboratory paradigms where the captured measure (i.e., attention subcomponent and their eye metrics biomarkers) are captured in 2D environments, constrained spatially and limited in complexity, ultimately reducing the ecological validity and the reliability of these indices (Bigler et al., 2025; Parsons, 2016; Pieri, Tosi, & Romano et al., 2023). As an alternative, immersive virtual reality (iVR) offers the possibilities of collecting eye metrices in complex, dynamic, 3D environments with 360° spatial exploration which more closely resemble real-world scenarios while preserving experimental control (Clay, König & König, 2019; Kaiser et al., 2022; Parsons, 2016; Pieri, Tosi, & Romano, 2023; Serino et al., 2022). Integrating eye-tracking into iVR tasks allows the study of attentional processes under conditions that approximate everyday demands, bridging the gap between controlled experiments and naturalistic behavior (Clay, König & König, 2019; Pieri, Tosi, & Romano et al., 2023). In this line, while conventional setups require several tools to collect and analyze eye metrics, modern head-mounted displays are equipped with embedded eye-tracking technology, facilitating not only data acquisition in both clinical and research contexts but also enables online use of eye-tracking data to adapt iVR scenarios in real time based on individuals' performance.

Given the potential differences in attentional demands between iVR environments and traditional 2D paradigms, where the majority of evidence linking eye metrics to attentional capacities has been obtained, it is therefore important to clarify whether these associations hold in immersive contexts.

To address this question, in the current study eye-tracking metrics from a large cohort of healthy participants were collected while performing iVR tasks. Specifically, we examine whether oculomotor parameters can reliably index three major attentional components: alertness, spatial attention, and selective attention. By disentangling the contributions of these subcomponents, we aim to establish which eye-tracking measures provide the most sensitive indices of individual differences in attentional capacities within immersive scenarios. Moreover, while multiple eye metrics have been highlighted as potential biomarkers of each attentional component, they are most often examined in isolation. This approach not only limits our understanding of whether individual metrics may also index other components but also risk underestimating their predictive value. Considering these measures jointly could reveal complementary contributions and enhance the ability to predict attentional capacities. Building on recent evidence applying machine learning to eye-tracking features (Daley et al., 2020; Franceschiello et al., 2022; Hougaard et al., 2021), the present study explores whether combining multiple metrics improves predictive capacity, while also clarifying which features are most informative for each attentional subcomponent.

6.2. Material and Methods

6.2.1. Participants

150 neurologically healthy volunteers aged between 18 and 85 years took part in the study[4]. All participants had normal or corrected-to-normal visual acuity and did not present history of neurological, neurodevelopmental, psychiatric disorders or epilepsy. Cognitive functioning within the normal range was confirmed using the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005), with a score equal or above 26. Two participants were excluded due to failed eye-calibration procedure during the experimental sessions. The resulting final sample comprised 148 participants (75 female, mean age = 44.86 years, SD = 18.23 years; mean educational level of = 13.72 years, SD

[4] The present study is part of a wider project conducted in collaboration between the Department of Psychology (University of Bologna, Italy), the Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland) and MindMaze SA (Lausanne, Switzerland).

= 3.73 years; mean MoCA score = 28.07; SD = 1.47). Of the final sample, 99 participants were tested at the Department of Psychology (University of Bologna) and 49 were assessed at the Lausanne University Hospital (CHUV, Switzerland). 110 participants were Italian-speaker, 36 French-speaker and 2 English-speaker.

Detailed information on the study sample can be consulted in Table 6.1.

All participants were fully informed about the procedure, the purposes of the study, and the processing of personal data, and provided written informed consent prior to participation. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained separately at the two sites: the Italian cohort provided informed consent according to the protocol approved by the Ethical Committee of the Department of Psychology "Renzo Canestrari," University of Bologna (*Prot. 0299113*), while the Swiss cohort provided informed consent according to the protocol approved by the Ethical Committee of the Lausanne University Hospital (*Prot. 2017-01588*). In accordance with the referred protocol, participants recruited in Switzerland received a compensation of 20 CHF per hour for their participation.

ID	*Age*	*Gender*	*Educational Level*	*Language*	*MOCA (cut-off < 26)*
ETCTRL_001	51	F	21	Fr	29
ETCTRL_002	25	M	16	Fr	30
ETCTRL_003	25	M	18	It	29
ETCTRL_004	29	M	18	Fr	30
ETCTRL_005	75	M	21	Fr	27
ETCTRL_006	38	M	13	Fr	30
ETCTRL_007	22	M	13	En	30
ETCTRL_008	74	F	8	Fr	29
ETCTRL_009	85	F	11	Fr	29
ETCTRL_010	25	F	11	Fr	30
ETCTRL_011	24	F	13	Fr	30
ETCTRL_012	67	F	18	Fr	30
ETCTRL_013	69	F	21	Fr	27
ETCTRL_014	53	M	13	En	30
ETCTRL_015	84	M	13	Fr	28
ETCTRL_016	30	M	18	It	28
ETCTRL_017	29	M	21	It	29
ETCTRL_018	70	F	11	Fr	27
ETCTRL_019	35	F	11	Fr	29
ETCTRL_020	34	F	13	Fr	27
ETCTRL_021	26	M	18	It	29
ETCTRL_022	35	M	18	Fr	29
ETCTRL_023	57	M	16	Fr	27
ETCTRL_024	24	F	16	Fr	30

ETCTRL_025	50	F	8	Fr	28
ETCTRL_026	68	M	5	Fr	29
ETCTRL_027	63	F	13	Fr	28
ETCTRL_028	78	M	11	Fr	30
ETCTRL_029	20	M	13	Fr	30
ETCTRL_030	20	M	8	Fr	27
ETCTRL_031	59	M	13	Fr	29
ETCTRL_032	84	F	5	It	26
ETCTRL_033	59	F	8	It	27
ETCTRL_034	54	F	13	It	28
ETCTRL_035	69	F	8	It	29
ETCTRL_036	48	F	13	It	30
ETCTRL_037	24	M	8	It	27
ETCTRL_038	40	M	21	It	29
ETCTRL_039	40	M	8	It	26
ETCTRL_040	61	F	8	It	29
ETCTRL_041	21	M	13	It	29
ETCTRL_042	25	F	16	It	30
ETCTRL_043	26	M	16	It	29
ETCTRL_044	26	M	16	It	30
ETCTRL_045	27	M	16	It	30
ETCTRL_046	26	M	16	It	26
ETCTRL_047	25	F	16	It	28
ETCTRL_048	23	F	16	It	30
ETCTRL_049	25	M	13	It	30
ETCTRL_050	21	M	13	It	28
ETCTRL_051	24	F	16	It	29
ETCTRL_052	22	M	13	It	28
ETCTRL_053	21	M	13	It	27
ETCTRL_054	22	M	16	It	27
ETCTRL_055	22	F	13	It	28
ETCTRL_056	23	F	16	It	28
ETCTRL_057	25	F	16	It	27
ETCTRL_058	25	F	16	It	29
ETCTRL_059	22	M	13	It	27
ETCTRL_060	23	F	16	It	29
ETCTRL_061	25	F	16	It	28
ETCTRL_062	24	F	16	It	26
ETCTRL_063	25	F	16	It	30
ETCTRL_064	26	F	13	It	27
ETCTRL_065	22	M	13	It	28
ETCTRL_066	60	M	18	It	27
ETCTRL_067	54	F	16	It	27
ETCTRL_068	40	M	8	It	26
ETCTRL_069	59	F	11	It	29
ETCTRL_070	58	M	13	It	27
ETCTRL_071	55	M	13	It	26

ETCTRL_072	78	F	5	It	26
ETCTRL_073	55	M	11	It	29
ETCTRL_074	52	F	13	It	27
ETCTRL_075	55	M	13	It	27
ETCTRL_076	51	F	11	It	28
ETCTRL_077	40	F	13	It	26
ETCTRL_078	46	M	13	It	27
ETCTRL_079	48	F	13	It	28
ETCTRL_080	38	F	13	It	27
ETCTRL_081	47	F	16	It	30
ETCTRL_082	35	F	18	It	30
ETCTRL_083	34	M	13	It	30
ETCTRL_084	28	M	16	It	26
ETCTRL_085	25	M	16	It	29
ETCTRL_086	25	M	16	It	29
ETCTRL_087	60	F	13	It	28
ETCTRL_088	69	F	18	It	26
ETCTRL_089	53	M	13	It	26
ETCTRL_090	49	F	18	It	30
ETCTRL_091	57	M	13	It	28
ETCTRL_092	58	F	13	It	29
ETCTRL_093	47	F	21	It	28
ETCTRL_094	85	F	5	It	26
ETCTRL_095	72	F	16	It	28
ETCTRL_096	51	M	8	It	27
ETCTRL_097	58	M	8	It	26
ETCTRL_098	51	F	16	It	26
ETCTRL_099	49	M	13	It	29
ETCTRL_100	55	F	18	It	28
ETCTRL_101	49	M	13	It	23
ETCTRL_102	21	F	16	It	28
ETCTRL_103	21	F	13	It	30
ETCTRL_104	45	F	13	It	28
ETCTRL_105	71	M	8	It	26
ETCTRL_106	68	F	13	It	26
ETCTRL_107	36	M	11	It	27
ETCTRL_108	34	M	11	It	27
ETCTRL_109	49	M	5	It	30
ETCTRL_110	52	F	8	It	26
ETCTRL_111	30	F	13	It	29
ETCTRL_112	36	M	18	It	26
ETCTRL_113	49	M	13	It	30
ETCTRL_114	31	F	18	It	26
ETCTRL_115	52	M	13	It	26
ETCTRL_116	57	M	13	It	25
ETCTRL_117	24	F	16	It	27
ETCTRL_118	52	F	16	It	27

ETCTRL_119	79	F	5	It	26
ETCTRL_120	53	M	16	It	28
ETCTRL_121	36	M	13	It	29
ETCTRL_122	30	F	18	It	30
ETCTRL_123	31	M	16	It	29
ETCTRL_124	31	F	13	It	29
ETCTRL_125	56	F	13	It	27
ETCTRL_126	30	F	18	It	27
ETCTRL_127	32	F	13	It	30
ETCTRL_128	60	M	13	It	29
ETCTRL_129	57	M	8	It	30
ETCTRL_130	31	M	16	Fr	30
ETCTRL_131	53	F	8	Fr	28
ETCTRL_132	30	M	8	Fr	29
ETCTRL_133	38	M	11	Fr	29
ETCTRL_134	33	M	20	Fr	30
ETCTRL_135	44	F	16	Fr	30
ETCTRL_136	66	F	11	Fr	28
ETCTRL_137	47	F	16	Fr	29
ETCTRL_138	59	F	16	Fr	29
ETCTRL_139	54	F	16	Fr	29
ETCTRL_140	76	M	18	Fr	29
ETCTRL_141	66	M	18	It	27
ETCTRL_142	66	F	8	It	27
ETCTRL_143	66	M	18	It	27
ETCTRL_144	78	M	11	It	26
ETCTRL_145	74	F	13	It	26
ETCTRL_146	60	M	16	It	26
ETCTRL_147	53	M	18	It	28
ETCTRL_148	58	F	18	It	27

Table 6.1. Demographic characteristics of the study sample. The table reports individual participant information, including ID code, age, gender, educational level (in years), primary language (Fr = French, It = Italian, En = English), and Montreal Cognitive Assessment (MoCA) scores. A MoCA score below 26 is considered under the cut-off for normal cognitive functioning (Nasreddine et al., 2005).

6.2.2. Experimental Procedure and Devices

After providing written informed consent, participants underwent a brief eligibility screening. This included the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) and a computerized checklist to exclude neurological, psychiatric, or severe medical conditions. They also completed standardized questionnaires on anxiety and depression (STAI-I/II; Spielberger, 1983; HADS; Zigmond & Snaith, 1983) and a four-item scale assessing familiarity with digital technologies (smartphones, computers, videogames, virtual reality; 0–100: “not familiar” to “highly familiar”). All instruments were administered in the participants’ native language (Italian, French, or English) using validated translations. Upon completion of the initial screening phase, participants were seated at the center of the testing room to ensure freedom of movement, and they were fitted with one of the two Head-Mounted Display (HMDs): the HTC Vive Pro Eye or the Pico 4 Enterprise.

The HTC Vive Pro Eye HMD has a display resolution of 1440 x 1600 pixels per eye, a 90 Hz refresh rate and a field of view (FOV) of 110° (www.vive.com). It has embedded a Tobii® eye-tracking (ET) system operating at a binocular sampling rate of 90 Hz.

The PICO 4 Enterprise HMD features a maximum display resolution of 4320 × 2160 (2160 × 2160 per eye), a maximum refresh rate of 90 Hz, and a 105° FOV (www.picoxr.com). It also integrates a Tobii® ET with a binocular sampling frequency of up to 90 Hz.

Before starting the experimental tasks, participant's head position and interpupillary distance (IPD) were calibrated to ensure the virtual environments were properly displayed. Furthermore, a five-point eye-tracking calibration, enabled by the integration of Tobii Spotlight Technology within both HMDs, was conducted (Fig.6.1). Only after successful completion of all calibration steps, iVR experimental protocol was launched remotely by the experimenter employed the MindFocus WebApp (MindMaze SA, Lausanne, Switzerland), connected to the HMD via Wi-Fi network.

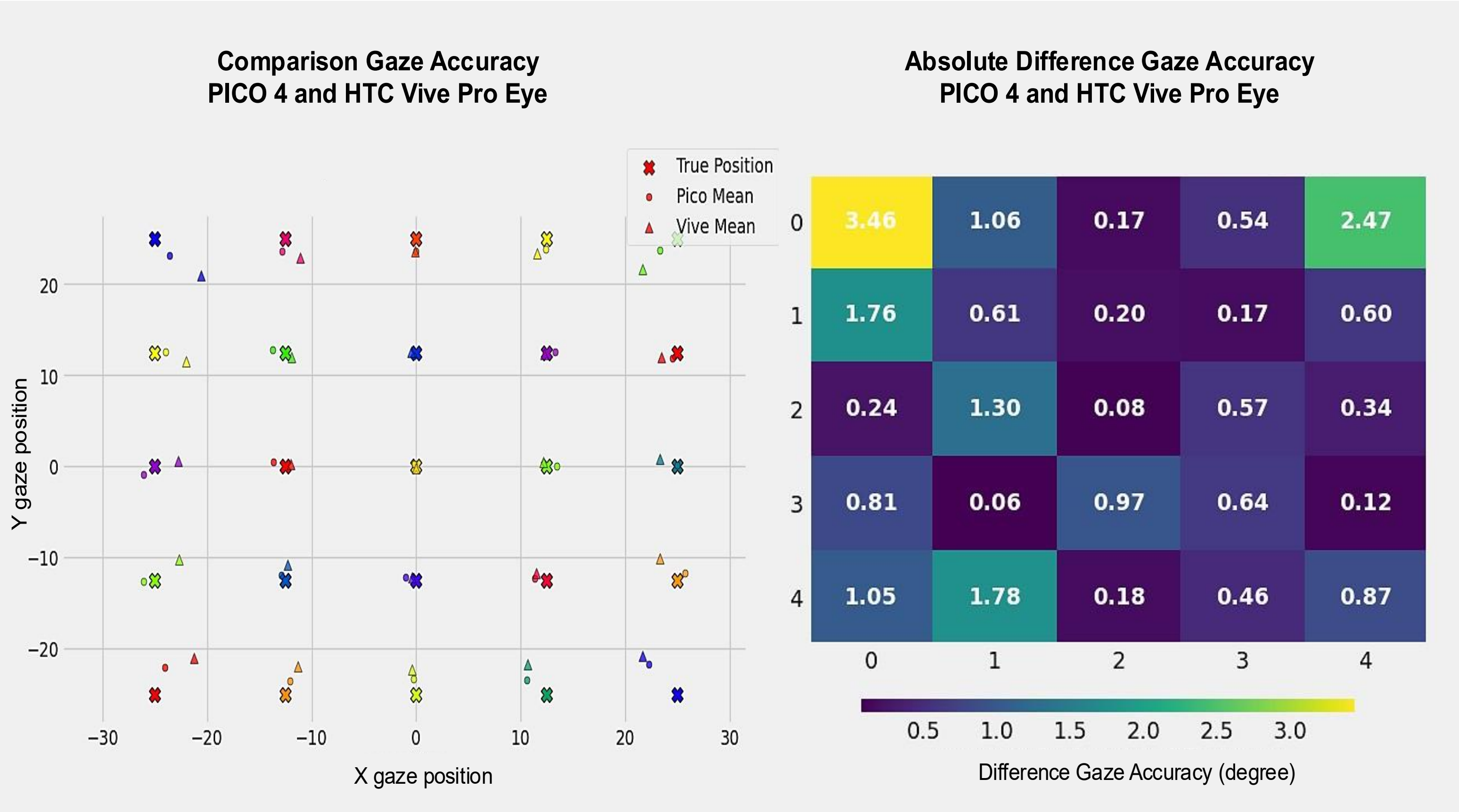


Fig.6.1. Comparison gaze accuracy performance between PICO 4 Enterprise and HTC Vive Pro Eye. On the left: The true position of the target is displayed along with the gaze accuracy (i.e., average difference between the real stimuli position and the measured gaze position) of the PICO 4 Enterprise and HTC Vive Pro Eye eye-tracking. On the right: absolute difference (degree) between gaze accuracy. The Vive and Pico have an average inner accuracy error of 1.25 and 1.69 degrees and an average outer accuracy error of 3.46 and 2.49 degrees, respectively. Overall, both devices demonstrate similar performance levels in terms of accuracy, particularly in the central region.

Participants completed seven tasks embedded within the "*Assessment Module*" of MindFocus iVR software (MindMaze SA). In the present study, the analyses were focused on three tasks: (a) a

FreeViewing Exploration task (see section *"iVR-Free Viewing Exploration Task, iVR-FVE"*); (b) a brief alertness task (see section "*iVR-Burst Alertness sub-test*"); (c) a short task targeting spatial and selective attention (see section "*iVR-Burst Spatial Selective sub-test"*).
All virtual environments were developed using the Unity game engine (Unity Technologies, www.unity.com) by MindMaze SA (Lausanne, Switzerland).

a) iVR-Free Viewing Exploration Task (iVR-FVE)

The iVR-FVE is an adaptation of the Free Viewing Exploration task originally developed by Nardo et al. (2019), implemented in an iVR environment. The task consists of 80 short videos, each lasting 1'500 milliseconds, showing everyday-life scenarios presented in two possible randomized sequences. Each video features a dynamic main event occurring either on the left side (Lateral Left), the right side (Lateral Right), or bilaterally. In bilateral conditions, the primary event is more prominent either on the left (Bilateral Left) or the right (Bilateral Right) .
All participants were presented with the same set of video stimuli in terms of content. However, the sequence of presentation was randomized across individuals, and the lateralization of the main event was counterbalanced: for a given video, some participant viewed the main event occurring on the left, while others viewed the same video with the event occurring on the right. To re-center participants' gaze between trials, a uniform grey screen with a central black cross was displayed for a randomized duration of 3'500 to 5'000 ms, in increments of 250 ms. The iVR-FVE has an overall duration of maximum 8 minutes. Participants were instructed to maintain fixation on the central cross during the inter-stimulus intervals and to freely explore the videos with their gaze during each trial. Head movements were not strictly prohibited; however, participants were advised to minimize head motion throughout the task to ensure stable ET performance (Fig. 6.2A). During this task, ET parameters were continuously recorded without generating behavioral performance indices.

b) iVR-Burst Alertness subtest

The iVR-Burst Alertness subtest is a 3D assessment of an individual's general readiness to respond to external stimuli. The task was inspired by the standardized TAP Alertness subtest (Zimmermann & Fimm, 2002) and is grounded in the established theoretical distinction between tonic and phasic component of alertness (Petersen & Posner, 2012). During each trial, a blue cube appears at the center of a virtual grey room, to which participants are instructed to press the trigger button of the controller as quickly as possible. In half of the trials, a warning auditory cue preceded the blue cubes (*phasic alertness* condition, 12 trials), in the other half there was no warning cue (*tonic alertness condition*, 12 trials). Each of the 24 trails begins with the presentation of a central black fixation cross, displayed

for a randomized duration between 1’800 and 2’700 ms. The blue cube remains visible until the participant responds, or for a maximum of 2’000 ms. The stimulus is always presented at the same central location. The total duration of the subtest is approximately 3 minutes. Participants were instructed to maintain visual fixation on the central cross throughout the task (Fig. 6.2B).
The median reaction time (RT) to detect the target was computed as the performance index of alertness. This behavioral measure served as the reference outcome against which ET parameters were tested as candidate biomarkers of alertness capacity.

c) iVR-Burst Spatial-Selective subtest

The iVR-Burst Spatial-Selective subtest is an immersive virtual reality task designed to assess visuo-spatial and selective attention. The task is based on the principles of Features Integration Theory (FIT; Treisman & Gelade, 1980) and employs lateralized target presentations to evaluate attentional deployment across the visual field. The subtest consists of three progressively challenging levels. In Level 1, a single blue cube (target) appears in isolation within a virtual grey room for a maximum of 2’000 ms. In Level 2, the target is presented for up to 5’000 ms among blues spheres serving as distractors. In Level 3, the target appears for up to 5’000 ms surrounded by both blue spheres and red squares as distractors. Each level is presented twice in the following order: 1-2-3-3-2-1, resulting in a total of 24 trials per level. Between trials, a central black fixation cross is displayed for a randomized duration ranging from 1’800 ms to 2’700 ms. The total duration of the task does not exceed 8 minutes. Target locations are pseudo-randomized according to fixed rules: for each level, 6 targets are presented on the left and 6 on the right, with no more than 3 targets appearing consecutively on the same side. The virtual environment is divided into a 3×7 grid of subsectors (from an underlying 3x3 by 9×21 spatial matrix), yielding 21 available subsectors per trial. One subsector is occupied by the fixation cross (center), one by the target, and the remaining 19 by distractors. During the task, participants are instructed to maintain fixation on the central cross and respond as quickly and accurately as possible by pointing a virtual laser at the blue cube and pressing the controller button. After each response, participants are required to return both their gaze and the laser pointer to the fixation cross (Fig. 6.2C).
The median RTs in Level 2 and Level 3 (target among distractors) were computed as the performance index of Selective Attention. In addition, separate median RTs to left- and right-lateralized targets were computed as indices of Spatial Attention. These behavioral outcomes served as reference

measures, against which ET parameters were evaluated as potential biomarkers of selective and spatial attention.

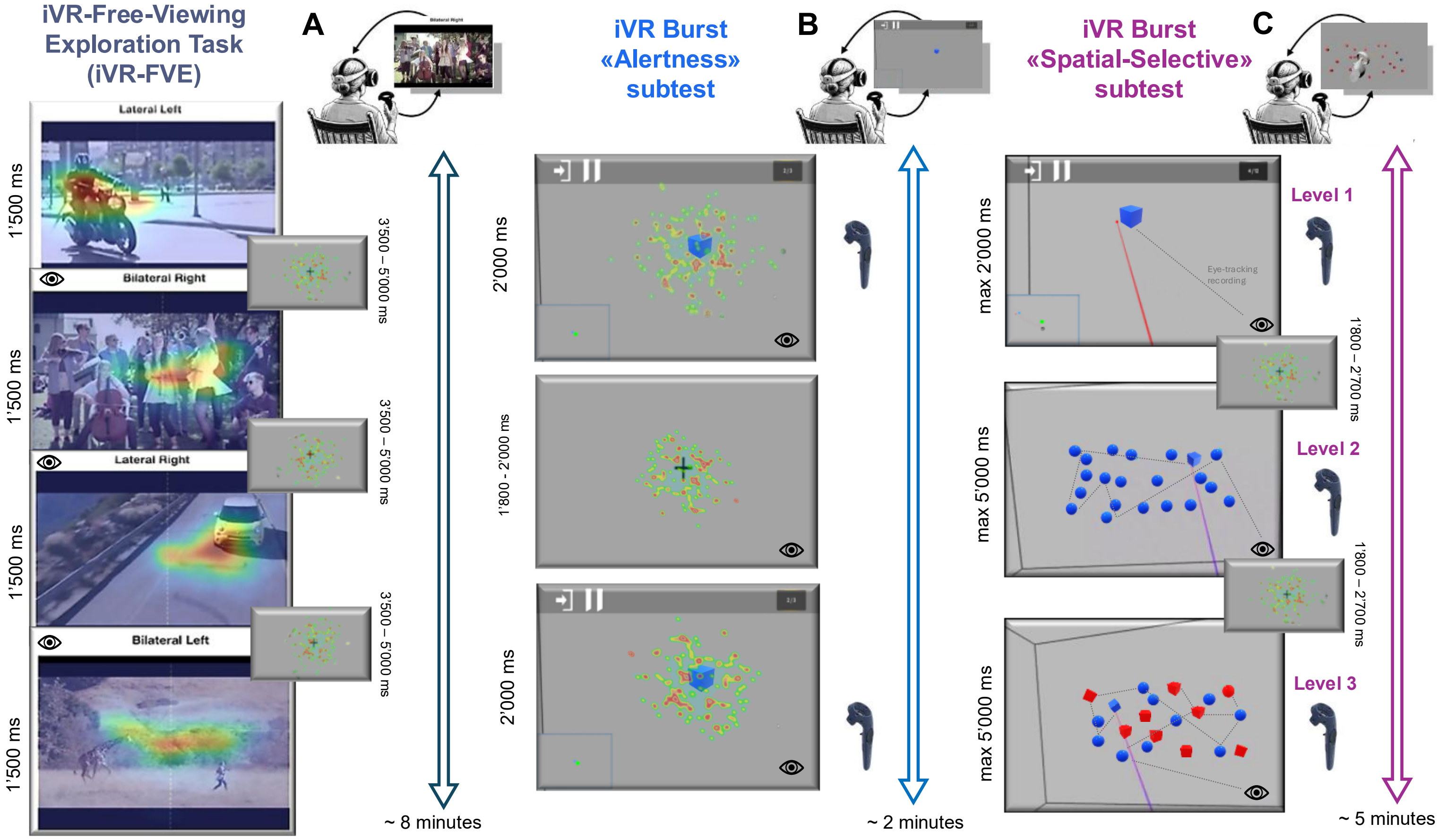


Figure 6.2. Overview of the Immersive Virtual Reality tasks implemented in the study. (A) iVR-FVE task: Examples of 4 videos and the intermediate fixation cross, picked up among the 80 videos illustrating the 4 experimental conditions: Lateral Left, Lateral Right, Bilateral Left, Bilateral Right. On top of the videos and grey screen, gaze heatmaps are shown to illustrate representative gaze patterns. **(B)** iVR-Burst Alertness: Examples of 2 target stimuli (central blue cube) to which the participants respond as quickly as possible by pressing a button on the controller (shown here on the right of the target stimuli). Each trial begins with a central black fixation cross. Heatmaps of the gaze are shown on top of screenshots to illustrate representative gaze patterns. **(C)** iVR-Burst Selective: This subtest assesses visuo-spatial and selective attention using lateralized target detection in a virtual environment. Participants must locate and respond to a blue cube presented either alone (Level 1), among blue sphere distractors (Level 2), or among both blue spheres and red squares (Level 3). Trials are interleaved with central fixation intervals. Eye-tracking data are continuously recorded also during this task.

6.2.3. Eye-Tracking recordings: Pre-processing and oculomotor features extraction

The raw eye-tracking signal acquired continuously during the three iVR-tasks was processed offline using custom scripts developed in RStudio (RStudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA, RStudio-2024.12.01.563 for Windows 11, R version 4.3.3 – 2025-02-28 ucrt) to extract oculomotor metrics already showed to have a relation with attention capacities (a summary description are in Table 6.2).

<u>*Fixation identification algorithm and derived metrics*</u>

To identify fixations an adaptation of the I-DT (Identification by Dispersion Threshold) algorithm originally proposed by Salvucci and Goldberg (2000) was implemented. Horizontal (θ) and vertical

(Φ) gaze angles were computed from the raw 3D focus point coordinates (x, y, z) using trigonometric transformation:

$$\theta = tan^{-1}\left(\frac{x}{z}\right), \qquad \Phi = tan^{-1}\left(\frac{y}{z}\right)$$

Fixations were identified as a sequence of consecutive gaze samples in which both θ and Φ remained within a spatial threshold of 1.5 degrees for a minimum duration of 100 ms. Each identified fixation was characterized by its onset and offset times, duration, and median gaze position, assigned to task events using synchronized logs. Fixations outside a 2° radius of the fixation cross were excluded from analysis, along with the entire corresponding trial.

From the resulting fixation data, the total number of fixations across the session was computed, along with their cumulative duration. Metrics included total and mean fixation counts, durations, and lateralized (left/right) distributions.

Fixation Stability

For every fixation identified in the dataset, horizontal (fix_x) and vertical (fix_y) gaze positions were centered by subtracting their respective means, and the Euclidean distance of each sample from the mean fixation point was calculated as following:

$$\sqrt{(x_i - \bar{x})^2 + (y_i - \bar{y})^2}$$

The interquartile range (IQR) of these distances indicate stability. Mean fixation stability was the average IQR across all fixations.

Gaze Laterality and Gaze Index

For each gaze sample, the gaze laterality was computed as the proportion of the horizontal gaze to the left of the midline (i.e., FocusPoint.x < 0) relative to the total number of samples. The Gaze Index was calculated as the total fixation time spent in rightward positions (fix_x > 0) subtracted from the total time spent in leftward positions (fix_x < 0) normalized by the total fixation duration across all trials. The resulting value ranged from −1 (left bias) to +1 (right bias).

First fixation side

For each trial, the event marked as 'Start' in the event log was used as a reference point. Initial orienting was determined based on the direction of the first fixation already ongoing or immediately after the reference point. The direction was coded as +1 (right) or −1 (left) and averaged across trials, yielding a mean first-saccade direction index with positive values indicating a tendency to initially orient gaze to the right, and negative values indicating a leftward bias.

Re-Fixation and perseverative re-fixations

Refixations were identified based on angular proximity between fixations within the same trial. For each fixation, horizontal (θ) and vertical (φ) gaze angles were compared to those of the preceding fixation. A fixation was classified as a refixation if the absolute angular difference in both θ and φ was less than 1.5 degrees and occurred within the same trial. Sequences were cumulatively indexed, allowing classification of single refixations (index ≥1) and perseverative refixations (index ≥2).

For both metrics, fixation counts were further stratified by gaze laterality, allowing for the extraction of total, left-sided, and right-sided refixations and perseverative refixations. This enabled the analysis of potential spatial asymmetries in refixation behavior during task performance.

Blink detection algorithm

A blink was operationally defined as a frame in which the eye openness value fell below 0.7 and the pupil diameter was equal to −1. Consecutive frames meeting these criteria were grouped into individual blink episodes. Two global blink metrics were derived from the resulting data. Blink frequency was calculated as the number of blink episodes divided by the total task duration. Total blink duration was computed as the sum of all blink episode durations across the entire session.

Total number of fixations on target, time to fixate the target and time spent on the distractors

To determine whether a fixation landed on the target, fixation coordinates (x_{fix}, y_{fix}) were compared with the target coordinates (x_{targ}, y_{targ}). To define the RO, half-width (*k*) was systematically varied (0.1-2.0 units). For each candidate half-width, the number of fixations classified as "on target" was computed as:

$$\sum 1\,(\,|x\_fix\, -\, x\_targ|\, \leq\, k\,, |y\_fix\, -\, y\_targ|\, \leq\, k\,)$$

The cumulative detection curve was fitted with a logistic function; its inflection point defined the optimal ROI half-width, k*.

Using this task-specific ROI size, a fixation was labeled "on target" if both its horizontal and vertical coordinates fell within the ROI during the target's on-screen interval:

$$|x\_fix\, -\, x\_targ|\, \leq\, k\, *\, ,\quad |y\_fix\, -\, y\_targ|\, \leq\, k\, *$$

The total number of on-target fixations was summed across trials, both overall and, when relevant, separately for left- and right-lateralized targets.

To define the time to fixate the target (fixation delay), the latency between target onset and the beginning of the first fixation falling inside the target ROI was computed. The time spent fixing the distractors was calculated as fixations directed at any location outside both the fixation cross and the target ROI.

Feature	Computation (summary)	Outputs	References
Fixation count & duration	Fixations identified with I-DT algorithm (dispersion ≤1.5°, duration ≥100 ms) (Salvucci and Goldberg, 2000). Each fixation is characterized by duration and position.	Total number of fixations, mean number of fixations, total fixation duration, mean fixation duration — overall and separately for left and right hemifields.	Cox & Davies, 2020; Di Stasi et al. 2013; Daley et al., 2020; Friedman & Komogortsev, 2024; Muri et al., 2009; Keiser et al., 2022; Hougaard et al., 2021

Fixation stability (IQR)	For each fixation, Euclidean distance of samples from mean fixation point was computed; interquartile range (IQR) used as stability index.	Mean fixation stability (average IQR across fixations).	Unsworth, Miller & Robison, 2020; Zhou et al., 2024
Gaze laterality	Computed as the proportion of gaze samples located in the left hemifield (FocusPoint.x < 0) relative to total samples.	Proportion of leftward gaze samples (0–1).	Cazzoli et al., 2015; Cox & Davies, 2020; Kaufmann et al., 2020; Franceschiello et al., 2022; Hougaard et al., 2021
Gaze index	Difference between total time spent on left vs. right hemifield, normalized by total fixation time. Positive values = right bias; negative = left bias.	Index ranging from −1 (left bias) to +1 (right bias).	Cox & Davies, 2020; Nardo et al., 2019; Hougaard et al., 2021
First fixation side	Direction of the first fixation after trial onset coded as left (−1) or right (+1), then averaged across trials.	Mean first-saccade direction index (−1 = left bias, +1 = right bias).	Cox & Davies, 2020; Keiser et al., 2022; Serino et al., 2007
Re-fixations	A fixation was classified as a refixation if its angular distance from the previous fixation was <1.5° within the same trial (index = 1).	Total number of refixations, separately for left and right hemifields.	Cox & Davies, 2020; Paladini et al., 2019; Cazzoli et al., 2011
Perseverative re-fixations	Subset of refixations where gaze returned repeatedly to the same region (index ≥2).	Total number of perseverative refixations, separately for left and right hemifields.	Cox & Davies, 2020; Paladini et al., 2019; Nys et al., 2008; Rusconi et al., 2002
Blink frequency & duration	Blinks identified as consecutive frames with eye openness <0.7 and pupil diameter = −1. Grouped into blink episodes.	Blink frequency (blinks per second) and total blink duration (ms).	Demiral et al.,2023; McIntire et al., 2014
On-target fixations	ROI half-width k varied (0.1–2.0 units). Logistic fit applied; midpoint defined optimal ROI size k*. Fixations within this ROI during target presentation labeled as on-target.	Total on-target fixations overall and by hemifield.	Hollingworth & Bahle, 2019; Ridderinkhof & Wijnen, 2011; Veiel et al., 2006;
Time to fixate target	Latency from target onset to the first on-target fixation.	Mean time to fixate target (ms).	Hollingworth & Bahle, 2029; Keiser et al., 2022; Skaramagkas et al., 2023
Time on distractors (Dwell Time)	Sum and mean duration of fixations not landing on the target ROI during target presentation.	Total and mean time on distractors (ms).	Cox & Davies, 2020; Hollingworth & Bahle, 2019; Ridderinkhof & Wijnen, 2011; Stefani & Sauter, 2023

Table 6.2. Summary of eye-tracking features extracted from iVR tasks. The table reports each metric, a brief description of its computation, and the corresponding outputs

6.2.4. Data Analysis

To test the predictive capacity of ET-derived for attention functioning, six regression Machine Learning (ML) models were fitted. In detail, to assess selective attention capacities, the ET-derived metrices from the iVR-Burst Spatial-Selective Attention subtest were used as input in a ML model to predict the overall median RT (ms) collected in Level 2 and 3 (with distractors). The same selective attention outcome was employed in a second ML model trained with ET parameters from the iVR-FVE. For Alertness, the median RT (ms) during the iVR-Burst Alertness subtest were predicted using the ET-derived metrics from the same task and from the iVR-FVE. Finally, for spatial attention abilities, lateralized ET metrics from the Spatial-Selective Attention subtest (Level 1, Level 2 and Level 3) and from the iVR-FVE were used in two separate ML models to predict the Median RT (ms) to left- and right-lateralized targets.

The six models implemented follow the same ML pipeline. All the ET-derived metrics were pre-processed via z-standardization. Missing values, when present, were addressed by single imputation, whereby each missing entry was replaced with the mean of the observed values for the corresponding variable.

The Boruta algorithm was implemented to retain only the important ET-features (Kursa & Rudnicki, 2010). This algorithm compares the relevance of actual predictors against randomly permuted "shadow" variables, iteratively removing those deemed irrelevant. Features classified as "tentative" were resolved through the *TentativeRoughFix* procedure, yielding a final set of confirmed predictors for each model.

Random Forest (RF) regression models were then trained on the confirmed predictors. Hyperparameter optimization targeted the number of candidate variables sampled at each split (*mtry*), which was systematically varied from 1 to the number of confirmed predictors, and the number of trees (*ntree*), explored at values of 50, 100, 250, 500, and 750. Model training and evaluation were implemented within the caret R-package framework using leave-one-out cross-validation (*LOOCV*). Model performance was quantified by mean absolute error (*MAE*), the coefficient of determination (R^2) and the root mean squared error (*RMSE*). The optimal model was defined as the configuration yielding the lowest MAE and RMSE along with the highest R^2. Variable importance for the best-performing model was extracted from RF mean decrease in accuracy scores, and model calibration was visually assessed through predicted-versus-observed plots with linear regression fit and 95% confidence intervals. Finally, ET metrics identified as most relevant were further explored through regression analyses (FDR-corrected) to assess their relationship with behavioral outcomes.

6.3. Results

6.3.1. Selective Attention

For selective attention, the best model resulted in the RF fitted with ET parameters from the iVR-Burst Spatial-Selective subtest. The optimal configuration was obtained with mtry = 12 and ntree = 50 yielding $R^2 = 0.69$, RMSE = 160.93 and MAE = 124.26. Conversely, the model trained on ET parameters from the iVR-FVE achieved lower performance for predicting the same selective attention index ($R^2 = 0.43$, RMSE = 199.11, MAE = 151.16). Given that the predicted total median RT - indexing selective attention capacity - ranged from ~600 to 2200 ms, the absolute prediction error of the best model corresponds to approximately 6-10% of the RT scale, indicating good predictive accuracy (Fig. 6.3A and Table 6.3). Among the 12 ET parameters retained by Boruta, total number of fixations and mean fixation duration showed the highest importance, as reflected by their mean decrease in accuracy in the RF importance ranking (Fig. 6.3A). Particularly, regression analysis revealed that the total number of fixations was positively associated with median RTs ($R^2 = 0.455$, $p < .001$), indicating that participants who employ a higher number of fixations before finding the target tended to respond more slowly. By contrast, participants who showed longer average fixation duration had faster RTs ($R^2 = 0.088$, $p < .001$; Fig. 6.3A).

6.3.2. Spatial Attention

The RF model trained with ET features from the iVR-FVE resulted in higher performance metrics in predicting lateralized median RTs from the iVR-Burst Spatial-Selective, indexing spatial attention capacity (R^2 = 0.55, RMSE = 266.78, MAE = 192.64; mtry = 11, ntree = 100) compared to the model fitted with ET-metrics gathered from the iVR-Burst Spatial-Selective (R^2 = 0.47, RMSE = 271.70, MAE = 198.50; mtry = 12, ntree = 250). Overall, the prediction error of this model corresponds to 7% of the RTs variability (Fig. 6.3B and Table 6.3). Particularly, the lateralized total number of fixation and the gaze-index (i.e., difference in total time viewing time between left and right hemifields) emerged as key predictors. Regression analyses revealed that the lateralized total number of fixations had a positive relation with lateralized RTs (R^2 = 0.314, p < .001), highlighting that strongly lateralized visual exploration was associated with slower responses. By contrast, the gaze index was negatively linked to RTs, meaning that a stronger left bias was linked to faster responses to lateralized targets (Fig. 6.3B).

6.3.3. Alertness

Participant's readiness to reply to an external stimulus (i.e., alertness) operationalized by the median RTs in the tonic segment of the iVR-Burst Alertness subtest, was better predicted by the model trained with ET parameters registered during the same task (R^2 = 0.62, RMSE = 46.27, MAE = 29.80) than the one fitted with ET parameters from the iVR-FVE (R^2 = 0.20, RMSE = 67.13, MAE = 47.96). A mtry = 6 and ntree = 50 were find as optimal parameters to fine-tune the model (Fig. 6.3C). With that configuration, the model obtained an absolute prediction error of about 6-9% of the outcome variable variability (see Fig. 6.3C and Table 6.3). Notably, among the 6 parameters selected by Boruta, mean fixation duration and fixation stability (i.e., interquartile range of gaze distance from the mean fixation position) had a higher weight on the overall model accuracy (Fig. 6.3C). Regression analyses confirmed that total fixation duration was negatively associated with median RTs (R^2 = 0.019, p = .018), suggesting that participants who maintained longer overall fixation time were quicker to respond. In contrast, fixation stability was positively associated with median RTs (R^2 = 0.021, p = .021), indicating that greater variability in fixation position corresponded to slower responses (Fig. 6.3C).

Attentional Component	**iVR- Free Viewing Exploration task**	**iVR-Burst Alertness subtest**	**iVR – Burst Spatial Selective subtest**
Selective Attention	MAE: 151.16 RMSE: 199.11 R^2: 0.43		MAE: 124.26 RMSE: 160.93 R^2: 0.69

Spatial Attention	MAE: 192.64 RMSE: 266.78 R^2: 0.55		MAE: 198.50 RMSE: 271.70 R^2: 0.47
Alertness	MAE: 47.96 RMSE: 67.13 R^2: 0.20	MAE: 29.80 RMSE: 46.27 R^2: 0.62	

Table 6.3. Prediction performance of eye-tracking features for attentional components across immersive VR tasks. Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), and coefficient of determination (R^2) are reported for each attentional subcomponent (selective attention, spatial attention, alertness) for the tested comparison among the iVR Free Viewing Exploration task, the iVR Burst Alertness subtest, and the iVR Burst Spatial Selective subtest.

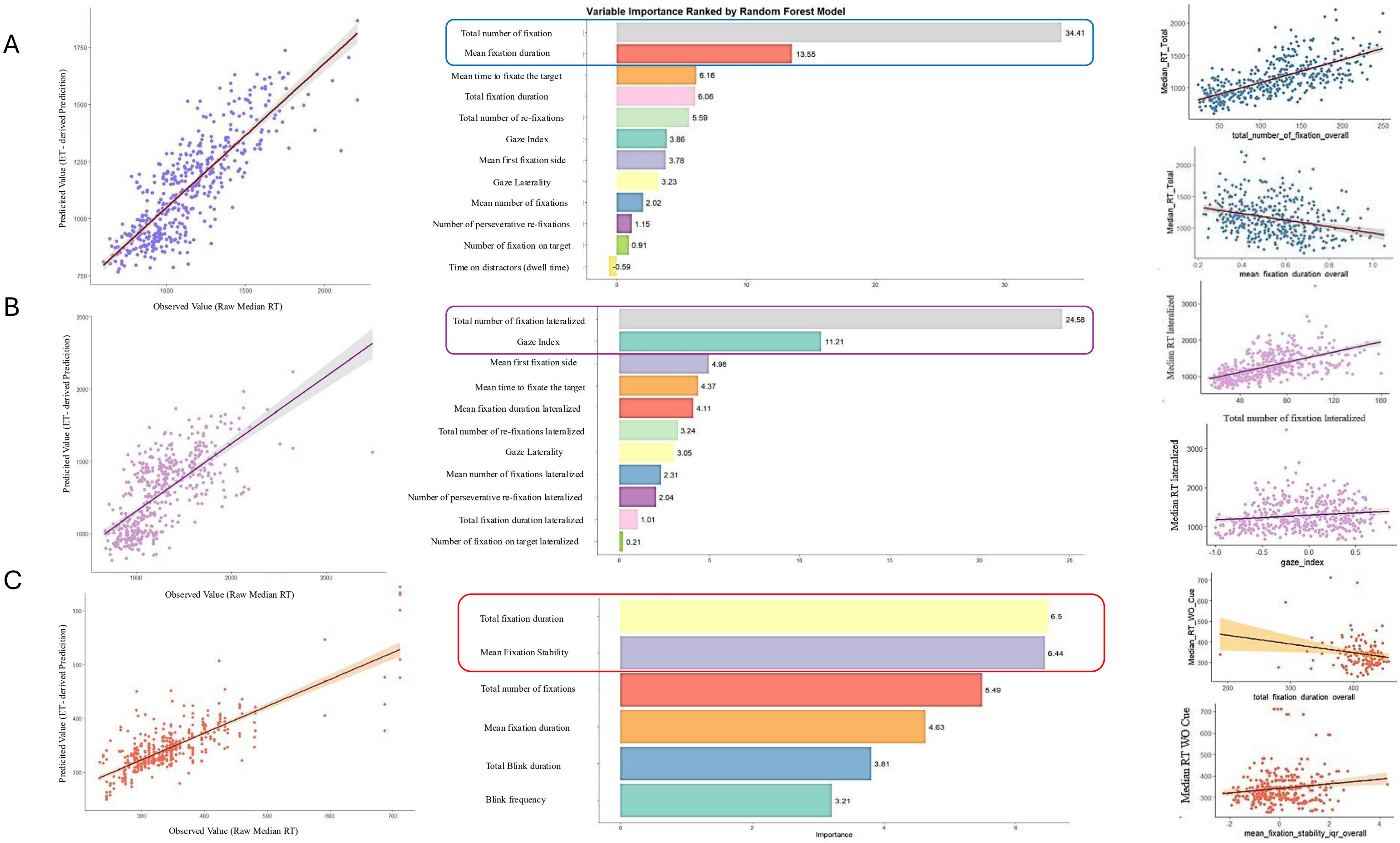


Figure 6.3. Predictive performance and eye-tracking predictors of selective attention (A), spatial attention (B), and alertness (C). *Left panels*: Scatterplots observed versus predicted median reaction times (RTs) from the best-performing random forest models for each attention capacity. Regression lines and 95% confidence bands illustrate model fit. *Middle panels:* Variable importance rankings (mean decrease in accuracy) from the Boruta-selected features included in the random forest models. For selective attention (A), the most relevant predictors were the total number of fixations and mean fixation duration. For spatial attention (B), the most relevant predictors were the lateralized total number of fixations and the gaze index. For alertness (C), the most relevant predictors were total fixation duration and mean fixation stability. *Right panels:* Regression plots showing the direction of associations between key predictors and RT indices. In selective attention (A), more fixations were associated with slower responses (positive relation), whereas longer mean fixation durations were associated with faster responses (negative relation). In spatial attention (B), stronger lateralization of fixation counts was linked to slower responses (positive relation), while a larger gaze bias toward one hemifield (gaze index) was linked to faster responses (negative relation). In alertness (C), longer total fixation duration predicted faster responses (negative relation), while greater fixation instability predicted slower responses (positive relation).

6.4. Discussion

Relatively to the starting question of whether it is possible to obtain meaningful eye-parameters in immersive virtual reality (iVR) environments, the present results clearly highlight the feasibility of integrating eye-tracking and iVR to detect individual differences in attention capacities. Moreover, our evidence goes in the direction of the possibility of having a pull of eye-metrics that result in specific attention subcomponents. In this perspective, our findings reveal that performance in selective attention, operationalized as the time required to find and respond to a target among distractors, can be predicted by two key oculomotor measures: total number of fixations and mean fixation duration. Specifically, a higher number of fixations was associated with longer search times, whereas individuals with longer fixation durations were faster in reaching the target. Since fixations represent stable temporal windows that facilitate visual information uptake (Salvucci & Goldberg, 2000), this pattern suggests that participants with erratic gaze behavior, characterized by many short fixations, may extract less information per fixation, leading to slower and less efficient target selection. Consistently, existing evidence demonstrates that individuals with diminished selective attention capacities show a higher number of fixations than those with stronger capacities (Geerlings et al., 2014; Skaramagkas et al., 2023). Such findings were interpreted as reflecting difficulties in suppressing visual distractors, making individuals more susceptible to bottom-up capture by salient, but task-irrelevant stimuli, and less efficient in applying top-down filtering (Ridderinkhof & Wijnen, 2011). Geerligs and colleagues (2014) further suggested that in older adults these difficulties may be partially compensated by a stronger reliance on top-down attentional resources, manifesting as more effortful and extensive visual exploration strategies. In this light, the increased fixation count observed in our study may reflect both greater distractibility and an attempt to sustain performance through compensatory search behavior (Goller, Mitrovic, & Leder, 2019; Schmidt et al., 2018). Supporting this interpretation, other eye metrics found to be predictive of selective attention in our data, such as a higher number of refixations, longer time to fix the target, and greater time spent on distractors, also point toward difficulties in filtering irrelevant information and a tendency toward erratic exploration strategies (see Stefani & Sauter, 2023).

Regarding spatial attention, our results reveal that participants with an imbalanced exploration of the two hemispaces were less efficient in orienting toward and selecting a target in immersive scenarios. Interestingly, greater time spent looking at the right hemispace, and a higher total number of rightward fixations, were associated with longer search times. These findings align with the body of research related to the *pseudoneglect* phenomenon, the leftward bias in spatial exploration observed in healthy individuals (Bowers & Heilman, 1980). Recent studies suggest that pseudoneglect support efficient attention allocation strategies and faster responses to lateralized stimuli (Bagattini et al., 2022; Chiffi et al., 2021; Guidali et al., 2023; Strauch et al., 2024). Given this evidence, we hypothesize that inviduals showing a weaker degree of this bias display overall dimished spatial attention capacities, as emerged from our results. Crucially, it has been highlight that pseudoneglect depends mostly on the interplay between the dorsal and ventral attention networks, whose activation during spatial attention tasks is greater in the right hemisphere (Nardo et al., 2019). Lesions to these right-lateralized networks often result in unilateral spatial neglect (USN), a syndrome characterized by a pathological rightward bias in gaze behavior and reduced efficiency in spatial attention (Cox & Davies, 2020; Kaufmann et al., 2020; Kaiser et al., 2022; Franceschiello et al., 2022). Corroborating this interpretation, our analysis further showed that participants who initiated exploration on the right (mean first fixation side) and displayed fewer fixations on the left (gaze laterality), mirroring USN-like gaze behavior, were less efficient in target selection compared to those exhibiting the natural leftward bias.

Our results on alertness showed that participants with longer fixation duration and greater fixation stability have faster reaction time in responding to upcoming target stimuli. Consistently, previous research revealed that shorter fixations are typical under high cognitive workload conditions (di Stasi et al., 2013; Friedman & Komogortsev, 2024) and sleep deprivation (van Egmond et al., 2022), states known to modulate the activity of the locus coeruleus-norepinephrine system (LC-NE), responsible for alertness capacities (Aston-Jones & Cohen, 2005; Petersen & Posner, 2012; Joshi, Kalwani, & Gold, 2016). Moreover, fixation stability is thought to index the ability to suppress unwanted saccades and microssacades, a function dependent on the efficient functioning of the frontal eye fields and superior colliculus (Krauzlis et al., 2017) and is linked to increased attentional control (Zhou et al., 2024) as well as faster reaction time (Unsworth, Miller, & Robison, 2020). Finally, blink parameters also emerged as important markers of individual differences in alertness abilities. In this perspective, recent works have shown that blink events are associated with a peak in BOLD signal across the cerebellum, insula, lateral geniculate nucleus, and visual cortex in drowsy state, and are interpreted as transient surges of arousal aimed at maintaining wakefulness and alertness. These events manifest as longer and more frequent blinks are also closely related with slower responses (Demiral et al., 2023; McIntire et al., 2014). Evidence from clinical populations further supports this link: prolonged blink duration has been reported in Parkinson's disease in association with reduced levels of alertness (Vasudevan et al., 2025), whereas schizophrenia, often characterized by hyperalert states, is associated with elevated blink rates (Nielsen, Dietz, & Jefsen, 2025).

Beyond the contribution of single measures, our results demonstrate that pools of oculomotor parameters can reliably predict each attentional component. Some metrics emerged as relatively specific to one domain, while others were shared across different components, revealing a partial overlap in the oculomotor signatures of alertness, spatial, and selective attention. This pattern reflects the broader nature of attention itself: attentional components are functionally separable but also interdependent, engaging distinct mechanisms while interacting dynamically during task performance (Posner & Petersen, 2012). As a result, some eye-tracking parameters may simultaneously index more than one attentional function, rather than mapping exclusively onto a single domain. Studying eye metrics in combination therefore provides a more comprehensive characterization of attentional functioning, allowing us to disentangle unique from shared contributions and to capture the integrative nature of attentional processes. Finally, our findings suggest that the optimal iVR task for capturing oculomotor markers varies across attentional components. For alertness, the iVR-Burst task, a simple reaction time paradigm, proved most effective, in line with its correspondence to classical alertness measures. For selective attention, the visual search task provided the strongest indices, consistent with its established sensitivity to target–distractor discrimination. By contrast, spatial attention was best captured by the free-viewing exploration task. This result accords with recent evidence indicating that free exploration paradigms better reflect natural strategies of attentional orientation and resource allocation than constrained tasks (Nardo et al., 2019; Kaufmann et al., 2020). Moreover, the use of immersive VR enhances ecological validity by enabling a more realistic and dynamic form of spatial exploration, thereby approximating everyday attentional demands more closely than traditional 2D settings (Kaiser et al., 2022). Summarizing, this study demonstrates the feasibility of integrating eye-tracking with immersive virtual reality to derive reliable markers of attentional capacities. By examining both single and combined oculomotor parameters, we showed that eye metrics index specific as well as overlapping aspects of alertness, spatial, and selective attention. Importantly, our results also indicate that different iVR tasks vary in their sensitivity to these components, underscoring the need to carefully consider task design when assessing attentional functions. Future research should include in the models demographic (e.g. age, educational level, gender) and cognitive performance variables (e.g. MoCA score) given their potential to account for variability in attentional functioning independently of oculomotor parameters (Kramer et al., 1999; Beurskens & Bock, 2011).

Together, these findings highlight the value of immersive paradigms for studying attention under conditions that approximate real-world demands and provide a basis for clinical applications, where iVR eye-tracking may help disentangle attentional deficits in patients with acquired brain injury and contribute to more precise assessment frameworks.

Chapter 7

Immersive VR Eye-Tracking Predicts Attention Deficits after Brain Injury through Machine Learning and Brain Damage Association

7.1. Introduction

Attention comprises distinct but interacting neurocognitive mechanisms, typically divided into intensity and selectivity subsystems (Bartolomeo, Thiebaut de Schotten, & Chica, 2012; Lindsay, 2020; Loetscher et al., 2019; Posner & Petersen, 2012; Spaccavento et al., 2019; van Zomeren & Brouwer, 1994). Whitin intensity subsystem, tonic alertness refers to the general level of arousal that can be top-down regulated (e.g., based on prior knowledge and current goals) to optimize responsiveness for incoming stimuli (Posner & Boies, 1971; Sturm et al., 2003; Weis et al., 2000). Complementarily, within the selectivity subsystem, spatial attention involves the allocation of attention resources toward relevant specific spatial locations, guided either by top-down control or bottom-up capture (e.g., based on stimuli salience or unexpectedness; Bartolomeo, Thiebaut de Schotten, & Chica, 2012; Corbetta & Shulman, 2011; Posner, Snyder, & Davidson,1980; Wolfe, 2018). These processes rely on widespread and interconnected brain networks. The alerting system depends primarily on the locus-coeruleus-norepinephrine system (LC-NE), which projects broadly the neocortex, including the frontopariental and salience networks, and receives afferents from the vmPFC and anterior cingulate cortex (Aston-Jones & Cohen, 2005; Bast, Poustka & Freitag, 2017; Moruzzi & Magoun, 1949; Petersen & Posner, 2012; Unsworth & Robison, 2017; Wang & Munoz, 2015). This system is predominantly right lateralized and overlaps with regions in the temporoparietal junction (TPJ) and the ventral frontal cortex (VFC), that constitute the ventral attention networks (VAN; Corbetta & Shulman, 2002, 2011; Kaufmann et al., 2023). Together with the dorsal attention network (DAN), encompassing the frontal eye fields (FEF) and the intraparietal sulcus/superior parietal lobule (Ips/PSL), these regions constitute the orienting network (Petersen & Posner, 2012).
Although DAN and VAN were initially linked to two segregated forms of attention control, top-down and bottom-up, respectively, contemporary models emphasize that attention processes arise from their dynamic interplay, enabling the flexible integration of internal goals and external salience to guide behavior (Corbetta & Shulman, 2011; Doricchi et al., 2008; Nardo et al., 2019; Ptak et al., 2012). Furthermore, converging evidence highlights that such functional coordination is sustained by structural connectivity, particularly through major white matter pathways, including, among others the superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFOF), and arcuate

fasciculus (AF), which, interconnecting these distributed attentional hubs, played a crucial role in sustained attentional processes (Alves et al., 2022; Favaretto et al., 2022; Doricchi et al., 2008; Thiebaut de Schotten et al., 2014; Kaufmann et al., 2023; Wiesen et al., 2022). Within this framework, attention and oculomotor control networks have been demonstrated to partly overlap (Beauchamp et al., 2001; Corbetta et al., 1998; de Haan et al., 2008; Lappi et al., 2016; Rizzolatti et al., 1987). Consequently, variations in oculomotor behavior can provide sensitive indices of attentional states: low alertness is associated with increased blink frequency and duration (Demiral et al., 2023; Demiral & Volkow, 2024; McIntire et al., 2014), greater fixation instability (Unsworth, Miller, & Robison, 2020; Zhou et al., 2024), and shorter fixation durations (di Stasi et al., 2013; Friedman & Komogortsev, 2024). Conversely, indices such as gaze index (i.e., time distribution across hemifields), gaze laterality (i.e., proportion of fixations per hemifield), refixation rate, and perseverative eye patterns have been proposed as reliable markers of spatial attention abilities (Cazzoli et al., 2011, 2015; Cox & Davies, 2020; Franceschiello et al., 2022; Hougaard et al., 2021; Kaufmann et al., 2020; Nardo et al., 2019; Paladini et al., 2019).

The large-scale cortical, subcortical, and white-matter organization that supports this shared attention-oculomotor system renders it particularly vulnerable to disruption following acquired brain injury (ABI). Consistently, attention disorders have been reported in approximately 46–92% of stroke survivors (Barker-Collo et al., 2009; Spaccavento et al., 2019), up to 60% of individuals with traumatic brain injury (TBI; Tsai et al., 2021), and in nearly 80% of patients with brain tumors (Tucha et al., 2000). Such impairments often result in pervasive difficulties with learning, daily functioning, and independence (Barker-Collo, 2009; Hyndman et al., 2008). Consistently, attentional deficits are linked to poorer rehabilitation outcomes, reduced return to work or education, limited social participation, and lower quality of life (Ponsford et al., 2014). Growing evidence further suggests that these deficits frequently persist in the long-term, with patients experiencing enduring cognitive impairments months or years post-injury (Mellon et al., 2015; Ponsford et al., 2014). Among the various components of attention, deficits in alertness and spatial attention seem to be associated with worse outcomes. According to the hierarchical model of attention, alertness provides the foundation for higher order attentional and cognitive processes (van Zomeren & Brouwer, 1994; Sturm et al., 1997), while unilateral spatial neglect (USN), reported in approximately 30% of patients after right hemispheric stroke, has been associated with poorer functional outcomes up to one year post-onset (Jehkonen et al., 2001). Early and precision detection of these disturbances is therefore crucial to ensure access to appropriate rehabilitation pathways and to mitigate their pervasive functional impact. However, current available neuropsychological assessments, mostly based on paper-and-pencil and computerized tools, often resulted in limited ecological validity and susceptible to subjectivity biases in administration and scoring (Pieri, Tosi, & Romano, 2023; Perez-Marcos et al., 2023; Spreji et al., 2022).

In this context, immersive virtual reality (iVR) has emerged as a valuable tool to face these limitations. By simulating real-world scenarios and offering precise control over stimuli, iVR holds the potential to enhance both the ecological validity and reliability of attention assessments. Evidence suggests that iVR-based paradigms can detect subtle yet clinically meaningful attention impairments that often go undetected with traditional methods (Hougaard et al., 2021; Thomasson et al., 2024). Moreover, moder iVR systems integrate embedded eye-tracking sensors, allowing real-time measurements of oculomotor behavior during assessment (Cavedoni et al., 2020; Pieri, Tosi, & Romano, 2023).

Considering the established role of eye movements as biomarkers of attentional functioning, and the higher ecological and controlled environments afforded by iVR, the integration of these two methodologies can help in acquiring more objective, non-invasive and reliable measures of attentional processes (Clay, König & König, 2019; Kaiser et al., 2022).

To date, most of iVR-based applications in this domain have focused on the assessment of USN, yielding insightful results (Thomasson et al., 2024; Hougaard et al., 2021; Belger et al., 2024; for a review see Kaiser et al., 2022), whereas no evidence is currently available regarding disorders of alertness. Moreover, most of the cited studies have relied on the analysis of single eye movement parameters, despite evidence that both USN and alertness deficits are characterized by modulations across multiple oculomotor indices, each defining and capturing distinct but complementary aspects. In line with recent findings, a multi-parameter approach may be better representative of the disorder's manifestation and enhance sensitivity in deficit detection (Daley et al., 2020).

Grounded on this framework, the present study aims to provide an iVR-based screening tool with automated diagnostic classification for alertness and spatial attention (USN) deficits in ABI patients. For each attentional component, we will employ a newly developed iVR-based task specifically designed to assess the corresponding process (alertness or spatial attention) and extract both oculomotor and behavioral performance metrics. In addition, oculomotor indices obtained during an immersive free-viewing exploration task will be analyzed both alone and in combination with all oculomotor and behavioral metrics derived from the corresponding iVR task. Building on previous work applying machine learning (ML) techniques to patient performance data (Daley et al., 2020; Franceschiello et al., 2022; Hougaard et al., 2021), we will apply ML models to systematically evaluate all possible combinations of iVR tasks and the derived performance metrics. This approach will enable the identification of the most informative and clinically effective configuration of

behavioral and/or oculomotor measures for differentiating patients with and without alertness or spatial attention deficits.
Finally, given the shared neural substrates of attentional and oculomotor systems and to further validate the proposed diagnostic measures, we will investigate the neuroanatomical correlates of the identified performance metrics using a lesional analysis. In particular, analysis will focus on cortical damage and structural disconnection within and between DAN and VAN.

7.2. Material and Methods

7.2.1. Participants

Patients were selected from the ones hospitalized in the Service Universitaire de Neuroréhabilitation (SUN) at the Lausanne University Hospital[5]. The inclusion criteria were age over 18 years, objective pathological performance on at least one standardized test or subtest on alertness and/or spatial attention; acquired brain injuries (including: stroke, traumatic brain injuries, and brain tumors, see Table 7.1) documented by routine neuroradiological examination; able to give informed consent; normal or correct-to-normal visual acuity; availability of eye-tracking recordings. Exclusion criteria were major psychiatric co-morbidity, major neurocognitive deficits, incapacity to discriminate colors, general cognitive state preventing from understanding and performing the tasks, decision to not be informed of incidental findings, presence of severe hemianopia.
The final sample entails a total of 31 patients (26 Males; mean age = 57.90 ± 13.75; time since onset = 49.77 ± 37.77; see Figure and Table 7.1). Across the patient cohort, lesions were bilateral but showed a clear predominance in the right hemisphere, affecting regions typically associated with attentional deficits (Corbetta & Shulman 2011; Karnath et al. 2004), particularly the fronto-parietal areas and subcortical structures such as the basal ganglia (Figure 7.1).

[5] The study is part of a wider project aimed at developing and testing a new immersive virtual reality protocol for the assessment and rehabilitation of attentional deficit in brain-damaged patients. (MindFocus - ClinicalTrials.gov: NCT05728840)

	Overall	AL +	AL -	USN +	USN -
Number of patients	N = 31	N = 18	N = 13	N = 16	N = 13
Mean age (years)	57.90 ± 13.75	59.01 ± 13.58	56.15 ± 14.31	60.5 ± 12.53	53.92 ± 14.33
Age range (years)	29-82	29-81	36-82	46-82	29-81
Gender (number of males)	26	16	10	15	9
Time since onset (days)	49.77 ± 37.77	50.67 ± 33.56	48.54 ± 52.29	58.63 ± 46.70	43.08 ± 36.43

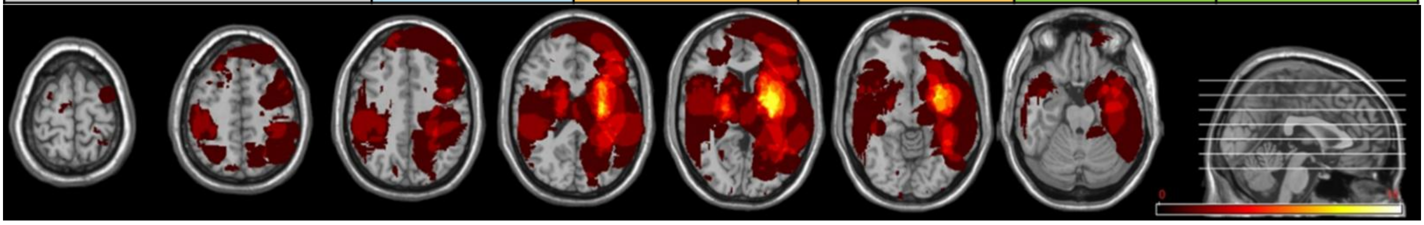


Fig.7. 1 Summary of demographic and clinical data and brain lesion overlap. For the overall sample, and for the groups defined by the presence or absence of alertness deficits (respectively AL+ and AL-) and of neglect symptoms (respectively USN+ and USN-) a summary of clinical and demographic data is described. Two additional patients with right-sided neglect were excluded from this overlay (total recruited N = 31). **Location and overlap of brain lesions:** The lesion overlay across the overall sample demonstrates a bilateral distribution, with a clear predominance in the right hemisphere, particularly within the fronto-parietal cortex and subcortical structures. The levels of the axial slices are marked by white lines on the sagittal view of the brain. The color bar indicates the number of overlapping lesions.

Attention deficits diagnosis

Alertness deficits were assessed using median reaction times (RTs) from the tonic segment of the "Alertness" sub-test in the battery Test of Attentional Performance (TAP, Version 2.3.3, 2012; Zimmermann & Fimm, 2002). In accordance with the Association Suisse de Neuropsychologie guidelines (ASN, 2018), deficits were defined as scores below the 16th percentile (AL+: 18, mean age = 59.01 ± 13.58; time since onset = 50.67 ± 33.56), while scores at or above the 16th percentile were considered within the normal range (AL-: 13, mean age = 56.15 ± 14.31; mean time since onset = 48.54 ± 52.29; Figure 7.1).

Whereas alertness can be defined as the speed in responding to an external stimulus, USN is a heterogeneous, multicomponent, disorder whose symptoms may manifest in different reference frames, sectors of space, input and output systems, modality of sensory input and stimulus type. To account for this heterogeneity, for the USN assessment we used clinical appreciations done by neuropsychologists as well as several standardized tests , including the "Neglect" and "Shifting of Attention" TAP sub-tests (Zimmermann & Fimm, 2002), the line bisection task (Schenkenberg, Bradford, & Ajax, 1980), the clock test (Shulman, Shedletsky, & Silver, 1986) and the BEN battery (Azouvi et al., 2006). Patients were classified as having USN if a clinical report indicated a diagnosis of USN or if at least one score on those tests fell below the 16th percentile. Otherwise, they were classified as within the normal range. Based on these criteria, two patients were identified as having right USN. Given both their limited number and the distinct neurocognitive characteristics typically associated with right USN, this subgroup was not adequately represented to allow reliable statistical characterization. Therefore, analyses exclusively related to the prediction of spatial attention deficits were conducted on the remaining 29 patients, including those with a clinical diagnosis of left-sided

USN (USN+: 16, mean age = 60.5 ± 12.53; mean time since onset = 58.63 ± 46.70) and those without (USN-: 13, mean age = 53.92 ± 14.33; mean time since onset = 43.08 ± 36.43; see Figure 1).

Demographic and clinical data are summarized in Figure 7.1; detailed information can be consulted in Table 7.1.

Patient	Age	Gender	Etiologies	Brain Lesion location	Lesion Side	Time since onset	Percentile tonic Alertness	Alertness deficit	Neglect (clinical diagnosis)	Neglected Side
Pat01	29	F	HSE	Temporal lobe (cortico-subcortical)	Left Hemisphere	18	16	N	N	/
Pat02	72	M	TBI	Fronto-parieto-temporal extra-axial (subdural & subarachnoid)	Right Hemisphere	147	4	Y	Y	Left
Pat03	53	M	HIS	Diffuse (fronto-parietal)	Bilateral	100	12	Y	Y	Left
Pat04	49	F	IS	Sylvian territory (cortico-subcortical)	Right Hemisphere	22	10	Y	Y	Left
Pat05	59	M	IS	Posterior cerebral artery (cortico-subcortical)	Left Hemisphere	19	4	Y	Y	Right
Pat06	80	M	IS	Internal capsule (subcortical)	Right Hemisphere	20	12	Y	Y	Left
Pat07	61	M	IS	Middle cerebral artery territory (cortico – subcortical - lenticulostriate)	Right Hemisphere	29	1	Y	Y	Left
Pat08	82	M	IS	Temporal, postcentral, and insular cortices (cortical)	Right Hemisphere	28	8	Y	Y	Left
Pat09	52	M	IS	Sylvian territory (cortico-subcortical)	Right Hemisphere	20	46	0	Y	Left
Pat10	78	M	IS	Posterior cerebral artery and splenium of corpus callosum (cortico-subcortical)	Left Hemisphere	26	3	Y	Y	Right
Pat11	61	M	IS	Median pons (brainstem)	Left Hemisphere	56	8	Y	N	Left
Pat12	56	M	HS	Thalamus (subcortical)	Bilateral	48	14	Y	N	/
Pat13	73	F	IS	Lenticulostriate territory (subcortical)	Left Hemisphere	34	4	Y	N	/
Pat14	54	M	IS	Anterior choroidal artery territory (cortico-subcortical)	Right Hemisphere	31	16	N	N	/
Pat15	65	M	IS	Sylvian territory (cortico-subcortical)	Right Hemisphere	49	3	Y	Y	Left
Pat16	61	M	HS	Sylvian territory (cortico-subcortical)	Left Hemisphere	59	50	N	N	/
Pat17	49	M	HS	Capsulo-thalamo-lenticulostriate (subcortical)	Right Hemisphere	73	14	Y	Y	Left
Pat18	81	F	IS	Anterior thalamic (subcortical)	Left Hemisphere	11	76	N	N	/
Pat19	36	M	IS	Parieto-occipital and frontal (cortico-subcortical)	Bilateral	25	12	Y	N	/
Pat20	40	M	HS	Fronto-cortico-subcortical	Bilateral	51	2	Y	N	/
Pat21	59	M	IS	Sylvian territory (posterior internal capsule)	Right Hemisphere	21	34	N	N	Right

Pat22	65	M	IS	Sylvian territory (cortico-subcortical)	Right Hemisphere	25	69	N	Y	Left
Pat23	52	M	Glial Tumor	Temporo-striato-insular (cortico-subcortical)	Right Hemisphere	75	7	Y	Y	Left
Pat24	79	M	IS	Multifocal (cortico-subcortical)	Bilateral	22	38	N	Y	Left
Pat25	44	F	IS	Sylvian territory (cortico- subcortical)	Left Hemisphere	20	42	N	N	/
Pat26	47	M	IS	Parieto-occipital (cortico-subcortical)	Bilateral	153	31	N	N	Left
Pat27	50	M	IS	Sylvian territory (cortico- subcortical)	Left Hemisphere	33	46	N	N	Right
Pat28	65	M	IS	Pontine and cerebellar (subcortical)	Bilateral	172	42	N	Y	/
Pat29	46	M	HS	Frontal lobe (intraparenchymal)	Right Hemisphere	33	1	Y	Y	Left
Pat30	46	M	IS	Sylvian territory (cortico- subcortical)	Right Hemisphere	46	24	N	Y	Left
Pat31	51	M	HS (SAH)	Anterior communicating artery (AComA)	Bilateral	77	14	Y	Y	/

Table 7.1. Detailed demographic, clinical and diagnostic for each patient included in the study. The table shows for each patient included in the study, demographic information (age and gender), clinical data (etiology, brain lesion location, damaged hemisphere, time since onset) and diagnostic data (Percentile tonic alertness, Alertness deficit, Neglect clinical diagnosis, Neglected side).
M = Male; F = Female. HSE = Herpes simplex encephalitis, TBI = Traumatic Brain Injuries, IS = Ischemic Stroke, HS = hemorrhagic stroke, HIS = Hypoxic-Ischemic Stroke; SAH = Subarachnoid Hemorrhage. Y = Yes; N = No; / = No info to report.

7.2.2. Experimental Procedure

Patients were seated at the center of the room ensuring freedom of hand movements. They were equipped with a head- mounted display (HTC Vive Pro Eye) with a display resolution of 1440 × 1600 pixels per eye, 90 Hz refresh rate and a field of view (FOV) of 110°. This head- mounted display integrates a Tobii® eye-tracking (ET) system with a binocular sampling rate set at 90 Hz and a gaze position accuracy ranging from 0.5° to 1.1° within FOV 20°.

Before starting the experimental procedure, patients' position was calibrated via HTC SteamVR 2.0 tracking system to ensure the virtual environments displayed were centered, and a 5-point eye-tracking embedded calibration procedure was performed to ensure accurate gaze data acquisition The VR training was delivered via MindFocus application (MindMaze SA, Lausanne, Switzerland) All virtual environments were developed using the Unity game engine (Unity Technologies). The instructions were standardized and delivered consistently across sessions and examiners.

To collect oculomotor and behavioral metrics aimed at predicting alertness and spatial attention deficits, three iVR tasks were included: (a) a Free Viewing Exploration task (section: "iVR-Free Viewing Exploration Task, iVR-FVE"); (b) a brief alertness task (section: "iVR-Burst Alertness subtest); and (c) a short task targeting spatial and selective attention (section: "iVR-Burst Spatial-Selective subtest"). In the context of a broader study, patients also completed other iVR subtests assessing different cognitive functions, which will not be analyzed here.

The tasks were interrupted if participants failed to comply with the instructions or if eye-tracking data were not reliably recorded, either due to non-compliance or technical issues.

a) iVR-Free Viewing Exploration Task (iVR-FVE)

The iVR-FVE is an adaptation of the Free Viewing Exploration task originally developed by Nardo et al. (2019), implemented in an immersive virtual reality environment. The task consists of 80 short videos, each lasting 1'500 milliseconds (ms), showing everyday-life scenarios presented in two possible randomized sequences. Each video (Fig. 7.3A) features a dynamic main event occurring either on the left side (Lateral Left), the right side (Lateral Right), or bilaterally. In bilateral conditions, the primary event is more prominent either on the left (Bilateral Left) or the right (Bilateral Right) .

All participants were presented with the same set of video stimuli in terms of content. However, the sequence of presentations was randomized across individuals, and the lateralization of the main event was counterbalanced: for a given video, 52% of the participants viewed the main event occurring on the left, while the remaining 48% viewed the same video with the event occurring on the right. To re-center participants' gaze between trials, a uniform grey screen with a central black cross was displayed for a randomized duration of 3'500 ms to 5'000 ms, in increments of 250 ms. The iVR-FVE has an overall duration of maximum 8 minutes. Participants were instructed to maintain fixation on the central cross during the inter-stimulus intervals and to freely explore the videos with their gaze during each trial. Head movements were not strictly prohibited; however, participants were advised to minimize head motion throughout the task to ensure stable eye-tracking performance (Fig. 7.3A).

b) iVR-Burst Alertness subtest

The iVR-Burst Alertness subtest is a 3D designed to assess an individual's general readiness to respond to external stimuli. The task was inspired by the standardized TAP Alertness subtest (Zimmermann & Fimm, 2002) and is grounded in the established theoretical distinction between tonic and phasic component of alertness (Sturm et al., 2001). During each trial (Fig. 7.3B), a blue cube appears at the center of a virtual grey room, to which participants are instructed to press the trigger button of the controller as quickly as possible. In half of the trials, a warning auditory cue preceded the blue cubes (*phasic alertness* condition, 12 trials), in the other half there was no warning cue *(tonic alertness* condition, 12 trials). Each of the 24 trials begins with the presentation of a central black fixation cross, displayed for a randomized duration between 1'800 ms and 2'700 ms. The blue cube remains visible until the participant responds, but for a maximum of 2'000 ms. The stimulus is always presented at the same central location. The total duration of the subtest is approximately 3 minutes. Participants were instructed to maintain visual fixation on the central cross throughout the task (Fig. 7.3B).

The performance metrics included Median RTs (ms), Accuracy (number of correctly detected targets divided by the total number of targets), the Inverse Efficiency Score (Median RTs divided by Accuracy), the Percentage of False Alarm and the number of Omissions.

c) iVR-Burst Spatial-Selective subtest

The iVR-Burst Spatial-Selective subtest evaluates visuo-spatial and selective attention. The task is based on the principles of Features Integration Theory (Treisman & Gelade, 1980) and employs lateralized target presentations to evaluate attentional deployment across the visual field. It consists of three progressively challenging levels. In Level 1, a single blue cube (target) appears in isolation within a virtual grey room for a maximum of 2’000 ms. In Level 2, the target is presented for up to 5’000 ms among blues spheres (as distractors). In Level 3, the target appears for up to 5’000 ms surrounded by both blue spheres and red squares as distractors. Each level is presented twice in the following order: 1-2-3-3-2-1, resulting in a total of 24 trials per level. Between trials, a central black fixation cross is displayed for a randomized duration ranging from 1’800 ms to 2’700 ms. The total duration of the task does not exceed 8 minutes. Target locations are pseudo-randomized according to fixed rules: for each level, 6 targets are presented on the left and 6 on the right, with no more than 3 targets appearing consecutively on the same side. The virtual environment is divided into a 3×7 grid of subsectors (from an underlying 3x3 by 9×21 spatial matrix), yielding 21 available subsectors per trial. One subsector is occupied by the fixation cross (center), one by the target, and the remaining 19 by distractors. During the task, participants are instructed to maintain fixation on the central cross and respond as quickly and accurately as possible by pointing a virtual laser at the blue cube and pressing the controller button. After each response, participants are required to return both their gaze and the laser pointer to the fixation cross (Fig. 7.3C).

The performance metrics entail Median RTs (ms) and Accuracy (number of correctly detected targets/total targets), each calculated separately for left- and right-sided targets. These measurements were used to compute a Spatial Index, defined as the ratio of the difference between right and left values to their sum.

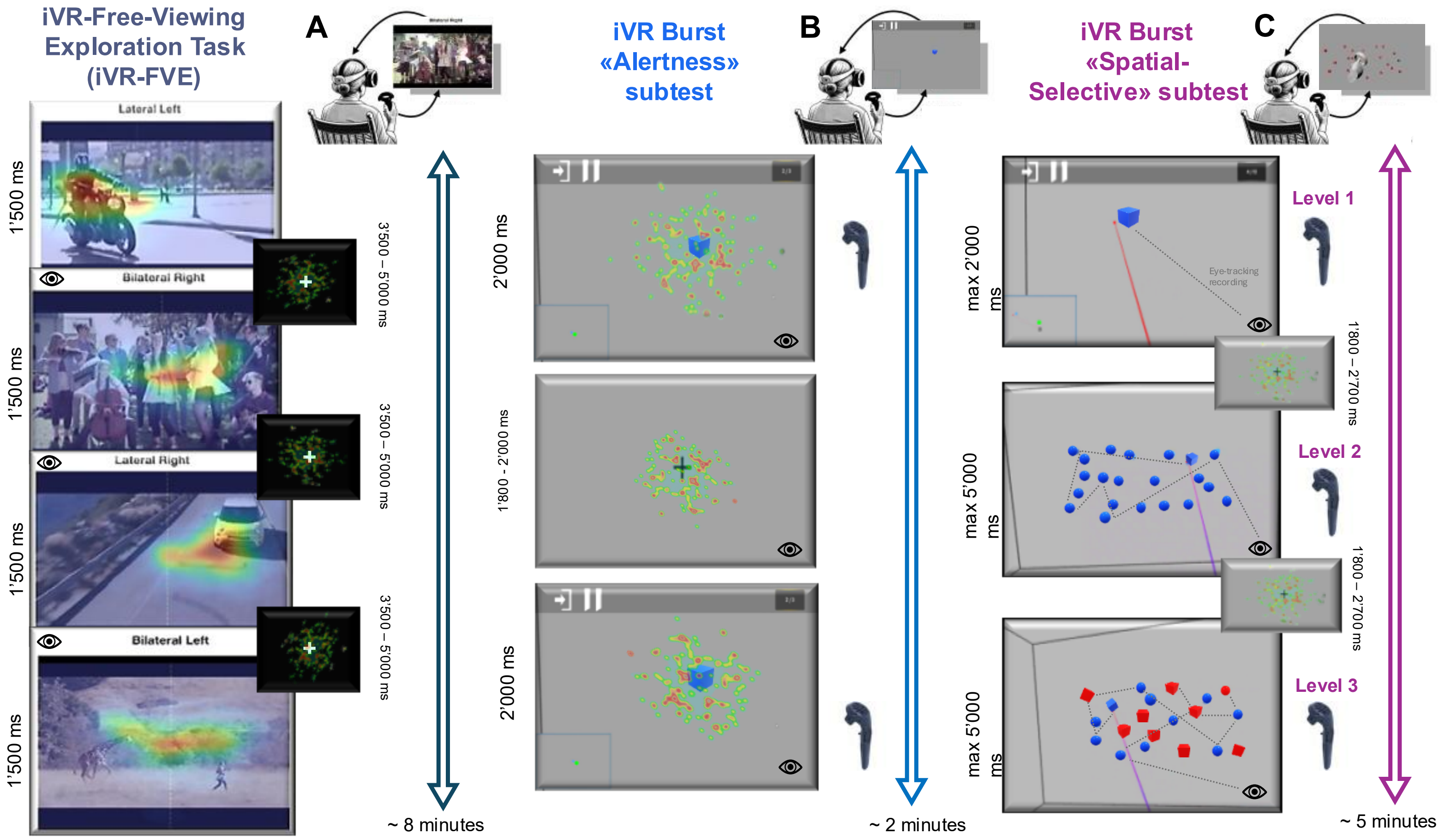


Figure 7.3. Overview of the Immersive Virtual Reality tasks implemented in the study. (A) iVR-FVE task: Examples of 4 videos and the intermediate fixation cross, picked up among the 80 videos, illustrating the 4 experimental conditions: Lateral Left, Lateral Right, Bilateral Left, or Bilateral Right. On top of the videos and grey screen, gaze heatmaps illustrate representative gaze patterns. **(B)** iVR-Burst Alertness: Examples of 2 target stimuli (central blue cube) to which the participants respond as quickly as possible by pressing a button on the controller (shown here on the right of the target stimuli). Each trial begins with a central black fixation cross. Heatmaps of the gaze are shown on top of screenshots to illustrate representative gaze patterns. **(C)** iVR-Burst Selective: This subtest assesses visuo-spatial and selective attention using lateralized target detection in a virtual environment. Participants must locate and respond to a blue cube presented either alone (Level 1), among blue sphere distractors (Level 2), or among both blue spheres and red squares (Level 3). Trials are interleaved with central fixation intervals. Eye-tracking data are continuously recorded also during this task.

7.2.3. Eye-Tracking recordings: Pre-processing and Oculomotor features identification

The raw eye-tracking signal acquired continuously during the three iVR-tasks was processed offline using custom scripts developed in RStudio (RStudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA, "www.posit.co", RStudio-2024.12.01.563 for Windows 11, R version 4.3.3 – 2025-02-28 ucrt) to extract oculomotor metrices. Particularly, the metrices extracted are among the ones already highlighted by scientific literature as biomarkers of Alertness abilities or Spatial Attention capacities, respectively (see Table 7.2).

ET-Metrices	Computation (summary)	Outputs	References
Alertness - related eye metrices			
Fixation count & duration	Fixations identified with I-DT algorithm (Salvucci & Goldberg, 2000; dispersion ≤1.5°, duration ≥100 ms). Each fixation is characterized by duration and position.	Total number of fixations, mean number of fixations, total fixation duration, mean fixation duration - overall, not lateralized	Di Stasi et al. 2013; Daley et al., 2020; Friedman & Komogortsev, 2024
Blink frequency & duration	Blinks identified as consecutive frames with eye openness <0.7 and pupil diameter = −1. Grouped into blink episodes.	Blink frequency (blinks per second) and total blink duration (ms).	Demiral et al., 2023; Demiral & Volkow, 2024; McIntire et al., 2014

Fixation stability (IQR)	For each fixation, Euclidean distance of samples from mean fixation point was computed; interquartile range (IQR) used as stability index.	Mean fixation stability (average IQR across fixations).	Unsworth, Miller & Robison, 2020; Zhou et al., 2024
Spatial attention – related eye metrices			
Gaze laterality	Computed as the proportion of gaze samples located in the left hemifield (FocusPoint.x < 0) relative to total samples.	Proportion of leftward gaze samples (0–1).	Cazzoli et al., 2015; Cox & Davies, 2020; Kaufmann et al., 2020; Franceschiello et al., 2022; Hougaard et al., 2021
Gaze index	Difference between total time spent on left vs. right hemifield, normalized by total fixation time. Positive values = right bias; negative = left bias.	Index ranging from −1 (left bias) to +1 (right bias).	Cox & Davies, 2020; Nardo et al., 2019; Hougaard et al., 2021
First fixation side	Direction of the first fixation after trial onset coded as left (−1) or right (+1), then averaged across trials.	Mean first-saccade direction index (−1 = left bias, +1 = right bias).	Cox & Davies, 2020; Keiser et al., 2022; Serino et al., 2007
Re-fixations	A fixation was classified as a refixation if its angular distance from the previous fixation was <1.5° within the same trial (index = 1).	Total number of refixations, separately for left and right hemifields.	Cox & Davies, 2020; Paladini et al., 2019; Cazzoli et al., 2011
Perseverative re-fixations	Subset of refixations where gaze returned repeatedly to the same region (index ≥2).	Total number of perseverative refixations, separately for left and right hemifields.	Cox & Davies, 2020; Paladini et al., 2019; Nys et al., 2008; Rusconi et al., 2002
Fixation count & duration	Fixations identified with I-DT algorithm (dispersion ≤1.5°, duration ≥100 ms). Each fixation is characterized by duration and position.	Total number of fixations, mean number of fixations, total fixation duration, mean fixation duration - lateralized (left and right)	Cox & Davies, 2020; Muri et al., 2009; Keiser et al., 2022; Hougaard et al., 2021

Table 7.2. Overview of the Eye metrics identified from the literature linked to alertness and spatial attention capacities, respectively.

7.2.4. Brain imaging

Lesion segmentation and lesion mask pre-processing

For each patient, structural MRI data was collected from the neuroimaging database of Lausanne University Hospital and were acquired for clinical purposes during the patient's first hospital access. The pre-processing pipeline followed the steps described below.

First, T1 images were converted to NifTi format. To ensure proper image orientation and improve the likelihood of successful normalization, the image origin was set at the anterior commissure by establishing reorientation matrices (Moore, 2022) using the Statistical Parametric Mapping (SPM12) software package (https://www.fil.ion.ucl.ac.uk/spm/).

Lesion delineation was subsequently performed on the T1-weighted images, which are widely used in stroke rehabilitation research for their high anatomical resolution and reliability in identifying lesion boundaries (Liew et al., 2022) using ITK-SNAP (Yushkevich et al., 2006; Yushkevich and Gerig, 2017; version 3.8.0; http://www.itksnap.org). ITK-SNAP represents segmentations by assigning unique integer values to each voxel, with non-zero values corresponding to damaged regions. The manual tracing approach was preferred over the semi-automatic method for greater control and was performed according to the recommendations of Lo and colleagues (2023). Regions corresponding to the lesion were delineated in individual slice views, with contours drawn every 2–3 slices to accommodate varying lesion shapes and sizes (Yushkevich et al., 2016). Interpolation was then applied to fill in the manually traced slices across the full volume. Once verified, the delineated polygons were assigned to a specified label and integrated into the 3D segmentation volume (Yushkevich et al., 2016).

Recognizing the inherent subjectivity of manual tracing, a single rater performed all manual tracing and quality control checks were conducted in collaboration with an expert neuroradiologist.

Following lesion segmentation, image preprocessing was performed using SPM12. This included spatial normalization and reslicing lesion masks to the Montreal Neurological Institute (MNI) space. Normalization was conducted using a bounding box defined by the coordinates [-90, -128, -72] to [90, 90, 108], with a voxel resolution of 1 × 1 × 1 mm. The normalized lesion masks were then resliced to match the MNI_T1 template, which shares the same isotropic voxel dimensions and has an image matrix size of 182 × 218 × 182.

7.2.5. Machine Learning Implementation and Structural Damage Quantification

Analyses were performed using R software (RStudio version 2024.12.1+563; R version 4.3.3, released 2025-02-28; Posit Software, PBC, Boston, MA) and MATLAB (Version R2024a; The MathWorks Inc., Natick, MA, USA) for Windows 11.

Machine Learning Classification Algorithms

To investigate whether the implemented iVR tasks (either individually or in combination) can provide performance metrics suitable for the automated detection of alertness and spatial attention disorders (USN), oculomotor metrics from each of the three iVR tasks and behavioral metrics from the iVR-Burst Alertness subtest and iVR-Burst Spatial-Selective Attention subtest were used to train supervised machine learning (ML) algorithms, following the pipeline summarized in Figure 4.

All candidate predictor variables were first preprocessed via z-transformation (i.e., scale and center transformation methods) implemented through the prePocess() function from the caret R-package. Missing values were assessed on column-wise basis, and any missing values were imputed using column mean. The target variables were encoded as binary (two-level) factors, represented the presence (1) or absence (0) of either an alertness deficit or USN diagnosis (Figure 4.1; Data Preprocessing). To reduce dimensionality and retain only informative predictors, the Boruta feature selection algorithm was applied (Kursa & Rudnicki, 2010). Only predictors classified as "Confirmed" were retained for model training. If, after reaching the maximum threshold of iterations, some features were left without a decision, the TentativeRoughFix() function was used to force a final decision (Figure 4.2; Feature Selection). The classification model was constructed using a Random Forest (RF) classifier (caret R-package) with Leave-One-Out Cross Validation (LOOCV) to obtain unbiased performance estimates given the small sample tested. Hyperparameter tuning was performed using a grid search over the number of features tried at each split (i.e., mtry). Furthermore, the number of trees (i.e., ntree) was systematically iterated from 5 to 200 in increments of 5. For each ntree, the optimal mtry was selected maximizing the F1 score (i.e., the harmonic mean of precision and recall), and the corresponding cross-validated predictions were recorded (Figure 4.3; Model Training with

Hyperparameter Tuning). Model performance was assessed on the aggregated LOOCV predictions. For each combination of ntree and its corresponding best mtry value, classification metrics were calculated by comparing predicted versus true classification labels. F1 score, accuracy, sensitivity and specificity were assessed to quantify classification performance. Empirical probabilities of the positive class were used to construct Receiving Operator Characteristics (ROC) curves, and the area under each curve (AUC) was computed to quantify model's discriminative capacity (Figure 4.4; Model Evaluation). Although F1 score was employed as the primary index for fine-tuning, as it offers a balanced measure of precision and recall given the class imbalance in our sample, it was observed that it can be overly sensitive to single misclassification, especially in small datasets. Therefore, final best model selection also considered both AUC maximization and the normalized out-of-bag (OOB) error minimization (Fig 4.4). Combining AUC and OOB error provided a complementary view of both discriminative performance and model generalizability, two crucial aspects to pursue the aim of developing an automated iVR-based screening tool with potential diagnostic application in clinical contexts involving samples with characteristics similar to those of the present study.
Finally, the relative importance of predictors from the final best model was quantified and visualized ranked by mean decrease in Gini impurity (Breiman et al., 2017).

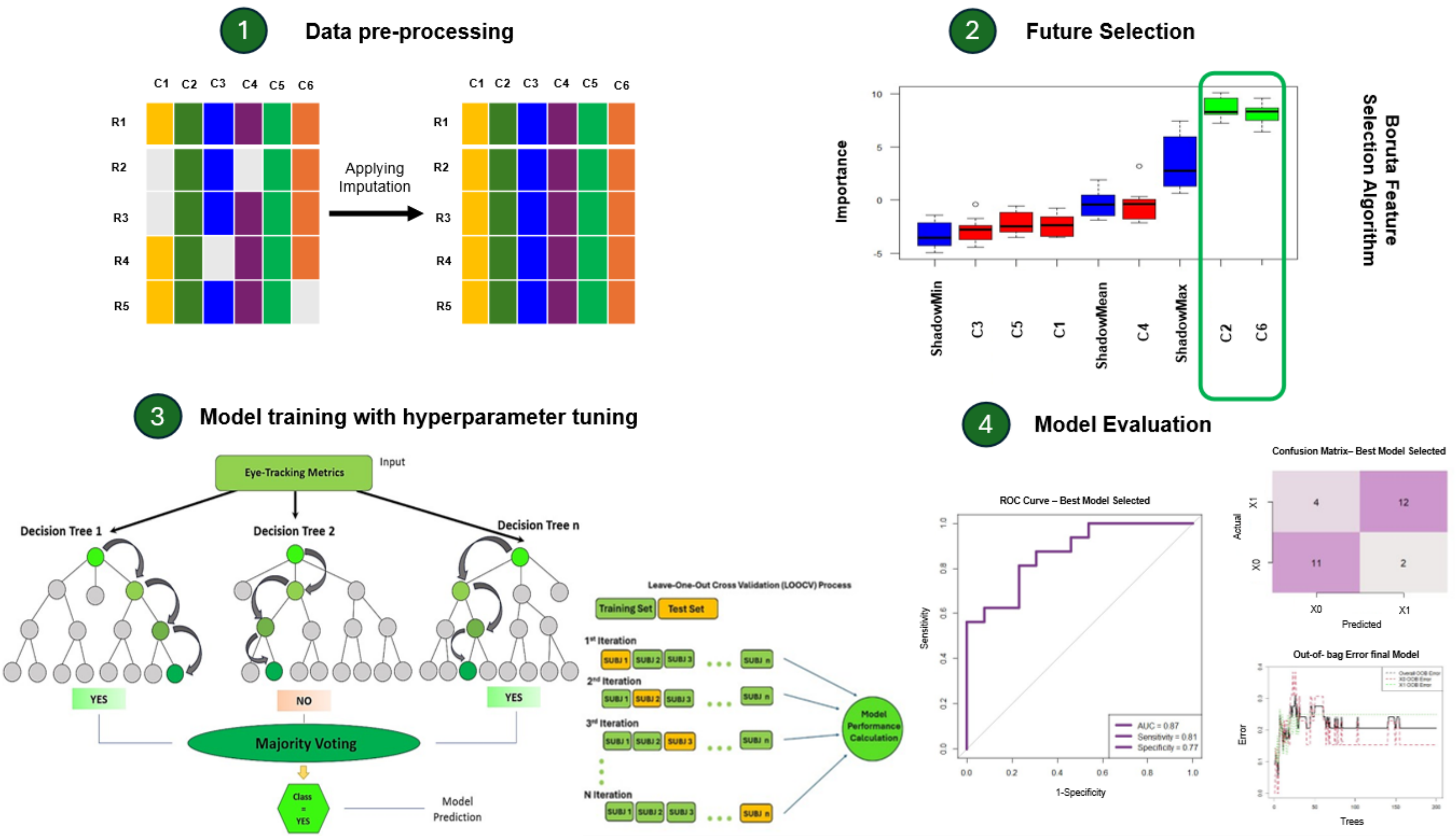


Figure 7.4. Overview of the machine learning pipeline for classification of attentional deficits using metrics from iVR tasks. (1) Data preprocessing: missing values were imputed, and all predictors were standardized to prepare for model training.

(2) Feature selection: the Boruta algorithm identified relevant predictors (green) by comparing their importance to that of randomized shadow features.
(3) Model training and hyperparameter tuning: a Random Forest classifier with Leave-One-Out Cross-Validation (LOOCV) was trained. Model performance was iteratively computed across subjects. Hyperparameter tuning was performed using a grid of mtry based on the number of retained predictors by Boruta. Number of trees (ntree) was iterated from 5 to 200 in increments of 5 and the optimal mtry was selected based on F1 score maximization.
(4) Model evaluation: the final model was assessed using AUC, sensitivity, specificity, confusion matrix, and out-of-bag (OOB) error to balance discrimination and generalization

To explore the contribution of distinct oculomotors and behavioral metrics, the full ML pipeline was applied separately to predict alertness deficits and USN diagnosis. Each clinical outcome was modeled through all the possible combinations between oculomotors and behavioral metrics derived from targeted iVR tasks. Finally, the importance of individual variables in the final model was quantified and visualized, ranked by the mean decrease in Gini impurity (Breiman et al., 2017) (Fig 7.4.4).

7.2.6. Application of ML Pipeline to Multiple Feature Combinations

<u>*Alertness Deficit Detection*</u>

For the classification of alertness deficits, ML models were trained using oculomotor metrics previously identify as biomarker of alertness gathered during the iVR-FVE and iVR-Burst Alertness subtest (see Table 7.2), along with behavioral metrics from the iVR-Burst Alertness subtest (see also section "*iVR-Burst Alertness subtest"*).

In Table 7.3, a schematic description of the metrics used to train the models can be consulted.

To systematically evaluate the diagnostic contribution of each metric set, seven model configurations were tested using alertness-related performance features as follows: (i) ET metrics from the iVR-FVE task only (*Movies_ET model*); (ii) ET features from the iVR-Burst Alertness sub-test only (*Burst_ET model*); (iii) Behavioral performance scores from the iVR-Burst Alertness sub-test only (*Burst_BH model*); (iv) A combination of ET and behavioral metrics from the iVR-Burst Alertness sub-test (*Burst_ETBH model*); (v) ET metrics from both the iVR-FVE and iVR-Burst Alertness tasks (*Movies_ET + Burst_ET model*); (vi) ET metrics from iVR-FVE combined with behavioral metrics from the iVR-Burst Alertness sub-test (*Movies_ET + Burst_BH model*); (vii) A full model combining ET and behavioral metrics from the iVR-Burst Alertness sub-test with the ET metrics from the iVR-FVE ET (*Movies_ET + Burst_ETBH model*).

iVR-tasks for Alertness assessment	**Eye-tracking Performance Metrics tested (Alertness related)**						**Behavioral performance metrics tested**				
	Extracted during overall duration of iVR-task (not lateralized computation)					Fixation cross	Extracted from tonic segment				
	Total fixations number	Total fixations duration	Mean fixations duration	Blink frequency	Total blink duration	Fixation stability (IQR)	Median RT (ms)	Accuracy (Target Hit/Total)	Efficiency (Median RT/Accuracy)	Percentage of False Alarms	Number of Omissions
iVR-FVE	✓	✓	✓	✓	✓	✓					
iVR-Burst Alertness	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 7.3. ET and behavioral alertness specifics metrics from the IVR-FVE and the IVR-Burst Alertness subtest. oculomotor alertness related parameters from the IVR-FVE and the IVR-Burst Alertness subtest along with Alertness behavioral performance metrics from the iVR-Burst Alertness subtest used in combination within the seven RF model to predict alertness deficit (clinical diagnosis based on the TAP Alertness subtest).

USN Deficit Detection

For the classification of USN, models were trained using oculomotor metrics linked to spatial attention abilities collected during the iVR-FVE and iVR-Burst Spatial-Selective subtest (see Table 7.2), together with behavioral metrics from the latter (see section "*iVR-Burst Spatial-Selective Attention subtest")*. Table 7.4 displayed a schematic description of the performance metrics employed to train the models for USN classification.

The models were trained employed the same seven configurations, but using the spatial attention related metrics, as following: (i) ET metrics from the iVR-FVE task only (*Movies_ET model*); (ii) ET metrics from the iVR-Burst Spatial-Selective subtest only (*Burst_ET model*); (iii) Behavioral metrics from the iVR-Burst Spatial-Selective subtest only (*Burst_BH model*); (iv) A combination of ET and behavioral metrics from the iVR-Burst Spatial-Selective subtest (*Burst_ETBH model*); (v) ET metrics from both the iVR-FVE and the iVR-Burst Spatial-Selective subtest (*Movies_ET + Burst_ET model*); (vi) ET metrics from iVR-FVE combined with behavioral metrics from the iVR-Burst Spatial-Selective subtest (*Movies_ET + Burst_BH model*); (vii) A full model combining ET and behavioral metrics from the iVR-Burst Spatial-Selective subtest with ET metrics from the iVR-FVE ET (*Movies_ET + Burst_ETBH model*).

iVR-tasks for Spatial Attention assessment	Eye-tracking performance metrics tested (Spatial Attention related)								Behavioral performance metrics tested	
	Extracted for each task condition or difficulty levels							Overall tasks	Extracted for each task condition	
	Gaze Laterality	Gaze Index	Total fixation numbers	Total fixation duration	Total Refixation number	Total perseverative refixation	First Fixation Side	First Fixation Side	Spatial Accuracy Index (Right-Left)	Spatial Median RT Index (Right-Left)
iVR-FVE	✓	✓	✓	✓	✓	✓		✓		
iVR-Spatial Selective	✓	✓	✓	✓	✓	✓	✓		✓	✓

Table 7.4. Oculomotor and behavioral spatial attention specifics metrics from the IVR-FVE and the IVR-Burst Spatial-Selective subtest. Oculomotor spatial attention related parameters from the IVR-FVE and the IVR-Burst Spatial-Selective subtest along with Spatial Attention behavioral performance metrics from the iVR-Burst Spatial-Selective attention subtest used alone or in combination within the seven RF model to predict USN diagnosis.

7.2.7. Lesion Quantification and Structure–Function Analysis

To investigate the structural underpinnings of attention-specific impairments identified through ET-specific profile, we conducted a structure–function analysis.

First, the set of features retained in the best-performing ML classification models was considered for alertness and USN, respectively. To reduce dimensionality and obtain a single interpretable score per patient, Principal Component Analysis (PCA) was applied to each set of the ET features retained in the best models. The first principal component (PC1) was extracted in each case, capturing the largest proportion of shared variance. This component served as a continuous latent biomarker dimension, summarizing the ET profile most predictive of the respective attentional impairment (alertness or USN). For structural analysis, we employed the R-implementation of the Lesion Quantification

Toolkit (LQT) (https://github.com/jdwor/LQT), quantifying both grey matter damage and white matter disconnection severity (Griffis et al., 2021). Using the MNI-registered lesion mask obtained for each patient (see section: *"Lesion segmentation and lesion mask pre-processing"*), both parcel-wise and tract-level atlas-based measures of damage were computed. According to the LQT pipeline, the parcel-wise grey matter damage was calculated, based on the Schaefer-Yeo 100-parcel functional parcellation, augmented with subcortical and cerebellar structures (Schaefer et al., 2018; Yeo et al., 2011), as the proportion of lesioned voxels within each atlas-defined region that overlapped with the lesion. Moreover, to determine the anatomical composition of each parcel within the DAN and VAN, a vertex-based anatomical mapping was performed using the Schaefer et al. (2018) parcellation. The cortical surface vertices corresponding to each parcel were extracted in MATLAB using the Brainstorm toolbox. For each parcel, the MNI coordinates (x, y, z) of all vertices were retrieved and converted to Talairach space using the online converter provided by BioImage Suite Web (https://bioimagesuiteweb.github.io/webapp/mni2tal.html). Each vertex was then assigned to its corresponding Brodmann area label based on the Talairach atlas. This procedure allowed the identification of the main cytoarchitectonic regions encompassed within each Schaefer 100-parcel.
Instead, tract disconnection severity was defined as the proportion of disrupted streamlines within each of 70 tracts derived from the HCP-1065 population-level tractography atlas (Yeh FC, 2022). When necessary, thresholding was applied at 0.5 to resolve binary ambiguities in lesion masks.
To summarize lesion extent across regions, a cumulative damage score was computed for each patient by summing the normalized lesion proportions across the structures belonging to the attentional networks (i.e., the dorsal and ventral attention networks, DAN and VAN), as defined by the considered tractography (Yeh et al., 2022) and parcellation atlases (Schaefer et al., 2018; Yeo et al., 2011). A linear regression was then fitted to regress PC1 scores against cumulative damage values. To increase robustness, statistical outliers were identified and excluded using a locally weighted regression (LOESS) fit (Cleveland & Devlin, 1988): cases exceeding the 95th percentile of residuals were removed from subsequent analyses. Finally, to investigate the specific brain regions (tracts/parcels) associated with the ET biomarker profile, Spearman's rank correlations were computed between PC1 and each structural component. A non-parametric permutation test (1,000 iterations) was applied for each correlation to assess the likelihood of observing the same or stronger correlation by chance.
All results were interpreted considering both significance thresholds ($p < 0.05$) and anatomical plausibility.

7.3. Results

Random Forest (RF) LOOCV Classification Performances

Alertness Deficit Detection

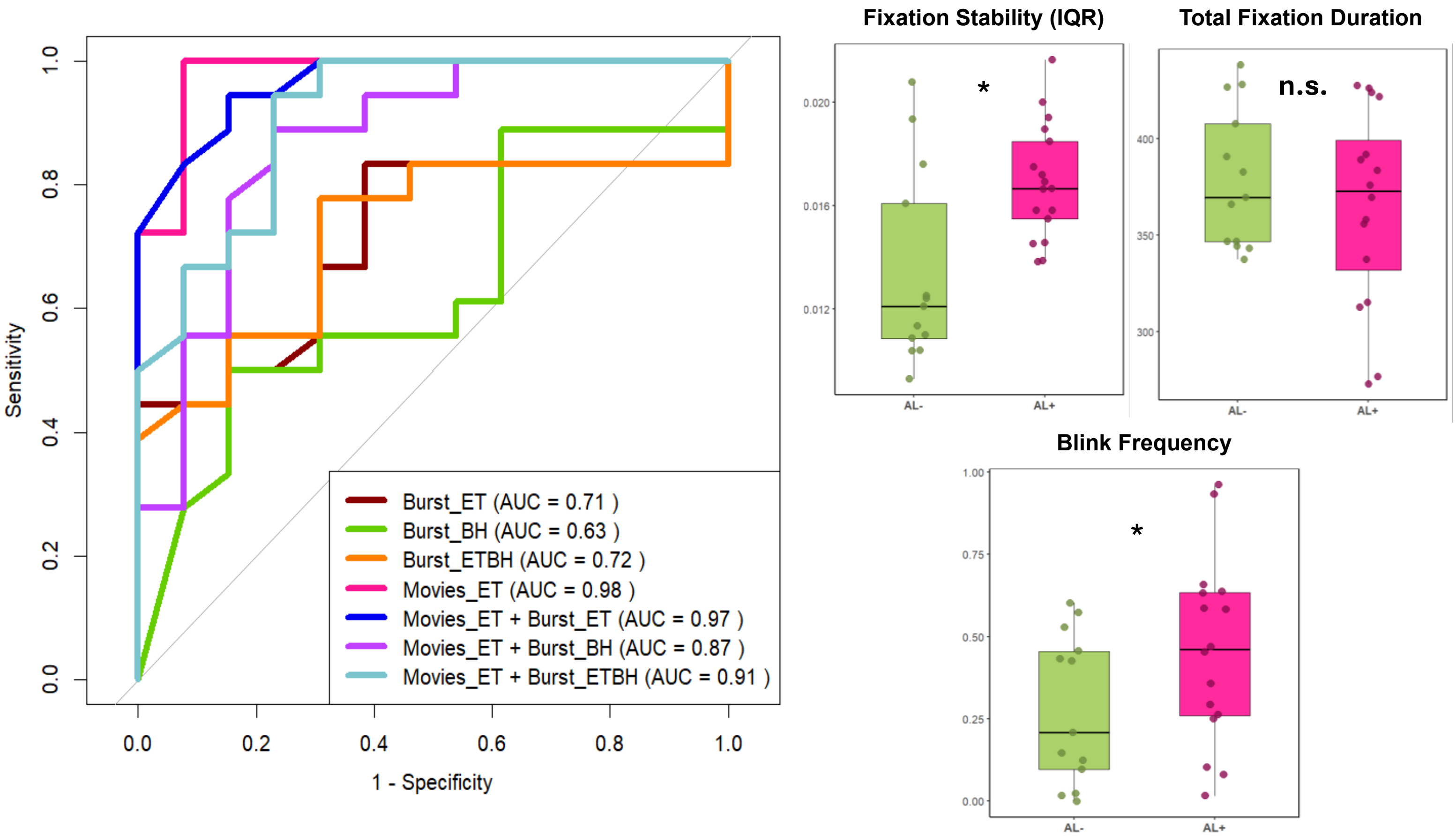
The table in figure 7.5 reported the performance indices separately for each of seven models tested, along with the behavioral and/or oculomotor metrics used to train them, respectively. A specification of the iVR tasks, from which the retained performance metrics were collected, are also available.

Across the seven RF models tested for the prediction of alertness deficits, substantial variability in performance emerged depending on the combination of oculomotor and behavioral features used.

In particular, models trained exclusively on metrics from the iVR-Burst Alertness subtest, either using eye metrics alone (*Burst_ET model)*, behavioral metrics alone (*Burst_BH model)*, or combined *Burst_ETBH*) exhibited low classification power. In detail, F1 scores showing small to moderate balance of classification abilities (*Burst_ET* = 0.71; *Burst_BH* = 0.63; *Burst_ETBH* = 0.71), reflecting in the values of sensitivity (*Burst_ET* = 0.67; *Burst_BH* = 0.56; *Burst_ETBH* = 0.67) and specificity (all *Burst models* = 0.69). Consistently, confusion matrix showed that among the 18 patients defined as having alertness deficit from standardized test (AL+) both the *Burst_ET* and the *Bust_ETBH* models correctly classified 12 patients (True positive, TP), whereas only 10 were detected by the *Burst_ETBH.* In addition, all models classified 9 patients out of 13 as AL- correctly. To note, *Burst_ET* and *Burst_ETBH* models consistently categorized 6 patients as not having alertness deficits even if they have a clinical AL+ diagnosis (False Negative, FN), while 4 patients were detected as having an alertness deficit even if they did not have a diagnosis based on clinical standardized evaluation (False Positive, FP). In contrast, *Burst_ETBH* model performance was lower: the FN was attested at 8 and the FP at 4. Overall, the accuracy detection (*Burst_ET* = 0.68; *Burst_BH* = 0.56; *Burst_ETBH* = 0.71) and AUC values (*Burst_ET* = 0.71; *Burst_BH* = 0.63; *Burst_ETBH* = 0.72) across the three Burst models were low, along with higher OOB error rate (*Burst_ET* = 0.32; *Burst_BH* = 0.35; *Burst_ETBH* = 0.26; see Figure 7.5). Collectively these results pointed out that using alertness related performance metrics from the iVR-Burst Alertness subtest either alone (ET or BH) or in combination (ETBH) results in model with low level of discriminability and generalization, so that diagnostic applicability in a more generalized clinical context may be not optimal. On the other hand, combining performance metrics from the iVR-Burst Alertness subtest (*Burst models*) with the ones collected during the iVR-FVE (*Movies models*) result in a consistent increase across all the model's performance indices. The F1 scores were moderate both when a combination of oculomotor metrics from the iVR-FVE and behavioral metrics from the iVR-Burst Alertness subtest were tested (*Movie_ET* + *Burst_BH model* = 0.86) and when oculomotor metrics from the iVR-FVE were merged

with oculomotor and behavioral metrics from the iVR-Burst Alertness subtest (Movies_ET + Burst_ETBH *model* = 0.89). Instead, F1 score became high when trained by a combination of only oculomotor metrics from both tasks (*Movies_ET* + *Burst_ET model* = 0.92), demonstrating a greater balance between sensitivity and specificity. Accordingly, the sensitivity and specificity values were systematically higher in the *Movies_ET* + *Burst_ET model* (sensitivity = 0.94; specificity = 0.85) compared to the other two models (*Movies_ET* + *Burst_BH model*: sensitivity = 0.83, specificity = 0.77; *Movies_ET* + *Burst_ETBH model*: sensitivity = 0.94, specificity = 0.0.77). Moreover, the *Movies_ET* + *Burst_ET model* model show higher balance in correct classification of single patients resulting in overall higher accuracy detection (TP = 17 out of 18; TN = 11 out of 18) with low degree of misclassification (FP = 2; FN = 1; accuracy = 0.90), compared to both the *Movies_ET* + *Burst_BH model* (TP = 16 out of 18; TN = 10 out of 13; FP = 3; FN = 2; accuracy = 0.83) and the *Movies_ET* + *Burst_ETBH model* (TP = 17; TN = 10; FP = 3; FN = 1; accuracy = 0.89). Finally, in line with the picture described, AUC value was higher and associated with lower OOB error rate in the model combining only oculomotor metrics from both tasks (*Movies_ET* + *Burst_ET model*: AUC = 0.97; OBB = 0.06), with respect to the others two models (*Movies_ET* + *Burst_BH model:* AUC = 0.87; OBB = 0.19; *Movies_ET* + *Burst_ETBH model:* AUC = 0.91; OBB = 0.16; see Figure 7.5).
Overall, the results highlighted that combining performance metrics collected during both tasks improve discriminative and generalizability capacities of the models. However, the last model to be described, the one trained exclusively with oculomotor metrics collected during the iVR-FVE task (*Movies_ET model*) resulted as the best performing. In fact, this model outperformed all the others across all the different indices. In detail, the model achieved an F1 score of 0.97, describing optimal balance between perfect sensitivity (1.00) and high specificity (0.92). Consistently, from the confusion matrix it emerges that all 18 AL+ were correctly identified (TP) and 12 out of 13 were correctly classified as AL- (TN). Only one FP occurred among the 13 AL-, for an overall accuracy of 0.90. The AUC was 0.98, which indicates that the classifier was able to accurately differentiate between AL+ and AL- across almost all possible decision thresholds. In parallel, the OBB error rate was approximately 3% demonstrates that the model's predictions remained consistent for data not used during training, suggesting strong generalizability and reliability of performance when applied to new, similar samples. This optimal performance was obtained using 190 trees (ntree = 190) and an mtry value of 2 when trained using three oculomotor metrics: mean fixation stability during the fixation cross, total fixation duration, and blink frequency across the entire task. These features were retained by Boruta algorithm as the most informative predictors, suggesting that they can considered effective biomarkers for distinguishing between AL+ and AL- in our sample. In this perspective, to further investigate these features, independent Welch's *t*-tests were conducted to compare AL+ and

AL– groups on each of the three oculomotor metrics, with *p*-values corrected for multiple comparisons using the False Discovery Rate method. The results suggests that AL+ showed significantly greater fixation instability (M = 0.0179) compared to AL- (M = 0.0134; $t_{(28.71)} = -2.94$, $p = 0.019$). Similarly, blink frequency was higher in the AL+ group (M = 0.562) than in the AL– group (M = 0.279; $t_{(27.39)} = -2.44$, $p = 0.032$). Although, the comparison between groups didn't reach statistical significance for the total fixation duration ($t_{(27.87)} = 1.54$, $p = 0.135$), indicating a not clear differences in the duration of visual exploration in the two groups of patients, from the mean of the value we can speculate that patient with alertness deficits (AL+) show a slightly higher fixation duration (M = 378.95) compared to patients without a clinical alertness deficit (AL-; M = 351.45).
From this evidence, it is possible to conclude that the *Movies_ET* models, trained with oculomotor metrics extracted from the iVR-FVE task alone, are highly informative for detecting alertness deficits. The optimal level of discriminability associated with low likelihood of error suggests the potential effective applicability in a more generalized clinical context for screening alertness impairments in samples of acquired brain-injured patients, similar to the one included in the present study.



ID Model	Eye Parameters (RF - Importance Ranked)	F1 score	Acc	Sen	Spec	TP	TN	AUC	OBB
Burst_ET	Total Fixation Duration (iVR-AL, Tonic Task); Total Number of Fixation (iVR-AL, Tonic Task)	0.71	0.68	0.67	0.69	12/18	9/13	0.71	0.32
Burst_BH	Median Reaction Time (ms) (iVR-AL, Tonic Task); Inverse Efficiency Score (iVR-AL, Tonic Task)	0.63	0.61	0.56	0.69	10/18	9/13	0.63	0.35

Burst_ETBH	Total Fixation Duration (iVR-AL, Tonic Task); Median Reaction Time (ms) (iVR-AL, Tonic Task): Inverse Efficiency Score (iVR-AL, Tonic Task); Total Number of Fixation (iVR-AL, Tonic Task)	0.71	0.68	0.67	0.69	12/18	9/13	0.72	0.26
Movies_ET	Mean fixation stability (IQR) (iVR-FVE, Fixation Cross); Total Fixation Duration (iVR-FVE, Overall); Blink Frequency (iVR-FVE, Overall)	0.97	0.97	1	0.92	18/18	12/13	0.98	0.03
Movies_ET + Burst_ET	Mean fixation stability (IQR) (iVR-FVE, Fixation Cross); Total Fixation Duration (iVR-AL, Tonic Task); Blink Frequency (iVR-FVE, Overall); Total Number of Fixation (iVR-AL, Tonic Task)	0.92	0.90	0.94	0.85	17/18	11/13	0.97	0.06
Movies_ET + Burst_BH	Mean fixation stability (IQR) (iVR-FVE, Fixation Cross); Inverse Efficiency Score (iVR-AL, Tonic Task); Median Reaction Time (ms) (iVR-AL, Tonic Task); Blink Frequency (iVR-FVE, Overall)	0.86	0.83	0.89	0.77	16/18	10/13	0.87	0.19
Movies_ET + Burst_ETBH	Mean fixation stability (IQR) (iVR-FVE, Fixation Cross); Total Fixation Duration (iVR-AL, Tonic Task); Blink Frequency (iVR-FVE, Overall); Total Number of Fixation (iVR-AL, Tonic Task); Median Reaction Time (ms) (iVR-AL, Tonic Task); Inverse Efficiency Score (iVR-AL, Tonic Task); Total Fixation Duration (iVR-FVE, Overall)	0.89	0.87	0.94	0.77	17/19	10/!3	0.91	0.16

Fig 7.5 Random Forest classification models for Alertness deficit detection. Comparison of seven models trained on eye-tracking (ET) and behavioral features from the iVR-FVE task ("Movies" and the iVR-Burst Alertness subtest ("Burst"). Top: Receiver Operating Characteristic (ROC) curves with Area Under the Curve (AUC) values reported in the legend. In the table: model performances (F1*, accuracy, sensitivity, specificity, AUC and out-og-bag [OBB] error) and the correspondent most predictive features ranked by RF mean decrease accuracy importance). The model Movies_ET, based on fixation stability (cross condition), total fixation duration, and blink frequency, achieved the highest performance (F1 = 0.97, AUC = 0.98, OBB = 0.03). On the right, the three oculomotor metrics retained by Boruta algorithm to train the ET_Movies model are plotted separately for the AL+ (violet) and AL- (green). The fixation stability (IQR) gathered during the fixation cross of the iVR-FVE reveal that AL+ patients showed higher instability of fixation compared to AL- (adjusted p-value = 0.019). The comparison of total fixation duration between the two groups was not significant (adjusted p-value = 0.13), however the higher mean of duration was reported for AL+ (M = 378.95) than AL- (M = 351.45). Finally, blink resulted as significant higher in frequency for AL+ compared to AL- (adjusted p-value = 0.032).
*p < 0.05; ** p < 0.01; *** p < 0.001; n.s. = not significant

USN Deficit Detection

The table in figure 7.6, performance indices for each of the seven models along with their behavioral and/or oculomotor metrics can be consulted. The details of the iVR tasks, from which the performance metrics were gathered, are also available.

Overall, the performance of the seven RF models tested for the prediction of USN resulted fairly homogenous with values oscillating from moderate to high. However, a certain degree of variability in performance emerged, depending on the combination of oculomotor and behavioral features used. Firstly, although the models trained with performance metrics alone (ET or BH) from both tasks (*Burst_ET, Burst_BH and Movies_ET*), showed reasonable values, overall, their classification ability was less strong compared to the other models.

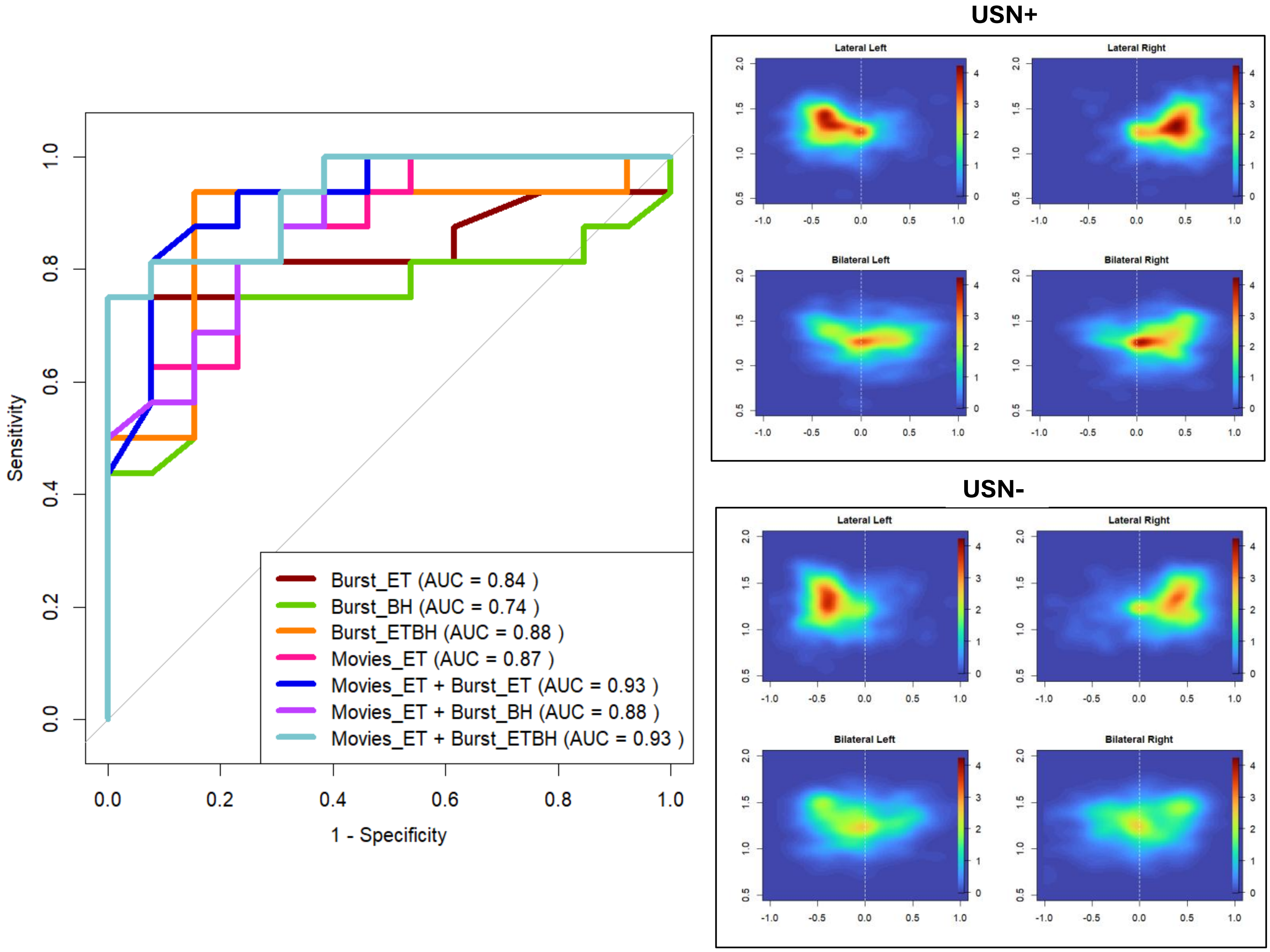
Particularly, the lower performance was achieved by the model trained with behavioral metrics derived from the iVR-Burst Spatial-Selective Attention (*Burst_BH model*) with moderate values across F1 (0.77), sensitivity (0.75) and specificity (0.77). In line with this, the confusion metrics evidenced that the *Burst_BH model* detected correctly 12 out of 16 patients (TP) with a clinical diagnosis of USN (USN+), and 10 out of 13 patients with no diagnosis of USN (USN-). Correspondingly, the patients wrongly defined as USN+ were 3, while as USN- were 4. Although the AUC values pointed out a modest discriminability capacity (0.74), the OOB error attested at 27% suggested limited potential for generalization (see Figure 7.6). On the other hand, the models trained with oculomotor metrices either collected from the iVR-FVE (*Movies_ET model*) or the iVR-Burst Spatial-Selective Attention subtest (*Burst_ET model*) achieved modest although not optimal performances (see Figure 6), with comparable values across all the considered indices (for both models: F1 score = 0.81; sensitivity = 0.81; specificity = 0.77; accuracy = 0.79; TP = 13 out of 16;

TN = 10 out of 13; FP = 3; FN = 3; AUC = 0.84; OBB = 0.21). A further amelioration of the classification for USN was evident when the oculomotor metrics from the iVR-FVE were combined with the behavioral metrics from the iVR-Burst Spatial-Selective Attention subtest (*Movies_ET + Burst_BH model*). Particularly, the model showed a good level of sensitivity (0.88) compared to a modest level of specificity (0.69) with an overall moderate F1 score (0.82). The confusion metrics reveal an acceptable level of accuracy (0.79) with a modest capacity to correctly identify USN+ (TP = 14 out of 16; FN = 2), while the classification of USN- resulted as more instable (TN = 9 out of 13; FP = 4).

Going higher in terms of achieved performance, the model combined behavioral and oculomotor metrics from the iVR-Burst Spatial Attention subtest (*Burst_ETBH model*), the model combined oculomotor metrics from both the IVR-FVE and the iVR-Burst Spatial Attention subtest (*Movies_ET and Burst_ET*) and the model trained with all the possible performance metrics from both tests (*Movies_ET + Burst_ETBH*) resulted as better compared to the ones previously described. Among them, the *Movies_ET + Burst_ET model* can be defined as the best performing in detecting USN.

In detail, the *Movies_ET + Burst_ET model* achieved the highest value of sensitivity (0.94) comparable with the one achieved by the *Burst_ETBH model* (sensitivity = 0.94), and higher when compared with the *Movies_ET + Burst_ETBH* (sensitivity = 0.82). Although, the specificity resulted higher in the *Movies_ET + Burst_ET* (0.77) model than for the *Movies_ET + Burst_ETBH* (0.69), it resulted slightly lower compared to the one achieved by the *Burst_ETBH model* (0.85) with corresponding a bit lower F1 score (F1: *Movies_ET + Burst_ET model* = 0.88*; Burst_ETBH model* = 0.91*; Movies_ET + Burst_ETBH model* = 0.82). In this line, from the confusion matrix it result that the *Burst_ETBH* and the *Movies_ET + Burst_ET model* are comparable in term of capacity to correctly identify AL+ (TP = 15 out of 16; FN = 1), while the *Burst_ETBH model* detected AL- better for only one observation, resulting in a slightly better accuracy (*Movies_ET + Burst_ET model*: TN = 10, FP = 3, accuracy = 0.86; *Burst_ETBH model*: TN = 11, FP = 2; accuracy = 0.90). Conversely, the overall accuracy of the *Movies_ET + Burst_ETBH model* was lower (TP = 14; FN = 2; TN = 9; FP = 4; accuracy = 0.79). Thus, the accuracy performance that result from sensitivity and specificity better for the *Burst_ETBH model* compared to the *Movies_ET + Burst_ET model*, these results were trained by only one correctly detected TN. Corroborating this conclusion, when taken into account the discriminative performance of the three model, the AUC values of *Movies_ET + Burst_ET model* (0.93) outperformed the one achieved by the *Burst_ETBH model* (0.88). Similarly, the *Movies_ET + Burst_ET model* show higher generalizability (OBB = 0.14) compared to the *Burst_ETBH model* (OBB = 0.17; see Figure 7.6). Finally, even if the *Movies_ET + Burst_ETBH model* showed a comparable value of AUC (0.93) and OBB (0.13) to the ones described for the *Movies_ET + Burst_ET* *model,* its overall accuracy was consistently lower so that at more general comparison the *Movies_ET + Burst_ET model* can be considered outperforming (see Figure 7.6).

In summary, when considering both the discriminative performance and the model's generalization capacity, the *Movies_ET + Burst_ET model* emerged as the most robust configuration for USN prediction. Despite comparable accuracy values across the top-performing models, its higher AUC (0.93) and lower OOB error rate (0.14) indicate a more optimal trade-off between sensitivity and specificity and a stronger ability to generalize beyond the training sample. These complementary metrics demonstrate that the *Movies_ET + Burst_ET* model not only achieved a good internal classification accuracy but also maintained consistent predictive stability across unseen data, minimizing overfitting effects (Figure 7.6). This optimal configuration was achieved using 65 tree (ntree = 65) and an mtry = 1 when trained with 15 oculomotor metrics derived from both the iVR-FVE and the iVR-Burst Spatial Selective Attention tasks. The 15 metrics was the one retained by Boruta as the most informative to detect USN. Taken together, these oculomotor metrics (e.g., direction of the first fixation, gaze laterality, gaze index) suggest that the characteristic distribution of fixation among the x axis can be used to distinguish between USN+ from USN- (see Figure 7.6).



ID Model	Eye Parameters (RF - Importance Ranked)	F1 score	Acc	Sen	Spec	TP	TN	AUC	OBB
Burst_ET	Gaze index (iVR-Spa,Level 3); Total Number of Fixations Right (iVR-Spa,Level 2); Total Fixation Duration Right (iVR-Spa,Level 2); Gaze Laterality (iVR-Spa,Level 3)	0.81	0.79	0.81	0.77	13/16	10/13	0.84	0.21
Burst_BH	Spatial Index MedRT (iVR-Spa,Level 3); Spatial Index MedRT (iVR-Spa,Level 2)	0.77	0.76	0.75	0.77	12/16	10/13	0.74	0.27
Burst_ETBH	Spatial Index MedRT (iVR-Spa,Level 3); Total Fixation duration right (iVR-Spa,Level 2); Spatial Index MedRT (iVR-Spa,Level 2); Gaze Index (iVR-Spa,Level 3); Total number of Fixations Right (iVR-Spa,Level 2); Gaze Laterality (iVR-Spa,Level 3)	0.91	0.90	0.94	0.85	15/16	11/13	0.88	0.17
Movies_ET	Total Number of Fixations Left (iVR-FVE,Bilateral Right); Total Number of Fixation Left (iVR-FVE,Bilateral Left); Mean First Fixation Direction (iVR-FVE,Overall); Gaze laterality (iVR-FVE,Bilateral Left); Gaze Laterality (iVR-FVE,Bilateral Right); Gaze Laterality (iVR-FVE,Lateral Right); Total Fixation Duration Left (iVR-FVE,Lateral Right); Gaze Index (iVR-FVE,Bilateral Right); Total Fixation Duration Left (iVR-FVE,Bilateral Right); Total Fixation Duration Right (iVR-FVE,Bilateral Right); Total Number of Fixation Left (iVR-FVE,Lateral Right)	0.81	0.79	0.81	0.77	13/16	10/13	0.84	0.21
Movies_ET + Burst_ET	Mean First Fixation Direction (iVR-FVE,Overall); Total Number of Fixation Left (iVR-FVE, Bilateral Left); Total Fixation Duration Right (iVR-Spa,Level 2); Total Number of Fixation Left (iVR-FVE,Bilateral Right); Total Fixation Duration Right (iVR-FVE,Bilateral Right); Gaze Laterality (iVR-FVE,Lateral Right); Gaze Index (iVR-Spa,Level 3); Total number of Fixation Right (iVR-Spa,Level 2); Gaze Laterality (iVR-FVE,Bilateral Right); Total Number of Fixation Left (iVR-FVE,Lateral Right); Gaze Index (iVR-FVE,Bilateral Right); Gaze Laterality (iVR-Spa,Level 3); Total Fixation Duration Left (iVR-FVE,Bilateral Right); Total Fixation Duration Left (iVR-FVE,Lateral Right); Gaze Laterality (iVR-FVE,Bilateral Left).	0.88	0.86	0.94	0.77	15/16	10/13	0.93	0.14
Movies_ET + Burst_BH	Mean First Fixation Direction (iVR-FVE,Overall); Spatial Index MedRT (iVR-Spa,Level 3); Total Number of Fixation Left (iVR-FVE,Bilateral Right); Total Number of Fixation Left (iVR-FVE,Bilateral Left); Gaze Laterality (iVR-FVE,Bilateral Right); Gaze Laterality (iVR-FVE,Bilateral Left); Gaze Laterality (iVR-FVE,Lateral Right); Total Fixation Duration Left (iVR-FVE,Bilateral Right); Total Number of Fixation Left (iVR-FVE,Lateral Right); Total Fixation Duration Right (iVR-FVE,Bilateral Right); Gaze Index (iVR-FVE,Bilateral Right).	0.82	0.79	0.88	0.69	14/16	9/13	0.88	0.17
Movies_ET + Burst_ETBH	Mean First Fixation Direction (iVR-FVE,Overall); Total Number of Fixation Left (iVR-FVE, Bilateral Left); Gaze Laterality (iVR-FVE,Bilateral Right); Total Number of Fixation Left (iVR-FVE,Bilateral Right); Spatial Index MedRT (iVR-FVE,Level 3); Total Fixation Duration Right (iVR-FVE,Bilateral Right); Gaze Laterality (iVR-FVE,Bilateral Left); Total Fixation Duration Right (iVR-Spa,Level 2); Total number of Fixation Right (iVR-Spa,Level 2); Gaze Index (iVR-FVE,Bilateral Right); Spatial Index MedRT (iVR-Spa,Level 2); Gaze Index (iVR-Spa,Level 3); Gaze Laterality (iVR-Spa,Level3)	0.82	0.79	0.88	0.69	14/16	9/13	0.93	0.13

Figure 7.6. Random Forest classification models for Unilateral Spatial Neglect (USN) diagnosis. Comparison of seven models trained on ET and behavioral features from the iVR-FVE task ("Movies" and the iVR-Burst Alertness subtest ("Burst"). In Figure 5 Receiver Operating Characteristic (ROC) curves with Area Under the Curve (AUC) values reported in the legend. The 15 oculomotor metrics retained by Boruta to train the best performing model, overall pointed for a specific pattern of fixation distribution across the two hemifield as biomarkers to differentiate between USN+ and USN-. In this line, on the right, the density map of eye fixations from the iVR-FVE tasks for each of the four conditions (Lateral Left, Lateral Right, Bilateral Left and Bilateral Right) are displayed, aggregated and plotted separately for patients with a clinical diagnosis of USN (USN+) and for patients without a clinical diagnosis of USN (USN-). Table 5: model performances (F1, accuracy, sensitivity, specificity, AUC and OBB error) and the most predictive features ranked by importance). The model Movies_ET + Burst_ET showed the best balance between accuracy detection (F1 = 0.88, AUC = 0.93) and generalizability (OBB = 0.14).

7.3.1. Structural Damage Correlates

<u>*Structural damage association with ET-profile for Alertness deficit*</u>

To gather a unique marker of alertness deficits, a PCA was performed on the three ET features selected by the best-performing model for alertness classification (*Movies_ET* model): mean fixation stability, total fixation duration, and blink frequency. The first principal component (PC1) explained 56.8% of the total variance and was used as a composite score to capture the main ET profile associated with alertness deficits. PC1 scores were then examined in relation to cumulative structural damage. The cumulative damage score was computed for each participant by summing the scaled lesion values across the parcels and tracts of the Ventral and Dorsal Attention Network (VAN and DAN). The raw cumulative damage scores (Mean = 8.46 ± 7.02; [0.00 - 28.89]), were standardized (z-scored) to ensure comparability across participants [-1.01 - 2.44]. The LOESS-based residual inspection (95th percentile threshold) identified and excluded two outliers, leaving 29 participants for each linear model.

Two outliers were excluded based on residuals from a LOESS smoothing fit. The subsequent linear regression model did not reveal any significant association between cumulative lesion load and PC1 scores (β = 0.089, *se* = 0.096, $t_{(17)}$ = 0.93, p = .365, R^2 = .05), indicating no clear relationship between total attention-network damage and the ET composite score of alertness.

To identify more specific structure-function relationships, we explored individual tracts and parcels using Spearman correlation with 1,000 permutation iterations. Among these, only one region showed a statistically significant association after correction for multiple comparisons: the right posterior node of the dorsal attention network (RH_DorsAttn_Post_1), which was positively correlated with PC1 scores ($\rho = 0.52$, adjusted $p = .024$; Figure 7.8A). Following the vertex-based mapping procedure, the resulted parcel encompasses the right visuo-associative cortex (Area 19), the angular gyrus (Area 39), and the fusiform gyrus (Area 37). This finding suggests that damage to this specific node may contribute to ET alterations linked to impairment in alertness.

Structural damage association with ET-profile for USN detection

The PCA was applied to the 15 ET features retained by the best-performing model for USN classification (*Movies_ET* + *Burst_ET* model). The first principal component (PC1) explained 60.3% of the total variance and was used as a composite ET-based biomarker of USN. Particularly, positive PC1 scores were primarily driven by right-ward directed gaze and fixation measures, indicating stronger rightward attentional bias, whereas lower PC1 values reflected a more left-lateralized exploratory behavior.

The residuals from the LOESS fit, applying to regress PC1 scores against the cumulative damage index resulting in two cases exceeding the 95th percentile thresholding and were excluded from the analysis. The linear regression model fitted on the cleaning dataset revealed a significant positive association ($\beta = 0.479$, $se = 0.107$, $t_{(17)} = 4.46$, $p < .001$) between cumulative structural damage and the composite ET-biomarker score (PC1). This indicates that greater lesion burden within the DAN/VAN was associated with more severe USN-related ET alterations. Overall, the model accounted for 54% of the variance in PC1 scores ($R^2 = 0.54$; adjusted $R^2 = 0.51$), with a residual standard error of 1.95 (Fig. 7.7).

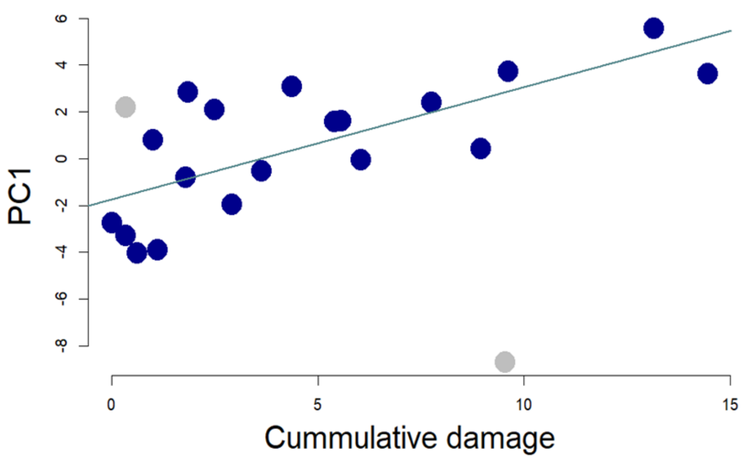


Figure 7.7. Relationship between cumulative damage to attention networks and the ET-derived composite biomarker (PC1). Scatterplot shows PC1 scores plotted against the cumulative damage index (sum of lesion proportions across dorsal and ventral attention network tracts and parcels). Outliers identified via LOESS regression (grey dots) were excluded from the analysis. The regression line fitted to the cleaned dataset reveals a significant positive association, indicating that greater structural damage within DAN/VAN is linked to more severe USN-related ET alterations.

To better understand the contribution of different components of the VAN and DAN to neglect, a Spearman rank correlation analysis with 1,000 permutation iterations was performed across individual tracts and parcels. This analysis reveals, among the significant associations, five regions which mostly contributed to the ET- biomarker profile (PC1). In detail, higher PC1 values, which reflected stronger rightward bias (i.e., USN-like pattern) were associated with three right-hemispheric white matter tracts: the right Frontal Aslant Tract (FAT_R; $\rho = 0.67$, adjusted $p = .005$), the right Uncinate Fasciculus (UF_R; $\rho = 0.59$, adjusted $p = .009$) and the right Inferior Fronto-Occipital Fasciculus (IFOF_R; $\rho = 0.53$, adjusted $p = .015$). At the cortical level, significant effects were found in two right-hemispheric parcels. The right frontal opercular–insular node of the VAN (RH_SalVentAttn_FrOperIns_1; $\rho= 0.83$, adjusted $p < .001$; Figure 7.8B) encompassed the insula (Area 13), entorhinal cortex (Area 34), opercular and triangular regions (Areas 44 and 45), primary motor cortex (Area 4), and pars orbitalis (Area 47). The right posterior node of the DAN (RH_DorsAttn_PrCv_1; $\rho = 0.52$, adjusted $p = .020$) included the opercular and triangular region (Area 44 and 45), pre-motor and supplementary motor regions (Area 6) and dorsolateral prefrontal cortex (Area 9; Figure 7.8B).

These findings underscore that damage to a right-lateralized VAN and DAN regions their interconnected major association tracts were associated with higher PC1 values, corresponding to a stronger rightward oculomotor bias. This pattern indicates that the oculomotor alterations captured by the *Movies_ET + Burst_ET model*, which most effectively differentiated USN+ from USN− patients, are grounded in structural brain regions within the canonical networks supporting spatial attention. Accordingly, the integrity of the DAN and VAN interplay, encompassing both cortical and subcortical components, appears essential for balanced gaze orientation and attentional deployment, while its damage gives rise to neglect-like oculomotor asymmetries. Ultimately, the derived oculomotor metrics represent reliable, structurally grounded biomarkers for the detection of unilateral spatial neglect.

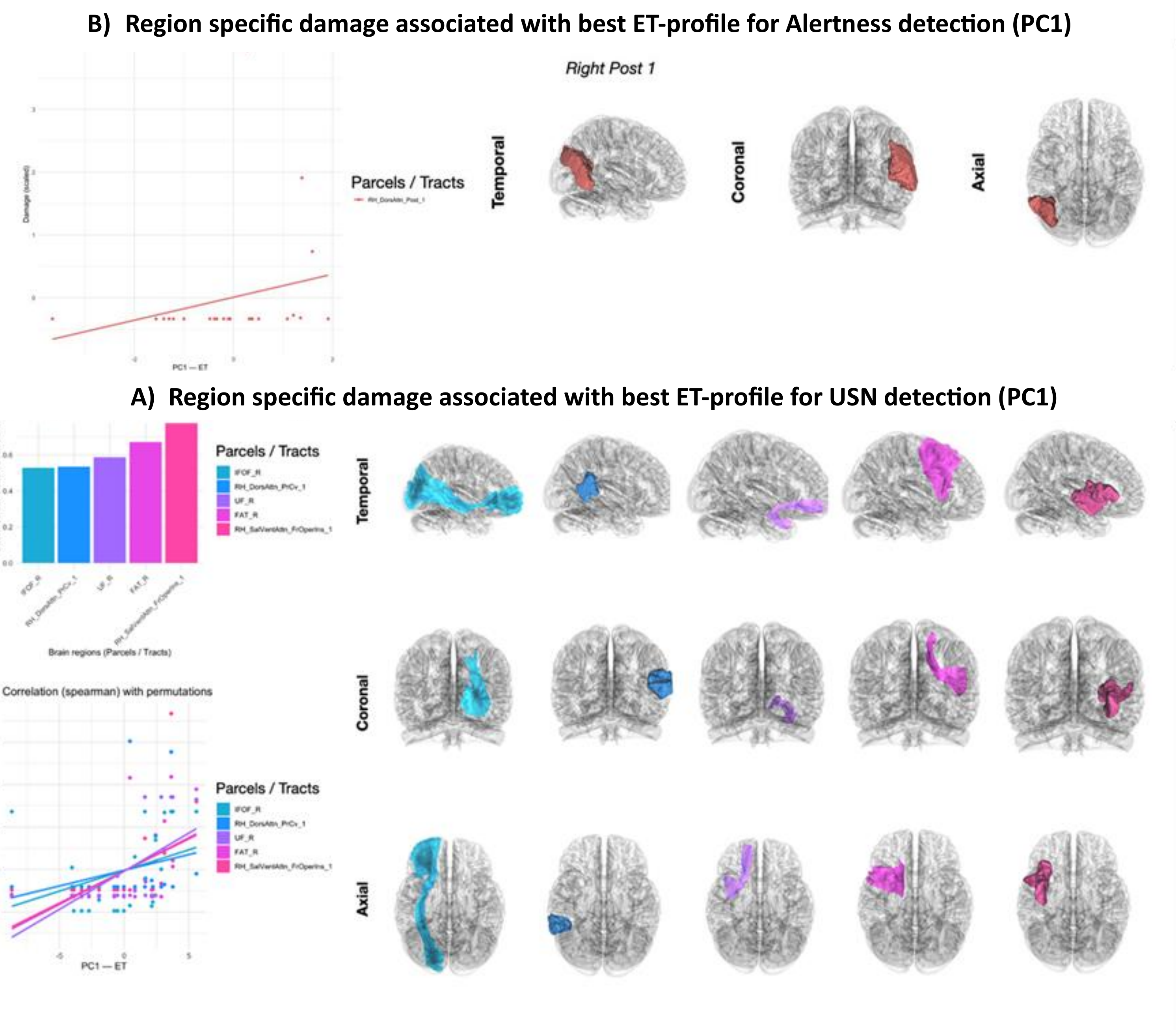


Figure 7.8. Structure–function association for alertness- and USN-related ET profile

(A). Spearman correlation (1,000 permutations) between the ET composite score (PC1) and lesion measures revealed a significant positive association with the right postcentral parcel of the dorsal attention network (RH_DorsAttn_Post_1; $\rho = .52$, adjusted $p = .024$). Left panel: scatterplot with regression fit line; right panels: anatomical localization of the RH_DorsAttn_Post_1 parcel in temporal, coronal, and axial views.

(B). Principal Component Analysis (PC1) of ET features from the best-performing USN classification model was regressed against lesion data. Top: bar plot showing Spearman correlations (ρ) with permutation-based adjusted p-values (1,000 iterations) between PC1 scores and lesion severity. Significant associations were observed in five right-lateralized regions: right Inferior Fronto-Occipital Fasciculus (IFOF_R; $\rho = 0.53$, adjusted $p = .015$), right postcentral DAN parcel (RH_DorsAttn_Post_1; $\rho = 0.52$, adjusted $p = .020$), right Uncinate Fasciculus (UF_R; $\rho = 0.59$, adjusted $p = .009$), right Frontal Aslant Tract (FAT_R; $\rho = 0.67$, adjusted $p = .005$), and right Frontal Operculum/Insula parcel of the salience/ventral attention network (RH_SalVentAttn_FrOperIns_1; $\rho = 0.83$, adjusted $p < .001$). Bottom left: scatterplots with regression lines illustrating parcel/tract-wise associations. Right panels: anatomical localization of implicated regions in temporal, coronal, and axial views.

7.4. Discussion

In the present study, we demonstrated that oculomotor assessment within immersive virtual reality (iVR) proved to be a sensitive and reliable approach for automated detection of alertness and spatial attention deficits in a sample of sub-acute brain damaged patients.

(i) At the behavioral level, across the two attentional domains examined, distinct oculomotor configurations provided optimal diagnostic performance. For alertness, the model trained exclusively on oculomotor metrics collected during the iVR Free Viewing Exploration task (Movies_ET model) achieved the highest classification accuracy, perfectly identifying all patients with clinically defined alertness deficits (AL+). For spatial attention, the model combining oculomotor metrics from both the iVR-Free Viewing Exploration and the iVR Burst Spatial-Selective Attention (Movies_ET + Burst_ET) reached the best balance between sensitivity and specificity, with strong generalization capacity in classified patient with (USN+) and without (USN-) a clinical diagnosis of unilateral spatial neglect. (ii) At the neuroanatomical level, lesion and disconnection analyses revealed that these oculomotor patterns were associated with damage to right-lateralized cortical regions and white matter tracts within the ventral and dorsal attention network (VAN and DAN), whose functional interplay is known to underpin alertness and spatial attention abilities.

Starting from oculomotor metrics commonly described as biomarkers of alertness abilities, our result demonstrated that the machine learning model trained combining total fixation duration, fixation stability and blink frequency gathered from the iVR-Free Viewing Exploration task (iVR-FVE) achieved the highest accuracy in detecting patient with (AL+) or without (AL-) alertness deficits as identified by standardized test. The pattern of these three parameters closely aligns with the theoretical definition of alertness as the readiness to respond to external stimuli (Moruzzi & Magoun, 1949; Petersen & Posner, 2012). The slightly longer fixation duration observed in AL+ suggests that, under reduced efficiency in regulating alertness level, greater effort is required for information processing, converging with evidence showing that fixation time increases when cognitive load exceeds available resources (Soler-Dominguez et al., 2017; Souchet et al., 2022). The concomitant increase in fixation instability further indicates altered top-down regulation of alertness, reflecting difficulties in suppressing microsaccades during fixation, phenomena thought to indicate reduced inhibitory influence from the frontal eye field and superior colliculus, which are essential to stabilize gaze for prioritizing incoming relevant stimuli (Unsworth, Miller, & Robison, 2020; Unsworth & Robison, 2017; Zhou et al., 2024). Within this condition of reduced system responsiveness and consistently with prior work linking blinks to transient surges in arousal supporting wakefulness and alertness (Demiral et al., 2023; Demiral & Volkow, 2024) the higher blink rate observed in AL+ can be viewed as a compensatory mechanism boosting top-down processes to transiently enhance arousal and try to maintain readiness.

For spatial attention, we found that a distinct pattern of oculomotor metrics derived from the iVR-Free Viewing Exploration and the iVR Burst Spatial-Selective tasks best captured imbalances in spatial attention allocation. Specifically, the distribution of fixations along horizontal axis emerged as the most informative index of spatial bias, converging with previous evidence from both standard laboratory settings (Cox & Davies, 2020; Franceschiello et al., 2022; Kaufmann et al., 2020; Nardo et al., 2019; Paladini et al., 2019) and iVR environments (Kaiser et al., 2022). Among the most discriminative features were the direction of the first fixation in the iVR-FVE, the total number of fixations on the left in bilateral viewing conditions, and the total duration of exploration of right-lateralized stimuli in the visual search task (iVR Burst Spatial-Selective Attention). Together, these metrics effectively differentiated patients with (USN+) and without (USN−) unilateral spatial neglect, reflecting the lateralized deployment of visual attention during naturalistic exploration.

Implementing lesion and disconnection analyses to investigate the neural underpinnings of the oculomotor profile that showed the highest diagnostic discriminability, we showed that higher values of PC1, used as an oculomotor marker profile differentiating AL+ and AL-, were associated with greater disruption in the right posterior visual regions of the DAN. Although a large body of studies has linked alertness deficits primarily to alterations in regions among the VAN (Corbetta & Shulman, 2011), the alerting system is mainly supported by the locus coeruleus-norepinephrine system (LC-NE) which has widespread and predominantly right-lateralized cortical projections (Aston-Jones & Cohen, 2005; Petersen & Posner, 2012; Joshi, Kalwani, & Gold, 2016). In line with this evidence, the posterior visual regions resulted here, including the angular, fusiform, and visuo-associative cortices, are among the most densely innervated by noradrenergic fibers (Morrison & Foote, 1986; Posner & Petersen, 1990; Petersen & Posner, 2012), suggesting that their disruption may contribute to the oculomotor pattern associated with reduced alertness. Collectively, these results show that the iVR-derived oculomotor pattern that most accurately classified patients with or without alertness deficits corresponds to damage within regions subserving the alerting system, providing a strong neurobiological foundation for its use as a reliable clinical biomarker of alertness functioning. According with evidence that spatial attention emerges from the interaction between cortical VAN and DAN regions and the white matter tracts connecting these distributed hubs (Alves et al., 2022; Favaretto et al., 2022; Doricchi et al., 2008; Thiebaut de Schotten et al., 2014; Kaufmann et al., 2023; Wiesen et al., 2022), the higher PC1 score, representing a more right-ward directed gaze and fixations measures was associated with a right lateralized network of areas within the VAN and DAN, converging also with the well-known right-hemispheric specification for spatial attention (Heilman

& Van Den Abell, 1980). Within the DAN, lesions involved the dorsolateral prefrontal cortex and frontal eye field/dorsal premotor complex, known as core hubs for top-down attention allocation and oculomotor control (Corbetta et al., 1998; Corbetta & Shulman, 2011). Whitin the VAN, alteration in insular/opercular regions and the inferior frontal gyrus, well established brain areas linked with bottom-up attention allocation, resulted as related to the retained oculomotor pattern. Consistently, disconnection of specific tracts was also associated with this pattern. The inferior frontal occipital fasciculus (IFOF), a ventral pathway connecting the inferior frontal gyrus/dorsolateral prefrontal cortex with occipital cortex (Rojkova et al., 2016; Sarubbo et al., 2013; Weiller et al., 2021), and the Frontal Aslant Tracts which interconnecting the inferior parietal lobule, the superior temporal gyrus, the frontal eye field, the inferior frontal gyrus and the presupplementary motor area (Corbetta & Shulman, 2002; Vossel, Geng, & Fink, 2014; Bartolomeo & Seidel-Malkinson, 2019), both supporting spatial attention abilities (IFOF: Hattori et al., 2018; Suo et al., 2020; Urbanski et al., 2008; 2011; Umarova et al., 2010; FAT: Doricchi et al., 2008; Karnath et al., 2011; Thiebaut de Schotten et al., 2011). Finally, the Uncinate Fasciculus connects the anterior temporal lobe with the orbital and polar frontal cortex (Thiebaut de Schotten et al., 2012; Von der Heide et al., 2013), has also been implicated in VAN connectivity (Alves et al., 2022) and appeared crucial for the emergence of chronic USN (Committeri et al., 2007; Karnath et al., 2011). This results further established our oculomotor biomarker profile as reliable tool for clinical diagnosis of spatial attention disorders.

An important aspect of our results concerns the specific iVR tasks that yielded the most informative oculomotor metrics for detecting attention disorders. The iVR-FVE has demonstrated the highest sensitivity in detecting alertness impairments, a result that can be explained by several complementary factors. Although free viewing paradigms have rarely been applied to direct alertness directly, they offer some advantages over conventional computerized alertness task, which typically require participants to maintain central fixation and respond to stimuli appearing repeatedly in the same spatial position (Posner & Petersen, 2012; Leclercq & Zimmermann, 2002). Indeed, such approaches capture response readiness through reaction times but provide limited insight into the continuous regulation of alertness as it operates in naturalistic environments. In contrast, the free exploration context of the iVR-FVE task allows alertness to emerge through the spontaneous monitoring and processing of dynamic visual information across space, more closely reflecting how the brain sustains readiness and responsiveness in everyday life. In this context, oculomotor behavior is shaped by both tonic alertness and top-down control processes that guide exploration. Consequently, reduced efficiency in maintaining top-down regulation may manifest as less dynamic scanning and greater susceptibility to bottom-up capture by salient stimuli, as previously proposed for states of low arousal or reduced attentional control (Corbetta & Shulman, 2011; Kaufmann et al., 2020; Nardo et al., 2019). Similar reasoning can be applied to spatial attention, where instead free viewing exploration has been widely applied also for evaluation purposes. Free-viewing exploration has long been recognized as a sensitive method for capturing spatial biases in neglect, as it predominantly engages stimulus-driven (bottom-up) components of attention that are often disrupted in unilateral spatial neglect (Corbetta & Shulman, 2012; Nardo et al., 2019; Kaufmann et al., 2020; Paladini et al., 2019). The ecological richness of iVR-FVE therefore makes it particularly effective in revealing spatial imbalances that may remain undetected in more constrained laboratory tasks (Hougaard et al., 2021; Kaiser et al., 2022). However, our results further demonstrate that combining free visual exploration with an active visual search task (iVR Burst Spatial-Selective) produces the highest classification accuracy for USN detection. This enhanced sensitivity can be explained in light of the theorization that USN is a multicomponent disorder in which alteration of top-down and bottom-down processes interacts together to determine the characteristic multifaceted symptomatology (Nardo et al., 2019; Bartolomeo, Thiebaut de Schotten, & Chica, 2012). Supporting this interpretation, our lesion analysis revealed concurrent damage to regions within both DAN and VAN, as well as disconnecting of major associative tracts mediating their interaction which contributes to determining the distinct oculomotor pattern.

Collectively, our study has several potential practical implications. Current standardized clinical assessment of attention are often characterized by low ecological validity and limited objectivity (Pieri, Tosi, & Romano, 2023; Perez-Marcos et al., 2023; Spreij et al., 2022), which may hinder the detection of subtle but clinically relevant manifestations of attention deficits (Hougaard et al., 2021; Thomasson et al., 2024). The present approach, combining the objectivity and reliability of oculomotor metrics as attention biomarkers with the higher controlled envirornment of iVR may help in overcoming these limitations (Clay, König & König, 2019; Kaiser et al., 2022). Moreover, the standard neuropsychological batteries typically used to diagnose alertness and USN rely on several tools that are time-consuming and, which can be particularly challenging to be performed by patients with severe motor and/or language impairments (Kaufmann et al., 2020). In contrast, the iVR-based method presented here represents a valuable initial screening tool, requiring approximately 15 minutes to administered both iVR-FVE and iVR-Burst SpatialSelective. With simple instruction and minimal motor demands, it enables acquiring reliable and sensitive measures for alertness and spatial attention. In addition, by implementing machine learning algorithms for automated classification, the approach eliminates the need for manual scoring procedures, further reducing evaluation time while augmenting the objective and reproducible diagnostic output. These features together can support clinicians in identifying patients who may benefit from more comprehensive diagnostic evaluation and in more personalized assessment pathways, facilitating early access to rehabilitative treatment, thereby mitigating the pervasive functional impact of these disorders.

Nevertheless, these observations are based on a relatively small sample. To strengthen the generalizability and clinical applicability of our findings, future research should test these methods in larger and more diverse cohorts of patients with acquired brain injury, enabling stratification according to lesion location and deficit severity. Notably, sample sizes comparable to the present study are commonly reported in previous clinical investigations applying eye-tracking and machine learning approaches for the detection of attentional deficits following brain injury (Franceschiello et al., 2022) also in immersive virtual reality environments (Hougaard et al., 2021).

Another limitation of the present study is that all participants presented with attention deficits, limiting an assessment of the specificity of the proposed oculomotor biomarkers. Future investigations should therefore include patients with different types of post-ABI disorders as well as healthy control participants, to determine the diagnostic specificity of these measures and to establish normative reference values or potential clinical cut-offs. Moreover, longitudinal and cross-validation studies comparing iVR-based classifications with detailed neuropsychological and functional outcomes would be essential to further establish the robustness and predictive value of these biomarkers. Since our models were trained using diagnostic labels derived from standardized assessments, some apparent misclassifications may actually reflect subtle attentional impairments not captured by conventional tools. If confirmed through such complementary validation, this would underscore the added clinical value of iVR-based oculomotor assessment in detecting early or mild attentional dysfunctions that may otherwise go unnoticed in routine clinical practice.

In conclusion, our findings demonstrate that iVR-based oculomotor assessment combined with machine learning enables rapid, objective, and reliable detection of alertness and spatial attention deficits. By linking these biomarkers to the underlying neural architecture of attention, this approach provides a clinically valid tool to improve the reliability and objectivity of attentional screening after brain injury. Therefore, the integration of automated oculomotor analysis within immersive environments offers a promising framework for advancing and complementing the current standardized neuropsychological assessment.

Chapter 8

Testing the feasibility and the use of eye-tracking metric as prognostic tools in a new immersive virtual reality rehabilitation protocol

8.1. Introduction

In recent decades, stroke has been identified as one of the leading causes of death and permanent disability worldwide (Bejot et al., 2016; Purroy & Montala, 2021). Among its repercussions on various aspects of people's lives, cognitive sequelae remain a major source of morbidity (Cramer et al., 2019; Rost, Brodtmann et al., 2022), long-term consequences and distress for patients (Brewer et al., 2013; Oyewole et al., 2020; Watson et al., 2020), with attention disorders being one of the most commonly observed and reported in 46% to 92% of cases (Barker-Collo et al., 2009; Loetscher et al., 2019; Spaccavento et al., 2019). Attention involves two subsystems (i.e., intensity and selection) comprising cognitive processes that are considered prerequisites for performing even basic daily activities (Bartolomeo et al., 2012; Bower et al., 2013; Leclercq & Zimmermann, 2002; Lindsay, 2020; Loetscher et al., 2019; van Zomeren & Brouwer, 1994; Watson et al., 2020). The intensity aspect refers to alertness, vigilance and sustained attention abilities that determine how many cognitive resources are allocated to meet the demands of a given task. The selection aspect refers to which stimuli, spatial locations or tasks these cognitive resources should be directed, delineating the selective, spatial and divided attention components, respectively. In addition, these attentional processes form the basis for high-order cognitive functioning such as memory, executive control, and language (Leclercq & Zimmermann, 2002). In pathological conditions, disruption of these fundamental processes leads to pervasive functional impairments, often associated with reduced return-to-work or education rates, limited social participation, and decreased quality of life (Barker-Collo et al., 2009; Brewer et al., 2013; Oyewole et al., 2020), which frequently persist in the long-term (Hyndman & Ashburn, 2003; Hyndman, Pickering, & Ashburn, 2008; Mellon et al., 2015). Similarly, unilateral spatial neglect (USN), reported in approximately 30% of cases following right-lateralized stroke (Esposito, Shekhtman, & Chen, 2021), is a prognostic indicator of functional impairment up to one-year post-onset (Di Monaco et al. 2011; Jehkonen et al., 2000). Given this framework and with projections indicating an overall increase in stroke incidence (Gimigliano & Negrini, 2017; Wafa et al., 2020), the adoption of effective strategies for managing these consequences is essential. Cognitive rehabilitation is recognized as one of the most important health strategies to modulate the functional and socio-economic burden for patients, caregivers, and society (Gimigliano & Negrini, 2017; Mancuso et al., 2025). However, the evidence on the effectiveness of the current rehabilitation protocols remained heterogeneous, with limitations and challenges to be addressed. Standardized protocols, mostly based on paper-and-pencil exercises, requiring 1-to-1 patient therapist interaction, are often suboptimal in intensity and duration, even though studies have shown that higher frequency and intensity of training can increase rehabilitation benefits (Cicerone et al., 2019; Donnellan-Fernandex, Ioakim, & Hordacre, 2022; Weicker et al., 2020). Despite computer-based training allowing for self-administration increasing the dose, they suffer from low ecological validity, limiting improvements and the consistent translation of gains to real-word situations (Chayton et al., 2003; Cicerone et al., 2019; Loestcher et al., 2019). In addition, hospital settings provide cognitive rehabilitation as part of the standard management for early-stage post stroke sequelae (Brewer et al., 2013). In contrast, after discharge, rehabilitation pathways are not always guaranteed or well-defined, with significant regional differences, even though chronic deficits are well-established (Brewer et al., 2013; Catania et al., 2024; Krakauer et al., 2021).

Recently, virtual reality (VR) has emerged as a valuable tool to overcome some of these limitations, with fully immersive virtual reality (iVR) appears particularly well-suited for cognitive rehabilitation (Chatterjee et al., 2022; De Luca et al., 2023; Maggio et al., 2025; Pedroli et al., 2022; Salatino et al., 2023). Like non-immersive and semi-immersive devices, iVR can support conventional therapy by facilitating high-dose, high-intensity personalized training, with auto-adaptive, remotely delivered and home-based unsupervised sessions, thereby supporting rehabilitation even in chronic stages (Choukou et al. 2023; De Simone et al. 2023). Furthermore, its higher degree of immersion enhances the sense of presence, increasing therapeutic engagement and intrinsic motivation, factors often low in traditional settings and linked to drop-out rate (Maggio et al., 2025; Makransky & Petersen, 2021: Riva et al., 2020; Slater & Sanchez-Vives, 2016). By engaging patients in environments that closely mirror real-world multimodality and complexity, while maintaining precise control over data acquisition and stimulus delivery, iVR can improve stimulation and promotes the transfer of skills to real-life situations (Chatterjee et al., 2022; Choi, Shin, & Bang, 2021; Serino et al., 2022).

Despite these advantages, studies investigating iVR-based cognitive rehabilitation have reported mixed results (Jahn et al. 2021; De Luca et al., 2023; Laver et al., 2021; Salatino et al., 2023). Some have found greater improvements in cognitive outcomes for iVR-trained groups compared to controls (Faria et al., 2016; Gamito et al. 2017), whereas others reported no significant differences (Wiley et al. 2022; Cavedoni et al., 2022). Moreover, the majority of research reporting attention improvements following VR-based rehabilitation has primarily focused on training executive functions and memory (Faria et al., 2016; Gamito et al., 2017). In other cases, the available evidence has stemmed from interventions targeting USN alone, that although an important stroke-related sequelae, it represents only one attentional subcomponent (see Salatino et al., 2023 for a review), or from studies conducted in neurodevelopmental disorders, such as ADHD, where attention alterations arise from different underlying neural mechanisms (Pollak & Finkelstein, 2020). Notably, most available VR-based interventions are designed as isolated or task-specific training activities (Choi, Shin, & Bang, 2021; Faria et al., 2016; Gamito et al., 2017; Martino Cinnera et al., 2024) rather than as components of comprehensive, theory-driven rehabilitation programs. In cognitive rehabilitation, however, it is crucial that training activities be integrated within structured frameworks grounded in well-established theoretical models that reflect the multidimensional nature of attention.

Based on these premises, the present study aimed to describe and evaluate the feasibility of MindFocus (MindMaze SA), a new auto-adaptive iVR-based attention rehabilitation program, grounded in the van Zomeren and Brouwer (1994) model of attention and structured according to the hierarchical organization of cognitive rehabilitation functions proposed by Sturm and colleagues (1997) and Solberg and Mateer (1989). The protocol was tested in patients with attention disorders during the subacute stage after stroke, as a preliminary step toward establishing its clinical applicability and potential effectiveness.

Importantly, modern head-mounted displays are equipped with embedded eye-tracking allowing the collection of additional meaningful parameters that may serve as biomarkers of attention capacities. Converging evidence indicates a functional overlap between oculomotor and attention-related brain regions (Corbetta & Shulman, 2012; Demiral et al., 2023; Kaufmann et al., 2020; Lappi et al., 2016; Nardo et al., 2019; Unsworth & Miller, 2021), with specific eyes metrics have been associated as markers of the two subsystems of attention. Specifically, pupil diameter, blink rate and fixation duration have been associated with the intensity aspect of attention, serving as indicator of alertness and cognitive effort (Unsworth & Miller, 2021; Unsworth, Miller, & Robison, 2020; Demiral et al., 2024; de Stasi et al., 2013), while gaze shifting along the x axis and time spent across visual hemifields have been related to the spatial-selective aspect of attention (Hougaard et al., 2021; Kaiser et al., 2022; Martino Cinnera et al., 2024). Leveraging these integrated eye-tracking capabilities of the iVR system, in the present study we also aim to explore whether pre-training eye metrics could be employed as prognostic biomarkers of recovery trajectories in our patients' sample. This approach may pave the way for the implementation of these biomarker measures to inform clinical pathways and the development of tailored, adaptive treatment strategies (Kim, Shin, & Chang, 2022; Martino Cinnera et al., 2024).

8.2. Material and Methods

8.2.1 Participants

Overview

This study[6] aimed at testing the feasibility of using iVR rehabilitation training in a sample of 17 patients (12 male; mean age = 57,17yo ± 13,60; mean time since stroke onset = 31.47 ± 14.61 days). All patients were recruited by the service Universitaire de Réhabilitation (SUN) among the ones hospitalized at Lausanne University Hospital. To be included, patients need to have age over 18 yo; unilateral hemispheric stroke (hemorrhagic or ischemic), documented by neuroradiological examination, as etiology; objectivated deficitary performance on at least one standardized attentional test; completed at least half of the study protocol (i.e., 10 iVR training sessions); successfully completed pre and post- standardized assessment; able to give informed consent as documented by signature; normal or correct-to-normal visual acuity and availability of eye-tracking recording from the iVR FreeViewing task (see section 2.2.3). Patients who could not be able to or have contraindication to undergo the investigated intervention were excluded. Other exclusion criteria were major psychiatric co-morbidity; major neurocognitive deficits; incapacity to discriminate colors; general cognitive state preventing understanding and performing the tasks; decision to not be informed of incidental findings; presence of severe hemianopia.

Attention deficits diagnosis

Attention deficits were evaluated through a clinical routine neuropsychological assessment made by neuropsychologists of the hospital.

The presence of Alertness deficits was assessed using the *"Alertness"* sub-test of the Test of Attentional Performance (TAP, Version 2.3.3, 2012; Zimmermann & Fimm, 2002). Patients were considered to have deficits in alertness (AL+) if they obtained a percentile of Median Reaction time (RTs) below 16th in the tonic segment of the task. Otherwise, patients were considered without alertness deficit (AL-). To make a diagnosis of Unilateral spatial Neglect (USN) clinical practices required several standardized tests in order to assess all the possible manifestations and symptoms of this syndrome. Thereby, the tests employed were the *"Neglect"* and *"Shifting of Attention"* TAP sub-tests (TAP, Version 2.3.3, 2012; Zimmermann & Fimm, 2002), the *line bisection task* (Schenkenberg et al., 1980), the *clock test* (Shulman et al., 1986) and the *BEN battery* (Rosseaux, Beis et al., 2001).

[6] This study is part of a wider project aiming at developing and testing a new immersive virtual reality protocol for the assessment and rehabilitation of attentional and executive deficits in brain-injured patients (MindFocus - ClinicalTrials.gov: NCT05728840)

Patients were considered as having USN deficits if the final clinical report and the clinical appreciation concluded a USN diagnosis (USN+). Otherwise, patients were considered having no USN deficits (USN-). To define a divided attention impairment, the performance at the TAP "Divided Attention" sub-test was considered. More in detail, if patients obtained a Median RTs percentile below 16th on the primary task (i.e., visual), a deficit in divided attention was assigned (DIV+). In all the other cases the absence of deficits in this component was concluded (DIV-). Details of clinical and demographic information for each patient are shown in Table 8.1.

Demographic and Clinical Data										Rehabilitation Protocol (timing)						
ID	Age	Gender	Etiology	Lesion Side	Time since onset	Alertness deficit	Neglect diagnosis	Neglected Side	Divided Attention Deficit	Alert	Select & Spa	Spa	Select Inhibition & Spa	Dived	Effective therapy time (total)	iVR sessions
P01	46	M	Stroke	R	33	Y	Y	L	Y	162	100	145	20	52	479	20
P02	44	F	Stroke	L	20	N	N	/	N	64	56	0	0	63	183	18
P03	65	M	Stroke	R	25	N	Y	L	Y	72	61	0	0	30	160	10
P04	59	M	Stroke	L	21	N	N	/	N	39	90	57	0	46	232	11
P05	81	F	Stroke	L	11	N	N	/	Y	28	43	0	4	24	99	14
P06	49	M	Stroke	R	73	Y	Y	L	/	2	0	0	3	3	8	10
P07	65	M	Stroke	R	49	Y	Y	L	N	82	54	75	17	4	231	10
P08	54	M	Stroke	R	31	N	N	/	N	28	0	16	12	0	56	20
P09	73	F	Stroke	L	34	Y	N	/	N	22	12	14	13	0	62	10
P10	56	M	Stroke	L	48	Y	N	/	N	197	228	0	62	39	527	20
P11	78	M	Stroke	L	26	Y	Y	R	Y	75	146	115	0	54	390	20
P12	24	F	Stroke	R	29	Y	Y	L	Y	85	62	519	7	58	229	16
P13	55	F	Stroke	R	28	Y	Y	L	Y	44	37	32	12	0	130	11
P14	52	M	Stroke	R	20	N	Y	L	Y	138	104	96	0	34	372	20
P15	61	M	Stroke	R	29	Y	Y	L	Y	104	55	134	25	72	390	20
P16	60	M	Stroke	R	39	Y	Y	L	N	88	41	52	56	28	264	20
P17	50	M	Stroke	L	19	Y	N	/	Y	140	65	0	63	49	316	20

Table 8.1. Demographic, clinical and training-related information for each patient. The table shows the details about the included sample and the rehabilitation protocol. Regarding the rehabilitation protocol: for each patient the effective time spent in iVR-activities is reported for each targeted attentional sub-component (in minutes). The Total effective therapy time and the iVR-sessions completed are also reported.
M = Male; F = Female; L = Left; R = Right; Y = Yes; N = No; / = No info to report. Spa = Spatial Attention; Select = Selective Attention; Divided = Divided Attention.

8.2.2. Study Procedure

During iVR sessions, patients were seated at the center of the room ensuring freedom of hand movements. For the visualization of virtual environments, a Head Mounted Display (HMD) HTC Vive Pro Eye with a display resolution of 1440 X 1660 pixels per eye, 90 Hz refresh rate and a field of view (FOV) of 110° with an embedded eye-tracking (ET) system Tobii® were employed. Patients' position was calibrated via HTC SteamVR 2.0 tracking system to ensure the virtual environments displayed were centered, and a 5-point eye-tracking embedded calibration procedure was performed to ensure accurate gaze data acquisition.

Pre and post assessments were carried out using several tests of the battery of Tests of Attentional Performance (TAP, Zimmermann & Fimm, 2002). In addition, an iVR Free Viewing Exploration Task (iVR-FVE) was done before and after the training program in order to investigate the potential of eye-tracking data as a prognostic tool. Details of the training program for each patient can be consulted in Table 8.1.

8.2.3 Rehabilitation Protocol

In addition to receiving standard cognitive rehabilitation, patients underwent from 10 up to 20 iVR-based sessions, at least three times a week, each lasting 45 minutes. The training activities from the Attention Module of MindFocus software were employed (MindMaze SA).

MindFocus: Attention Module

Given the multicomponent nature of attention, MindFocus software includes rehabilitation exercises for all components of attention, including alertness (phasic and tonic), sustained & selective attention, visuospatial attention (including lateralized and not lateralized spatial attention) and divided attention. Short ("burst") assessments for each of these functions are also available. Both training and assessments are provided in immersive virtual environments covering all the 3D space and are developed using the Unity game engine (Unity Technologies) by MindMaze SA (Lausanne, Switzerland). Patient assessment, exercise guidance, and approval by the medical professional is required prior to use.

The activities provide audiovisual, tactile feedback and graphic movement representations, as well as patient performance metrics for both patients and healthcare professionals. For each of the core attentional components, the software provides one main activity to rehabilitate the targeted function (Fig. 8.1). However, they can also be employed to train other functions as a secondary objective, by adapting the settings accordingly (see Fig. 8.1).

The training activities entail several levels progressing in autoadaptive mode based on patients' performance. Particularly, when an accuracy score of at least 80% is achieved an upper level was unblocked, whereas if they obtain a score below or equal to 20%, they regress to the previous level.

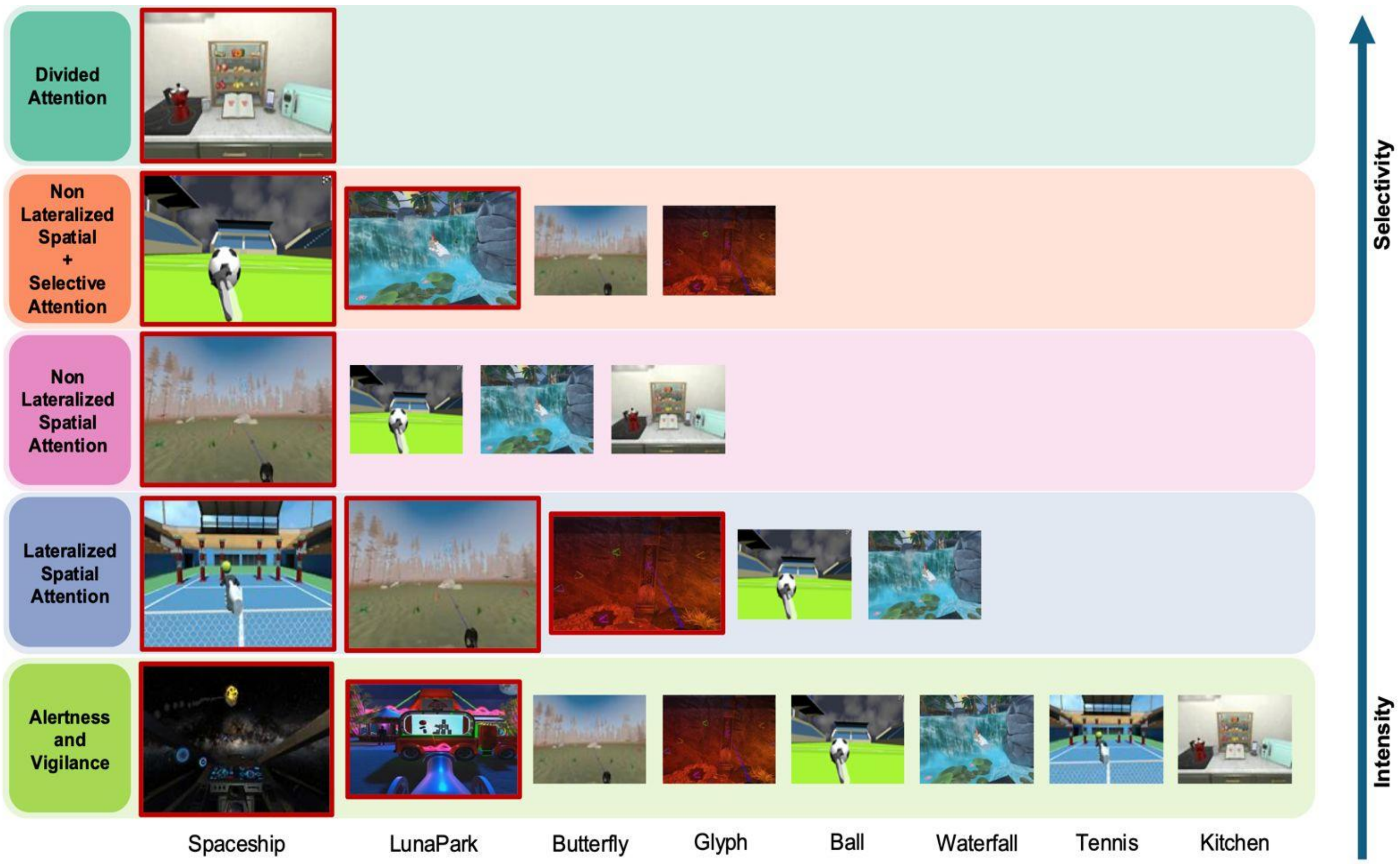


Figure 8.1. Summary of cognitive functions trained by each iVR-training activities. Training activities circled in red have as their main objective the rehabilitation of the indicated cognitive function. Training activities of a smaller size target the cognitive functions as a secondary objective.

MindFocus Attention Module: Training activities

Alertness and Vigilance (Spaceship/LunaPark) - The aim of these games is to improve alertness and processing speed. In Spaceship activity, patients are immersed in a spaceship cockpit where they must destroy incoming asteroids (target) as quickly as possible to protect their ship. To destroy the asteroids, patients must press the trigger button on the controller within the permitted reaction time, otherwise an electromagnetic shield will be activated to protect the ship by dissolving the asteroid. The higher the level, the shorter the permitted reaction time. Each level has two modes to train either tonic or phasic alertness. In the phasic alertness mode, an alarm sounds to warn of incoming asteroids. The LunaPark activity follows the same logic: participant has to press the trigger as soon as the curtain opens to make the cans fall.

Lateralized Spatial Attention (Tennis) - The aim of this game is to train both lateralized and non-lateralized visuospatial attention, and it is based on prismatic adaptation [Rossetti et al,1998]. Patients take the role of a tennis player and must catch balls coming from both sides of a tennis court. The task is divided into three phases: first, patients are asked to point to six static balls in succession without seeing their virtual hand. Then, in a traditional tennis game, they must catch balls thrown from tennis ball machines, with their virtual hand shifting left or right according to their side of neglect. Between each ball, the patient must place their hand on their chest to activate the mechanism. The final phase is the same as the first. The higher the level, the quicker the balls reach the patients.

Non-Lateralized Spatial attention (Butterfly/Glyph) - The primary aim of these games is to train visuospatial attention. In Butterfly activity, patients are immersed in a field full of animals. Their goal is to identify and catch the targeted butterfly by scanning the environment using the template shown at the top of the virtual environment. At higher levels, distractors increase in both quantity and similarity to the target. The target can be selected using the laser pointer by pressing the trigger while pointing at it. Based on the same principles, the Glyph activity required finding a glyph target inside a cave.

Non-Lateralized Spatial + Selective Attention (Ball/Waterfall) - The main objective of these games is to improve selective attention. Players take on the role of goalkeeper during a training session. They must catch footballs coming from all directions while ignoring other types of ball, such as basketballs and volleyballs. The higher the level, the faster the balls are thrown. In the Waterfall activity, participant has to catch the fishes to put them back in the water while avoiding trash coming from the waterfall to clean the river.

Divided Attention (Kitchen) - The main objective of this game is to train divided attention. Patients are immersed in a kitchen environment where they must pick the correct ingredients for a cooking recipe from several other ingredients on a shelf, by looking at the book in front of them. They also have to respond to audio cues from the microwave or coffee pot by selecting the correct kitchen appliance. At a higher level, they also must avoid other noises, such as the phone or timer ringing.

In accordance with the patient's specific clinical profile, clinicians can structure the training session through a tailored combination of activities, while also determining the duration required for the patient to adequately train a targeted attentional component. (see Fig. 8.2 for the representation of the tailored rehabilitation protocol completed by our sample).

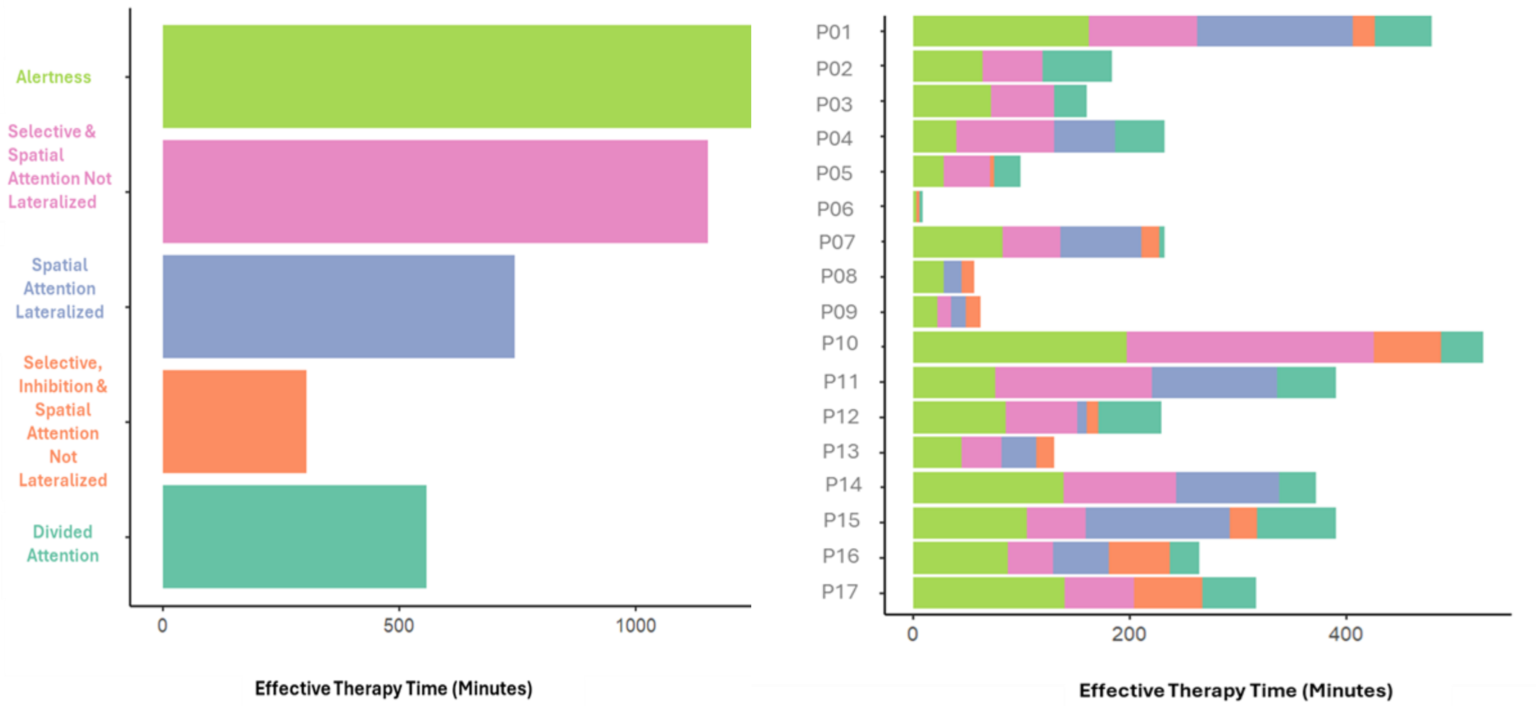


Figure 8.2. Distribution of effective therapy time (minutes) across attentional components during iVR rehabilitation.
Left-Panel: Cumulative time (in minutes) spent across all patients in each iVR training module, grouped by targeted attentional components. Categories include Alertness, Spatial Attention (Lateralized and Non-Lateralized), Divided Attention, and Selective/Inhibitory Attention.
Right-Panel: Individual patient-level distribution of training time across the specific iVR attention sub-component highlighting the personalized nature of MindFocus iVR-rehabilitation, with varying activity tailored to patient clinical profiles. Each activity is color-coded according to its associated attentional focus.

8.2.4 Assessments Protocol

To evaluate improvements in the primary attentional components targeted by the iVR rehabilitation protocol, three subtests from the TAP battery were administered.

Grounded in the two core dimensions of attention (van Zomeren and Brouwer, 1994; Spaccavento et al., 2019), pre- and post-training data from the *Alertness* TAP subtest were collected to measure changes along the intensity dimension, whereas the *Shifting of Attention* and *Divided Attention* subtests were employed to assess the selectivity dimension. As part of the study protocol, participants also completed other TAP subtests (i.e., *Sustained Attention*, *Go/Nogo*, *Neglect*, *Flexibility*, *Working Memory*) which will not be analyzed here.

Finally, to explore the potential contribution of eye-tracking in explaining the clinical improvement, patients performed an iVR FreeViewing Exploration task (iVR-FVE), before starting the rehabilitation protocol.

iVR-Free Viewing Exploration Task (iVR-FVE)

The iVR-FVE task is an adaptation of the original 2D version of Nardo and colleagues (2019) task presented in the iVR environment. It entails 80 short videos, of 1.5 seconds, depicting dynamic everyday life scenarios. The main event of the videos was lateralized, either on the left (Lateral Left, LL) or on the right (Lateral Right, LR). It could also take place bilaterally with a higher saliency on the left (Bilateral Left, BL) or on the right (Bilateral Right, BR). Between each video, patients were asked to fix a cross, lasting from 3.5 to 5s, that appears at the center of the visual field, no additional instructions were given. The overall duration of the task was 8 minutes. (Fig. 8.3).

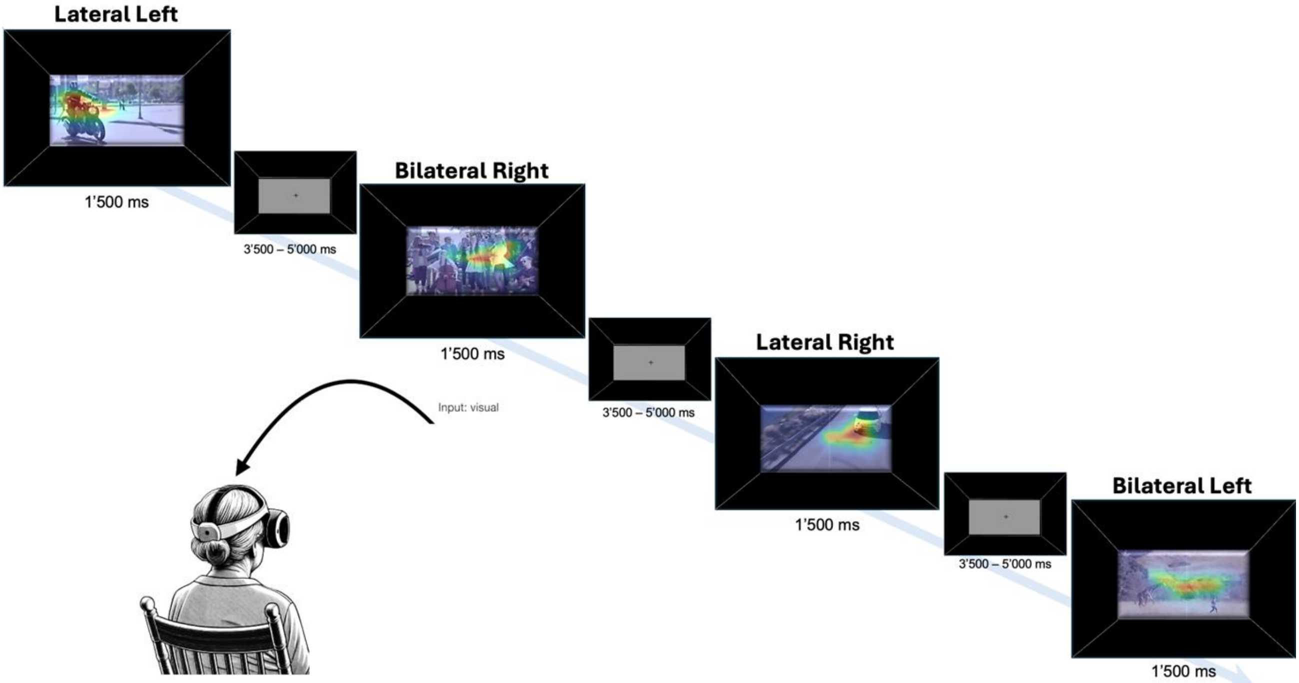


Figure 8.3. Immersive Virtual Reality Free-Viewing Exploration task implemented at pre-assessment session. Participants were immersed in a virtual environment using the HTC Vive Pro Eye head-mounted display and passively viewed a sequence of 80 short videos (1,500 ms each) depicting everyday-life scenarios. Videos were categorized according to the spatial location of the main dynamic event: Lateral Left, Lateral Right, Bilateral Left, or Bilateral Right. To re-center gaze and reduce carryover effects between trials, a grey screen with a central black fixation cross was shown for a jittered interval ranging from 3,500 to 5,000 ms (in 250 ms increments). The entire task lasted approximately 8 minutes. Heatmaps illustrate representative gaze patterns during video presentation for each condition.

8.2.5 Data Analysis

To explore the effects of the iVR rehabilitation protocol we analyzed the pre- post-intervention changes from a behavioral and clinical point of view. We then checked if improvement can be explained by the time spent on function-specific activities and if it can be predicted by eye-tracking data.

All statistical analyses were performed using R software (RStudio-2024.12.01.563 for Windows Posit team, PBC, Boston, MA). In both behavioral and eye-tracking analysis conducted, when a spatial component was involved, we horizontally flipped the data of the single patient who has a clinical diagnosis of Right Neglect, aligning his patterns with those of patient who has a diagnosis of Left Neglect. This ensured all neglect-related biases were represented on the same side (i.e., left hemispace). Statistical significance was set at an alpha level of 0.05 throughout all the analyses.

Behavioral data

To explore potential changes in attention functioning following the iVR rehabilitation protocol, three Linear Mixed Models (LMMs, using lme4 R-package) were fitted. Each model examines one of the main attentional subcomponents targeted by the iVR training clustered into the two core dimensions of attention (van Zomeren and Brouwer, 1994; Spaccavento et al., 2019).
For the intensity dimension, the dependent variable was the median Reaction Times (RTs; ms) from the TAP *Alertness* subtest. For the selectivity dimension, two separate models were conducted: one for Spatial Attention, using the Median RTs (ms) difference between no-neglected (right-side) and neglected (left-side) target position, regardless of the validity of the cue (i.e., Position Effect) from the *Shifting of Attention* TAP subtest; and one for Divided Attention, using the median RTs (ms) on the visual task in dual-task condition from *Divided Attention* TAP subtest. All models included session (pre- vs post-intervention) as a within-subject factor to assess potential change over time, diagnosis (presence or absence of a baseline deficit in the respective attentional component) as a between-subject factor and their interaction effect. Age at the inclusion and time since stroke onset were added as covariates to control for demographic and clinical variability. Random intercepts were specified for participants to account for repeated measures. For each model the formula employed is the following:

*dependent variable ~ session * diagnosis + time since stroke onset + age + (1 | patient)*

In the presence of significant interaction effects, post hoc comparisons were conducted using planned contrasts with False Discovery Rate correction applied to control for multiple testing (Benjamini & Hochberg 1995).

Clinical data

To evaluate if the potential changes in behavioral scores were mirrored in clinically meaningful improvements, the corresponding percentile of the dependent variables used in each of the LLM models were considered. More in detail, for alertness abilities, the percentile of median RT from the tonic segment of the *Alertness* subtest. For spatial attention the percentile of median RT separately for the invalid-left and valid-left conditions (i.e., neglected target position) of the *Shifting of Attention* subtest was considered. Finally, for divided attention, the median RT percentile of visual task of the *Divided Attention* subtests was employed.
According to the guidelines provided by the Association Suisse de Neuropsychologie (ASN; 2018) Swiss Association of Neuropsychologists', these percentiles allow classification of individuals' performance into clinically interpretable categories. A percentile equal to or above the 16th reflects performance within the normal range (*no-deficit*). Values between the 5th and 16th percentile indicate a mild deficit. Scores equal to or between the 2nd and 5th percentile correspond to a moderate deficit,

while performances below the 2nd percentile, but greater than or equal to 0, are considered indicative of a severe deficit. The single patients' percentiles at both pre- and post-intervention were used to calculate the overall percentage of patients falling under the *no-deficit* category across the entire sample. Additionally, the percentage of patients who showed an improvement in their clinical classification after the training was computed, to assess potential shift in deficit severity following the iVR-intervention.

Time-in-rehabilitation

To investigate if the clinical changes could be in function of the time spent in function-specific iVR training activities, a normalized delta score (Δ) were computed, employing the percentiles described above for each of the targeted attentional component as the ratio of the difference between pre and post values to their sum.

$$\Delta = (post\text{-}pre)/(post+pre)$$

Specifically, to isolate the specific contribution of training time, while controlling for potential confounding effects, a stepwise multiple regression procedure was applied. The procedure started with a baseline model including only the intercept and was compared with a full model incorporating all candidate predictors (i.e., function-specific training time, time since stroke onset and age). The time spent on spatial attention (i.e., Tennis, Butterfly/Glyph and Ball/Waterfall games), alertness (i.e., Spaceship/LunaPark game), and divided attention (i.e., Kitchen game) activities were used as function-specific predictors, respectively. All predictors were iteratively added or removed according to the Akaike Information Criterion (AIC), resulting in the most parsimonious model for explaining variability in the delta scores.

Eye-Tracking data

ET features were extracted from the raw gaze data using a custom R script, generating a dataset of feature values for each participant across different video categories (Lateral Left, Lateral Right, Bilateral Left, Bilateral Right, Bilateral Right, overall task, and fixation cross segment). The initial feature set included metrics commonly associated with visual attention and alertness, such as fixation, saccade, gaze and blink rate, selected among the ones already evidenced in literature as biomarkers of these cognitive functions. Each ET parameter was computed within the relevant video conditions: those related to spatial attention were extracted within each video condition (LL, LR, BL, BR), while those related to alertness were assessed over the entire iVR-FVE task. Five ET parameters were extracted for the analysis of alertness, while six parameters were computed for the analysis of spatial attention.

To investigate whether pre-rehabilitation ET features could predict patients' clinical improvement in alertness and spatial attention, the same normalized delta score derived from behavioral analysis was employed. All ET features were z-scored prior to dimensionality reduction. A Principal Component Analysis (PCA) was then performed on the scaled dataset. The number of components was determined using Horn's parallel analysis (Horn, 1965), implemented with the *paran* R-package, which employs Monte Carlo estimates based on a user-specified percentile criterion; 5,000 iterations were used. A 75th-percentile criterion was applied to both alertness and spatial attention to ensure consistency across domains. This departs from common practice (e.g., 95th/99th-percentile thresholds in the modified procedure of Glorfeld, 1995) but it was adopted because of the small sample size and the exploratory nature of ET data implementation as prognostic tool in clinical practice. Retained principal components were then used as predictors in a stepwise multiple linear regression (*MASS* package; AIC method) to estimate normalized improvement scores.

8.3. Results

8.3.1 Behavioral and Clinical Improvements

Alertness

We conducted LMM to examine the effects of session (pre vs. post) and alertness impairments diagnosis at baseline (AL+ vs. AL−) on median RTs from the TAP Alertness subtest. The results reveal a significant main effect of session, with faster responses at post- compared to pre-intervention (β = -103.91, *se* = 20.91, $t_{(15)}$ = -4.97, p < .001, $\eta^2_{partial}$ = .29). A main effect of diagnosis also emerged, indicating that participants in the AL- group responded faster overall than those in the AL+ group (β = -175.51, se = 42.51, $t_{(18.25)}$ = -4.13, p = .001, $\eta^2_{partial}$ = .40).

Importantly, a significant interaction session x diagnosis was significant (β = 121.74, p = .004, $\eta^2_{partial}$ = 0.44), revealing that changes in performance differed by group (Fig. 8.4, top-left). As shown in planned contrasts at pre-session AL+ were significantly slower than AL- (β = 175.51, *se* = 42.51, $t_{(18.25)}$ = 4.13, p = .0012), but this difference was no longer evident at post-rehabilitation (β = 53.83, *se* = 42.51, $t_{(18.25)}$ = 1.27, p = .296). Within-group comparisons showed a significant pre–post improvement in AL+ (β = -103.91, *se* = 20.91, $t_{(15)}$ = −4.97, p = .0007), while no change was observed in AL- (β = -17.83, *se* = 28.30, $t_{(15)}$ = -0.63, p = .538; see Fig.4, top-right).

Neither the effect of age (β = 0.89, *se* = 1.20, $t_{(13)}$ = 0.74, p = .473, $\eta^2_{partial}$ = .04) nor the time since stroke onset (β = -1.96, *se* = 1.31, $t_{(13)}$ = -1.50, p = .159, $\eta^2_{partial}$ = .15) were significant, indicating they did not substantially influence the observed outcomes.

This pattern was mirrored in diagnostic classification data (Fig. 8.4, bottom-left). On the overall sample, before the intervention, 35.3% of participants were classified as not having alertness deficit; this proportion increased to 64.7% post-intervention, alongside reductions in moderate and severe classifications. Particularly, the percentage of AL+ who entered in the "no deficit" category post-rehabilitation is 63.6%. Notably, 90.9% of AL+ ameliorate category classification post-rehabilitation. Individual percentile changes (Fig. 8.4, bottom-right) further illustrated consistent improvements in AL+, with many patients shifting to higher functioning categories. In contrast, performance in AL- remained largely stable throughout sessions.

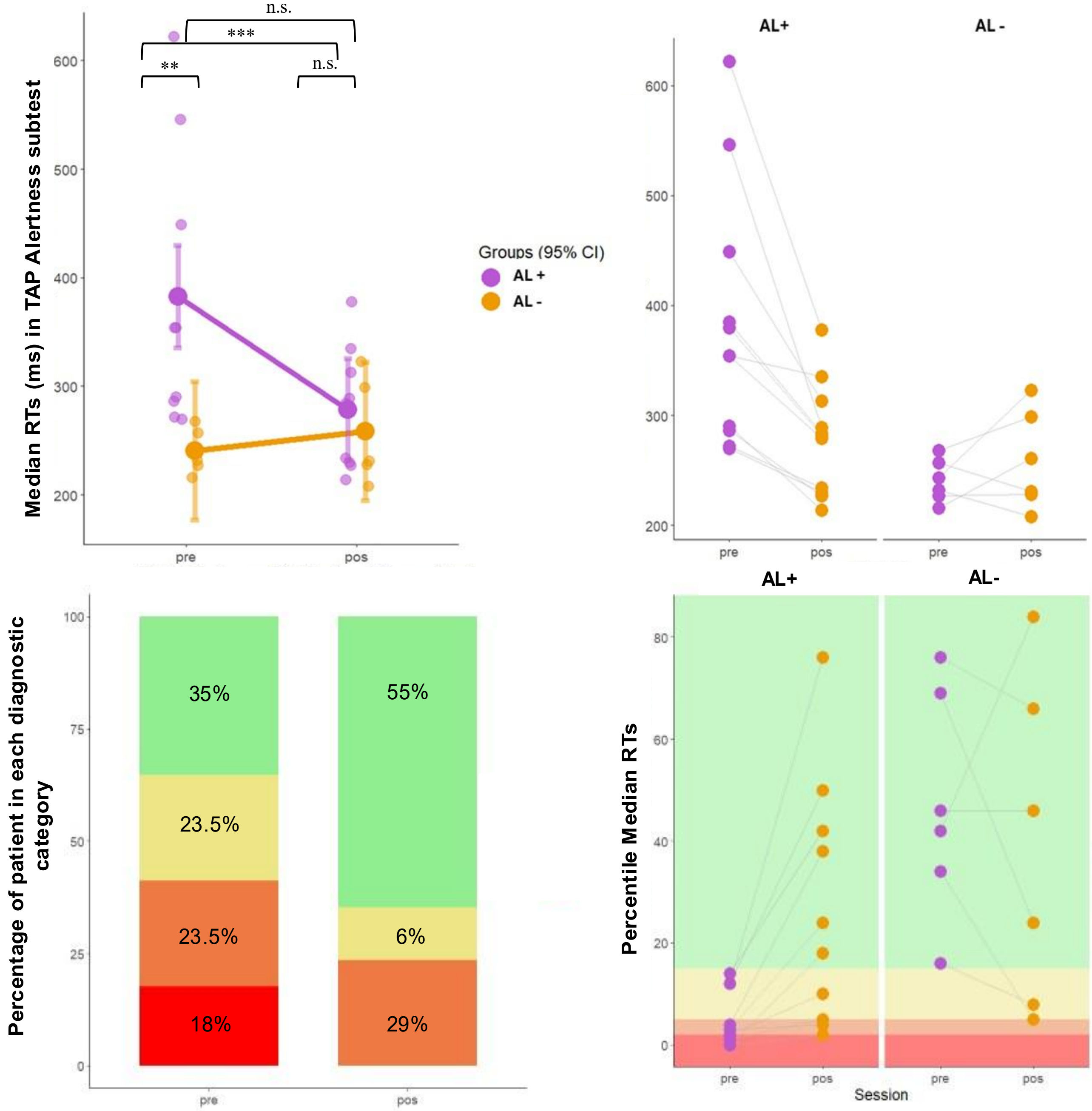


Figure 8.4. Changes in Median RTs (ms) and diagnostic classification based on TAP "Alertness" subtest at pre vs. post iVR-training
<u>Top left:</u> Significant session x diagnosis interaction (p = .004) displays median RTs from the TAP Alertness subtest for the AL+ (patients with objectively confirmed alertness deficit at pre-assessment; in violet) and AL− (patients without objectively confirmed alertness deficits at pre-assessment; in orange) groups at pre- and post-intervention sessions. Error bars represent 95% confidence intervals.
<u>Top right:</u> Individual RTs trajectories separated by group (AL+ and AL-) and session ("pre" in violet and "post" in orange), illustrating greater pre–post improvement in AL+ group compared to AL- (p = .0007).

Bottom left: Percentage of patients within each diagnostic category (severe, moderate, mild, no deficit) before and after the intervention, based on Median RTs percentiles.
Bottom right: Individual changes in Median RTs percentile scores from pre- (in violet) to post-session (in orange) for each diagnostic group (AL+ and AL-). Green shading reflects normal performance (“no deficit” category: ≥16th percentile); yellow shading describes mild deficit category (from 6th to 15th percentiles); orange shading reflects moderate deficit category (from 2nd to 5th percentiles) and red shading indicates severe deficit category (less than 2nd percentile).
*p < 0.05; ** p < 0.01; *** p < 0.001; n.s. = not significant

Spatial Attention

We conducted LMM examining the effects of session (pre vs. post) and baseline USN diagnosis (USN+ vs. USN-) on the Position Effect from *Shifting of Attention* TAP subtest. The results evidence a significant main effect of session, indicating a reduction in the imbalance between the two hemispaces (i.e., reduction in Position Effect) post-training across the sample ($\beta = 68.50$, $se = 22.80$, $t_{(15)} = 3.00$, $p = .009$, $\eta^2_{\text{partial}} = .22$) (Fig. 8.5A, left panel). A significant main effect of diagnosis at baseline was also found, with USN- showing smaller Position Effects than USN+ ($\beta = 150.31$, $se = 33.78$, $t_{(22.05)} = 4.45$, $p < .001$, $\eta^2_{\text{partial}} = .57$), confirming visuo-spatial attention asymmetry associated with USN+ (Fig. 8.5A, center panel).
Neither age ($\beta = -1.67$, $se = 1.03$, $t_{(13)} = -1.62$, $p = .130$, $\eta^2_{partial} = .17$) nor time since stroke ($\beta = 0.78$, $se = 1.00$, $t_{(13)} = 0.79$, $p = .447$, $\eta^2_{partial} = .05$) were significant predictors of Position Effect.
The session × diagnosis interaction showed a trend toward significance ($\beta = -63.64$, $se = 35.53$, $t_{(15)} = -1.79$, $p = .093$, $\eta^2_{partial} = .18$), suggesting a potentially greater improvement in Position Effect in USN+ compared to USN- (Fig. 8.5A, right panel). Descriptively, individual-level data indicated that many USN+ patients exhibited large reductions in Position Effect from pre- to post-intervention.
Changes in percentile scores for RTs in left-sided invalid and valid cue conditions further support this interpretation (Fig. 8.5B and Fig. 8.5C, bottom panels). Across the sample, in the invalid-left condition, the percentage of patients classified as having no deficit increased from 47.1% to 64.7%, while those in the moderate and severe categories decreased. More in detail, considering only USN+, those who entered the *no-deficit* category post-rehabilitation are 33.3%, whereas the percentage who ameliorate the classification category is 77.8% (Fig. 8.5B, left panel). In the valid-left condition, the proportion in the no deficit category increased from 58.8% to 82.4% overall. Among USN+ those who have no deficit post-rehabilitation are in a percentage of 57.1%, while 85.7% of USN+ ameliorate their diagnostic classification category (Fig. 8.5C, left panel).
Individual-level changes in percentile ranks highlighted that several USN+ patients moved into higher functioning categories, indicating clinically meaningful improvements in spatial attention abilities (Fig. 8.5B and Fig. 8.5C, right panel).

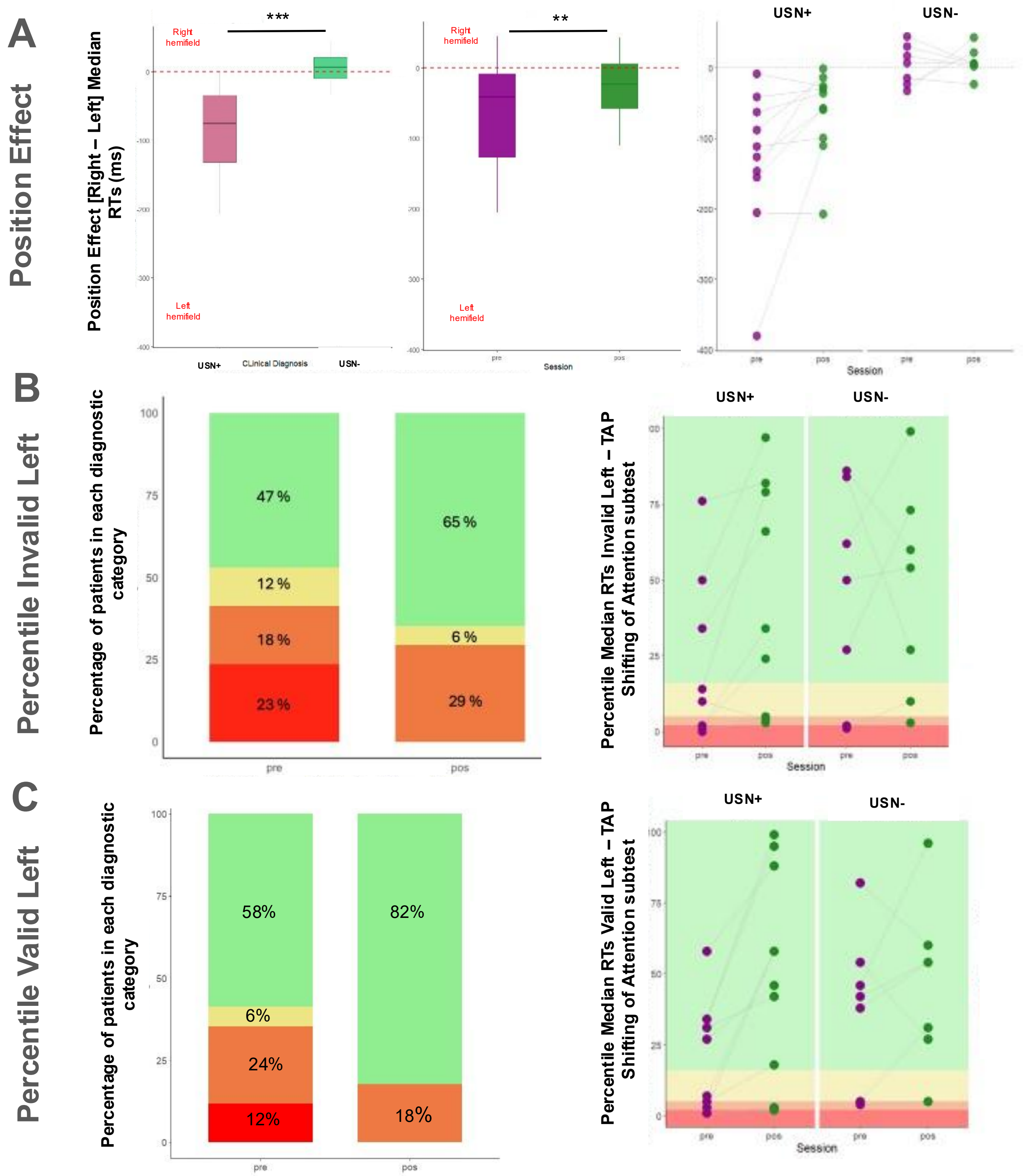


Figure 8.5. Changes in spatial attention performance (Position Effect, ms) and diagnostic classification based on TAP "Shifting of Attention" subtest at pre vs. post iVR-training

Panel A-left: Main effect of session on the Position Effect (difference in RTs between right- and left-sided targets), showing overall improvement (reduction in spatial bias; p = .009) from pre- (in purple) to post-intervention (in dark-green).

Panel A-center: Main effect of diagnosis (p < .001) with patients diagnosed with unilateral spatial neglect (USN+, in pink) exhibiting significantly larger Position Effects than those without neglect (USN−, in light-green).

Panel A-right: Individual Position Effect (ms) trajectories across sessions ("pre" in purple and "post" in dark-green), separated by clinical diagnosis at pre-assessment.

Panel B and C-left: Percentages of overall sample classified within each deficit severity category based on percentiles of median RTS for invalid-left and valid-left trials at pre- and post-intervention.

Panel B and C-right: Individual percentile scores for invalid-left and valid-left trials at pre- (in purple) and post-session (in dark-green) for each diagnostic group (USN+ and USN-).

Green shading reflects normal performance (“no deficit” category: ≥16th percentile); yellow shading describes mild deficit category (from 6th to 15th percentiles); orange shading reflects moderate deficit category (from 2nd to 5th percentiles) and red shading indicates severe deficit category (less than 2nd percentile).
*p < 0.05; ** p < 0.01; *** p < 0.001

Divided Attention

To evaluate divided attention performance, median RTs from the visual dual-task condition of the TAP were analyzed. A significant main effect of session was found, with overall faster RTs at post- compared to pre-intervention (β = -270.78, *se* = 68.78, $t_{(14)}$ = -3.94, p = .001, $\eta^2_{partial}$ = .32) (Fig. 8.6, top-left). Additionally, the main effect of diagnosis was revealed: DIV- performed significantly faster overall than DIV+ (β = -594.05, *se* = 117.91, $t_{(17.61)}$ = -5.04, p < .001, $\eta^2_{partial}$ = .61).
Covariates such as age (β = 3.16, *se* = 3.38, $t_{(12)}$ = 0.94, p = .367, $\eta^2_{partial}$ = .07) and time from stroke onset (β = 7.00, *se* = 5.28, $t_{(12)}$ = 1.33, p = .209, $\eta^2_{partial}$ = .13) were not significant predictors.
Importantly, a significant interaction session x diagnosis was observed (β = 271.64, *se* = 103.99, $t_{(14)}$ = 2.61, p = .020, $\eta^2_{partial}$ = .33), suggesting that the improvement over time differed between groups (Fig. 8.6, top-left). Planned contrasts revealed that DIV+ showed a robust reduction in RTs from pre- to post-session (β = -270.78, *se* = 68.78, $t_{(14)}$ = -3.94, p = .003), whereas no change was seen in the DIV− group (β = -0.86, *se* = 78.00, $t_{(14)}$ = -0.01, p = .991). At pre-test, the DIV+ group was significantly slower than DIV- (p = .0004), though this group difference narrowed post-intervention (p = .0184) (Fig. 8.6, top-right).
Clinical relevance of these changes was reflected in percentile-based classifications. The general proportion falling in the “no deficit” category increased from 43.8% to 68.8% post-intervention (Fig. 8.6, bottom-left), while the percentage of patients classified with severe deficits dropped. More in detail, among DIV+, 55.6% fall inside the no deficit category post-rehabilitation, while 77.8% ameliorate their classification category.
Individual-level percentile data (Fig. 8.6, bottom-right) demonstrated that most DIV+ patients improved their clinical categorization following the intervention.

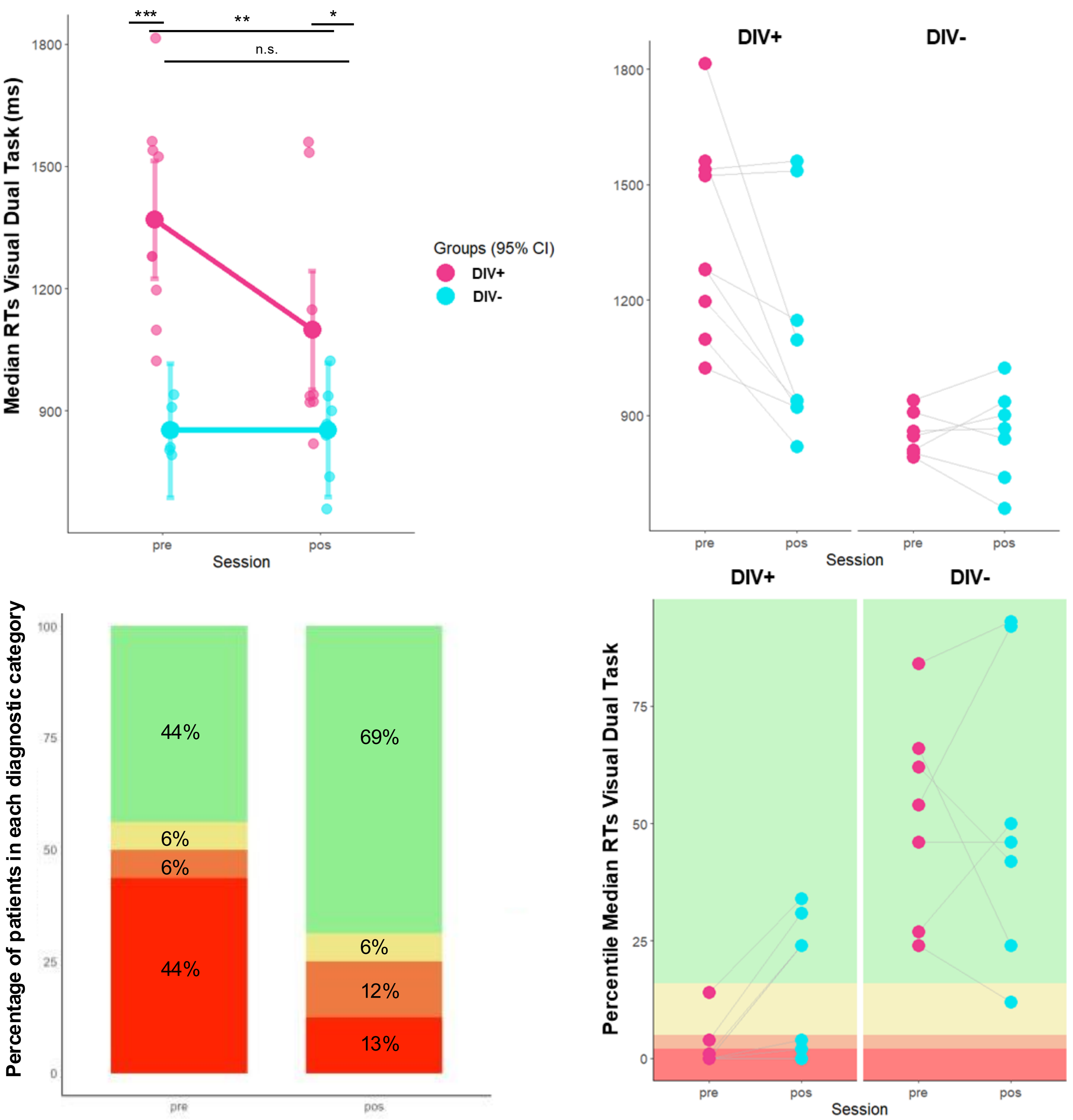


Figure 8.6. Changes in divided attention performance and diagnostic classification by deficit status.
Top left: Significant session x diagnosis interaction (p = .004) displays group-level median RTs on the visual dual-task condition of the TAP for DIV+ (in fuchsia) and DIV− (in cyan) at pre- and post-intervention. Error bars indicate 95% confidence intervals.
Top right: Individual RT trajectories across sessions ("pre" in fuchsia and "post" in cyan), separated by diagnostic groups (DIV+ and DIV-), showing marked improvement in DIV+ (p = .003).
Bottom left: Percentage of the overall sample in each deficit severity category based on TAP percentiles before and after intervention.
Bottom right: Percentile scores for individual patients in DIV+ and DIV− at pre- (in fuchsia) and post-sessions (in cyan).
Green shading reflects normal performance ("no deficit" category: ≥16th percentile); yellow shading describes mild deficit category (from 6th to 15th percentiles); orange shading reflects moderate deficit category (from 2nd to 5th percentiles) and red shading indicates severe deficit category (less than 2nd percentile).
*p < 0.05; ** p < 0.01; *** p < 0.001, ns = not significant

8.3.2. Time-in-rehabilitation effects

Alertness

In the alertness domain, the stepwise regression procedure compared a baseline intercept-only model with a full model including function-specific training time (i.e., Spaceship/LunaPark), age, and time since stroke as predictors. None of the candidate predictors improved model fit, and the stepwise procedure therefore retained the intercept-only model as the most adequate solution (AIC = -21.0). The final model indicated that participants showed, on average, a positive normalized delta score (β = 0.36, *se* = 0.13), which was significantly different from zero ($t_{(16)} = 2.83$, $p = .012$). The residual standard error of the model was 0.52. These results suggest that while patients generally improved in alertness following the intervention, the observed changes could not be explained by training time (see Fig. 8.7A), age, or time since stroke.

Spatial Attention

For spatial attention, we examined delta scores separately for valid-left and invalid-left conditions. In both cases, stepwise regression identified time spent in spatial attention–specific training activities (i.e., Tennis, Butterfly/Glyph, Ball/Waterfall) as the only predictor that improved model fit compared to the intercept-only model.

In the invalid-left condition, the final model (AIC = -29.02) outperformed the intercept-only model (AIC = -26.29) and revealed that longer training time significantly predicted improvements in delta scores ($\beta = 0.0024$, $se = 0.0011$, $t_{(15)} = 2.19$, $p = .044$). This model explained about 24% of the variance ($R^2 = 0.24$, adjusted $R^2 = 0.19$) with a residual standard error of 0.40 (Fig. 8.7B, top).

Similarly, in the valid left condition the retained model (AIC = –39.25) outperformed the intercept-only model (AIC = -37.55) and showed a positive association between training time and clinical improvements ($\beta = 0.0016$, $se = 0.0008$, $t_{(15)} = 1.91$, $p = .076$). Although this effect did not reach statistical significance, the model accounted for approximately 20% of the variance ($R^2 = 0.20$, adjusted $R^2 = 0.14$), with a residual standard error of 0.30 (Fig. 8.7B, bottom).

Taken together, these results indicate that while training time in spatial attention–specific activities was positively associated with improvements in both valid- and invalid-left conditions, the association reached statistical significance only in the invalid-left condition. This specific association suggested a stronger relationship between spatial-related training intensity and rehabilitation gains in the invalid condition.

Divided Attention

For divided attention, the stepwise regression procedure ultimately retained a model including time since stroke and age as predictors (AIC = -22.36). This model provided a better fit than both the intercept-only model (AIC = -19.82) and the model including divided attention training time (i.e., Kitchen activities) as the sole predictor (AIC = -21.16). Adding training time to the clinical predictors did not improve model fit (AIC = -21.20).

The final model indicated a negative trend for time since stroke (β = -0.023, *se* = 0.012, $t_{(13)}$ = -1.96, *p* = .072), suggesting that patients with a shorter interval since stroke tended to show greater improvements. Age was also negatively, though non-significantly, associated with the delta score (β = –0.015, *se* = 0.009, $t_{(13)}$ = -1.75, *p* = .104). The model explained about 34% of the variance in change scores (R^2 = 0.34, adjusted R^2 = 0.23), with a residual standard error of 0.46.

Overall, improvements in divided attention were better explained by clinical and demographic variables (time since stroke and age) rather than by function-specific training time (Fig. 8.7C).

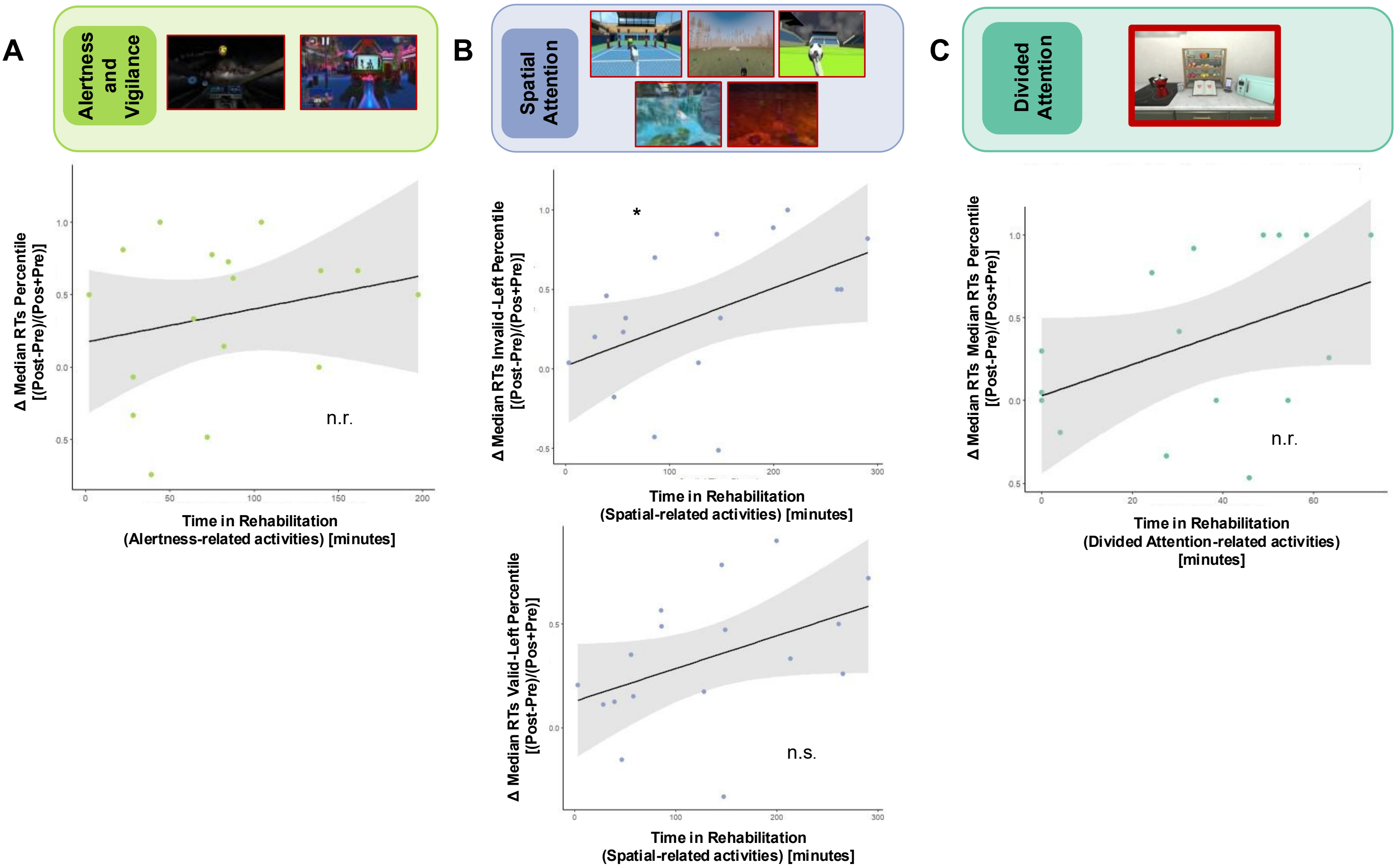


Figure 8.7. Time-in-rehabilitation effect across the three main attentional components trained. A) Time in Rehabilitation with Alertness-related activities were not selected as predictors to predict Δ percentile in stepwise regression model (n.r. = not retained; final model: Δ-Alertnees ~ intercepet). Although the plot shows a slightly general improvement, it can not be explained by the time patients spent performing Spaceship or/and Lunapark activities. B) top-panel - Stepwise procedure retained time in spatial attention-related activities (i.e., Tennis, Butterfly, Ball, Waterfall and Glyph) as relevant significant predictor of Δ Invalid-left percentile (p = 0.44; final model: Δ Invalid-left ~ time-in-spatial-activities; R^2 = 0.24, adjusted R^2 = 0.19). Similarly, in the bottom-panel, the Δ Valid-left percentile although retained in the final selected model (final model: Δ Valid-left ~ time-in-spatial-activities; R^2 = 0.20, adjusted R^2 = 0.14), its effect was not significant (p = 0.07; n.s. = not significant). C) To predict Δ percentile in Divided Attention, the model selected include time since stroke onset (p = .072) and age (p = .104) as relevant variables (final model: Δ-Divided Attention ~ time since stroke + age; R^2 = 0.34, adjusted R^2 = 0.23). The time patients spent on Divided Attention-targeted activities (i.e., Kitchen) was not retained (n.s.) as relevant to explain the clinical improvement in that function.

8.3.3. Eye Tracking as a Prognostic Tool of Alertness and Spatial Attention Recovery

Alertness

The PCA with parallel analysis identified the first principal component as the only significant factor that captures the maximal variance from the initial ET-specific biomarkers of alertness. Results from the stepwise regression analysis for alertness revealed a significant relationship between the first principal component (PC1) and the delta percentile. The model showed that lower values of PC1 were significantly associated with greater improvements in alertness, (β = -0.134, se = 0, $t_{(15)}$ = -2.15, p = .049, 95%). The overall model was significant at the same level ($F_{(1,15)}$ = 4.60, p = .049; R^2 = 0.235, adj. R^2 = 0.184; Fig. 8.8A).

Spatial Attention

Based on parallel analysis, the first three components were retained as the ones that capture the higher variance from the initial ET-specific biomarkers of spatial attention. Stepwise linear regression for model selection, identified a model including PC1, PC2, PC3 and their two-way interaction terms (PC1:PC2, PC1:PC3, PC2:PC3) as the best fit for explaining improvement in spatial attention performance. Within this model, PC1 (β = 0.122, *se* = 0.0496, $t_{(10)}$ = 2.46, p = .034; Fig.8B1), PC3 (β = -0.241, se = 0.105, $t_{(10)}$ = 2.302, p = .044; Fig. 8.8B2), and the interaction term PC1:PC3 (β = 0.050, *se* = 0.020 , $t_{(10)}$ = -2.519, p = .031) emerged as significant predictors of clinical improvement on the invalid-left percentile. However, the overall model did not reach statistical significance (F(6, 10) = 1.46, p = .286, R^2 = .466, adj. R^2 = .146.; Fig. 8.8B).

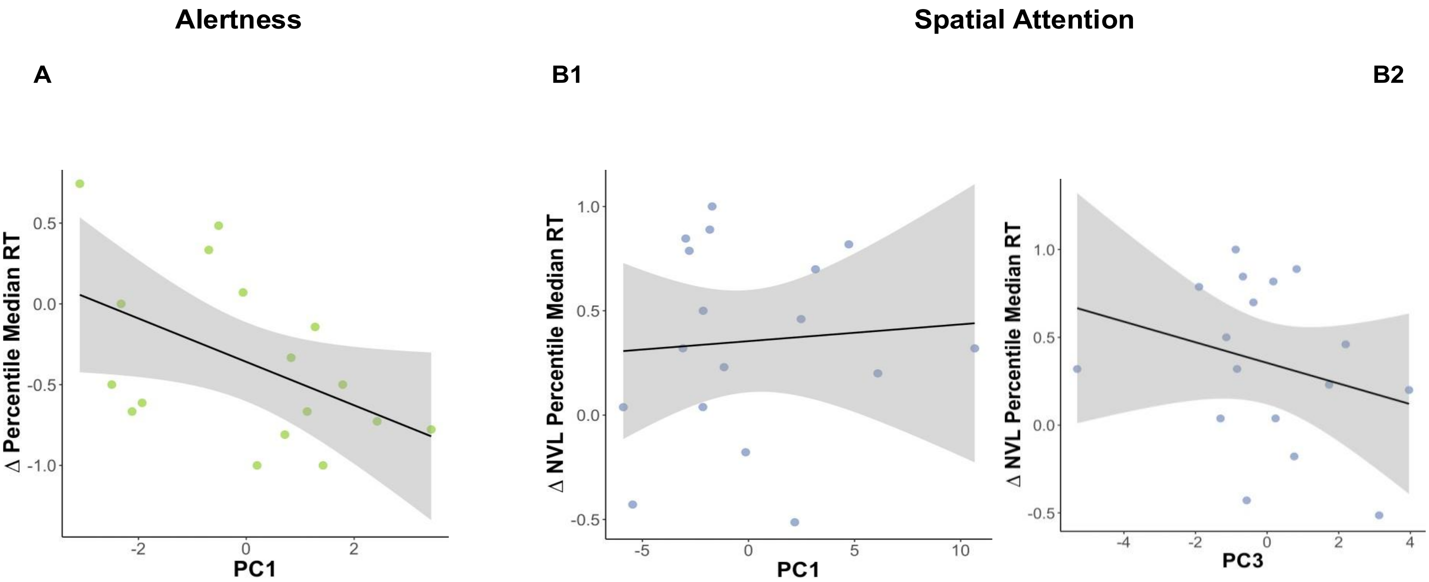


Figure 8.8. Associations between principal components (PCs) and TAP outcomes. Panel A (Alertness): PC1 is significantly associated with the change in percentile median RT (p = .049). Panel B (Orienting attention): PC1 (B1) and PC3 (B2) are each significantly associated with the change in NVL percentile median RT (p = .034 and p = .044, respectively)

8.4. Discussion

The results of the present study converge in demonstrating the feasibility of MindFocus iVR-based rehabilitation software for the management of attention disorders following stroke, providing insights into how such immersive technologies can be integrated within structured clinical practice. The findings also highlight the added value of the system's integrated eye-tracking component for the acquisition of oculomotor metrics as sensitive indicators of patients' recovery trajectories. Indeed, the potential of iVR for cognitive rehabilitation has been widely reported. However, most of the available evidence on post-stroke attention deficits has relied on single, task-specific VR applications that were not often grounded in evidenced-based theoretical models of attention. Furthermore, many of these systems were typically designed primarily for other cognitive domains or implemented in semi-immersive or non-immersive environments (Faria et al., 2016; Gamito et al., 2017). Within this heterogeneity, our study provides results from a dedicated iVR software specifically designed for attention rehabilitation, conceptualized on the bases of van Zomeren and Brouwer (1994) model and the hierarchical organization of attention subcomponents (Sturm et al., 1997, 2001, 2003; Solberg & Mateer, 1989). Accordingly, our findings encompass both intensity and selectivity aspects of attention, supported not only by performance related metrics, but also by clinically meaningful improvements.

In terms of intensity processes, analyses of performance related to alertness revealed that, following MindFocus training, reaction times become significantly faster in patients with baseline alertness impairments (AL+ group). In addition, performance between the AL+ and AL- groups were no longer distinguishable at the TAP Alertness subtest post-training, possibly reflecting a re-establishment of general attentional readiness. Consistently, at clinical level, 63.6% of AL+ reached performance within the normal range, and 90.9% of cases showed improved clinical classification. Interestingly, the regression analysis did not show a clear association between the time spent on alertness-specific activities (i.e., *Spaceship and LunaPark*) and the magnitude of behavioral improvement. This outcome could be interpreted in light of the hierarchical organization of attentional processes, where alertness, and more broadly, intensity processes, are considered a prerequisite for higher-order attentional components (van Zomeren & Brouwer, 1994; Sturm et al., 1999; Spaccavento et al., 2019). Accordingly, it can be hypothesized that improvements in alertness may have emerged not only from function-specific training, but also from the broader cognitive engagement in other MindFocus activities that, incorporating intensity processes, indirectly stimulated alertness mechanisms, in line with evidence showing that training higher-order attention functions can also enhance more basic components within a hierarchically organized system (Mayas et al., 2014). An additional consideration is that the immersive, game-like nature of MindFocus environment, requiring sustained monitoring, rapid responses, and adaptive feedback, may have further contributed to the observed improvements in alertness. Such environmental stimulation has been shown to enhance attentional intensity even in healthy individuals (Anguera et al., 2013; Green & Bavelier, 2012; Toril et al., 2014). This overall enrichment may therefore have to be taken into account when explaining the absence of a linear relationship between time spent on specific alertness tasks and the broader behavioral gains observed.

Concerning the selectivity aspect of attention, MindFocus training led to significant improvements in both spatial and divided attention. Consistent with prior evidence (e.g., Bourgeois et al., 2022; Choi, Shin, & Bang, 2021; Kim et al., 2011), our results demonstrated reduced asymmetry in reaction time toward stimuli presented in the two hemifields. Specifically, both the USN+ and USN- groups benefited from training, showing a more balanced distribution of spatial attention, although USN+ group remained less efficient. Improvements were also reflected clinically, where USN+ showed a more consistent increment in performance. Consistently, within the USN+ group, 33.3% of patients achieved performance within the normal range, and 77.8% ameliorated clinical classification post-training in their capacities of detecting unattended targets appearing on the neglected (left) side, indicating enhanced bottom-up attention allocation. In a similar way, when responding to attended stimuli presented toward the neglected (left) side, 82.4% performed within the normal range and 85.7% improved their diagnostic classification, collectively reflecting an improvement in top-down spatial attention orientation. The observation that spatial attention improvements were not limited to USN+ patients but were evident across the entire sample may be related to the intrinsic characteristic of immersive environments. The three-dimensional and the potential of 360° spatial configuration of iVR scenarios requires participants to actively distribute and shift attention across a wider visual field compared with standard rehabilitation tools (Serino et al., 2022; Pedroli et al., 2015). These enriched scenarios are known to promote spatial orienting and visuospatial exploration in both clinical and healthy populations (Bavelier et al., 2019; Huygelier et al., 2025). Accordingly, MindFocus activities targeting spatial attention were designed to stimulate exploration across wide spatial fields, requiring fast and flexible responses, likely facilitated improvements even in participants without initial spatial attention deficits. In line with this hypothesis, regression analysis highlighted that pre-post performance changes were associated with the total time patients were engaged in spatial attention related activities (i.e., *Tennis, Ball/Waterfall and Butterfly/Glyph*). However, this relationship reached significance only for the change in median RTs percentiles for invalid-left stimuli, while it showed a trend towards significance for valid-left conditions. The stronger correlation with invalid-left trials is consistent with the well-documented disengagement deficit in USN, whereby patients show prolonged RTs when shifting attention from the ipsilesional (right) to the contralesional (left) field

(Corbetta & Shulman, 2002). Studies using the Posner cueing paradigm have similarly demonstrated that RTs are disproportionately delayed for unattended or invalidly cued left-sided targets compared with attended ones (Corbetta & Shulman, 2011; Rengachary, Shulman, & Corbetta, 2011). This behavioral asymmetry has been linked to a disruption of the ventral attention network (VAN), which mediates stimulus-driven, bottom-up orienting, while top-down mechanisms governed by the dorsal attention network (DAN) remain relatively preserved (Corbetta & Shulman, 2002, 2011). Accordingly, the improvement for invalid-left stimuli following MindFocus spatial attention training likely reflects a strengthening of bottom-up orienting mechanisms and a partial restoration of balance between the VAN and DAN, facilitated by iVR activities.

Furthermore, regarding the effect of MindFocus training on divided attention abilities, our results show that patients with initial impairments in performing the main visual task of the TAP divided attention subtest (DIV+) exhibited greater improvements at post-assessment than the group of patients without baseline deficits (DIV-), ultimately the two groups become comparable in divided attention performance following MindFocus training. Clinically, 55.6% of DIV+ did not show any clinically meaningful alteration and 77.8% ameliorated their diagnostic category. These findings converge with previous evidence that computerized cognitive rehabilitation favored divided attention abilities (Loescher et al., 2019), while there is a lack of studies assessing specifically divided attention abilities after iVR protocols in stroke patients. Considering the high prevalence of divided attention deficits due to stroke, reported around 41% of cases (Spaccavento et al., 2019), our findings expand current knowledge by demonstrating the benefits of iVR training for this high-level attentional component. However, the described behavioral and clinical improvements can not be explained by the total time spent playing divided attention related activities (i.e., Kitchen). In this line, it is important to note that, given the theoretical frameworks around which the current protocol is constructed, each patient began the training with activities targeted intensity processes (i.e., alertness). As a higher-level component of attention, divided attention related activities were inserted later in the rehabilitation, once patients have reached sufficient recovery in the prerequisite lower-level attentional processes. This conceptualization may in part explain why a specific relation is missed between time in divided attention rehabilitation and the observed behavioral improvements. In addition, the regression analysis revealed that higher is the improvement in pre-post performance changes the lower the time since stroke onset. This aligns with evidence that plasticity window for cognitive recovery is maximal within the first 3 months post stroke (Desmond, 1996) and with evidence that rehabilitation initiated in early sub-acute stage yields more favorable outcomes (Mancuso et al., 2025; Xuefang, Guihua, & Fengru, 2021). Nevertheless, time since stroke explains about 34% of the variance in delta score, leaving open the possibility that additional factors can intervene in explaining the behavioral improvement. Accordingly, previous studies have shown that training more basic components of attention such as alertness lead to improvement also in not-trained high-order attentional components both for divided attention (Sturm et al., 1997; Loetscher et al., 2019) and spatial attention (Van Vleet et al., 2020). In our protocol, the time spent on alertness as well as spatial attention-related activities may favor the reported gains in divided attention abilities.

Finally, our results highlighted the potential value of incorporating eye-tracking metrics as prognostic indicators within the MindFocus platform. Specifically, the analysis suggests that multiple oculomotor parameters, acquired prior to the rehabilitation, can provide meaningful insights into the patient's recovery trajectory. Particularly, higher PC1 scores were associated with poorer improvement in alertness (i.e., delta percentile of median RTs at the TAP Alertness subtest) after training. PC1 represented a multidimensional eye-tracking profile encompassing several oculomotor metrics, often described in literature as biomarkers of alertness, including fixation count, fixation duration and stability, and blink activity. High PC1 values were characterized by a pattern of many and short fixations, frequent and prolonged blinks, and increased fixation instability, reflecting an erratic scanning strategy. This oculomotor profile suggests difficulties in maintaining focused attention, consistent with prior work showing that numerous short fixations correspond to fragmented attention and difficulties sustaining focus on specific visual elements (Stefani & Sauter, 2023), while frequent blinking reflects attempts to restore arousal and is associated with slower reaction times (Demiral et al., 2023; McIntire et al., 2014). As prognostic indices this information can give insightful information to the clinician, particularly patients with high PC1 profiles might benefit from higher-intensity or longer-duration interventions, compared to the ones that show lower PC1 profiles in which a protocol similar to the one applied here can be suitable.

For spatial attention, two principal components (PC1 and PC3) emerged as the main predictors of pre–post changes in non-valid left (NVL) conditions. Patients who, at pre-assessment, exhibited a more balanced exploration pattern between the left and right hemifields (as captured by PC1) tended to show greater improvements after training. Conversely, patients showing a more lateralized and imbalanced exploration pattern (reflected by PC3) exhibited smaller gains. This aligns with previous findings identifying spatial exploration asymmetry as a robust marker of neglect severity (Kaufmann et al., 2020; Nardo et al., 2019; Hougaard et al., 2021). Overall, using oculomotor metrics can inform clinicians about the recovery trajectory in both alertness and spatial attention components, supporting more personalized and adaptive rehabilitation strategies.

In conclusion, this study provides preliminary evidence supporting the feasibility of MindFocus as an immersive tool for attention rehabilitation after stroke and highlights the potential of integrated eye-tracking measures as sensitive markers of recovery trajectories. The promising results obtained emphasize the importance of extending these findings in future research. Several factors, however, should be taken into account when interpreting the present data. Although the sample size is consistent with previous feasibility and pilot studies investigating immersive or semi-immersive VR-based cognitive rehabilitation in stroke and brain injury populations, which typically enrolled between 15 and 25 patients (e.g., Faria et al., 2016; Gamito et al., 2017; Choi, Shin, & Bang, 2021; Cavedoni et al., 2022) and reflect the feasibility-oriented nature of the study it may constrain the generalizability of the results. In addition, patients did not receive an identical amount or intensity of rehabilitation, which could have introduced further variability across outcomes. The exploratory nature of the eye-tracking analyses should also be acknowledged, as the prognostic value of these metrics requires validation in larger and more controlled samples. It is therefore possible that the absence or attenuation of some effects is related to these methodological aspects. Future studies should include larger and more homogeneous cohorts and adopt controlled designs to confirm and refine these preliminary observations, thereby strengthening the clinical relevance of both behavioral and oculomotor findings. In addition, future research should include engagement measures to provide better insights into the acceptability of iVR-based rehabilitation. In this direction, we are currently conducting a randomized controlled trial (RCT) with a three-arm design aimed at validating and expanding the present results under more rigorous conditions. Further details on the RCT study protocol are available at ClinicalTrials.gov: NCT05728840.

Chapter 9

General Discussion

Cognitive sequelae following acquired brain injuries (ABI) remain a major source of morbidity, long-lasting disabilities, and functional alterations (Béjot et al., 2016; Cramer et al., 2019). Among cognitive deficits, attentional impairments are one of the most frequently reported (Braker-Collo et al., 2009; Tsai et al., 2021; Tucha et al., 2000). The fundamental importance of attention lies in its role as a multicomponential neurocognitive construct, encompassing distinct but interconnected processes supported by widely distributed brain networks (van Zomeren & Brouwer, 1994; Corbetta & Shulman, 2011; Kaufmann et al., 2023). A wealthy body of experimental studies in both neurologically healthy and brain damaged patients, has shown that different attentional components, such as alertness, sustained, spatial, and divided attention, engage partially segregated, but interacting brain regions, which work together to support even the simplest everyday actions (for a detailed review, see Chapter 2). Whether studying, working, conversing, preparing a meal or dressing, attention is continuously engaged and represents a primary, essential mechanism. Consequently, disruption of attentional processes, as the ones reported after ABIs, leads to pervasive functional limitations, including reduced return-to-work or education rates, restricted social participation, and decreased quality of life (Barker-Collo et al., 2009; Brewer et al., 2013; Oyewole et al., 2020), often persisting over the long term (Hyndman & Ashburn, 2003; Hyndman, Pickering, & Ashburn, 2008; Mellon et al., 2015). Combined with global projections of increasing ABI incidence (WHO, 2017; Wafa et al., 2020), these impairments place substantial demands on healthcare systems to provide appropriate management strategies. This poses the need to foster a reflection on the limitations of currently available neuropsychological tools and to develop and investigate more sensitive, ecologically valid, and potentially effective tools for both assessment and rehabilitation procedures.
From this perspective, this thesis builds on recent evidence identifying immersive virtual reality (iVR) as a powerful tool with unique features able to complement conventional approaches (see Chapter 3). Furthermore, drawing on studies in both healthy individuals and brain-lesioned patients showing that heart rate variability (HRV) and oculomotor metrics are sensitive to specific attentional processes (see Chapter 4), it investigated whether these measures, collected through newly developed iVR-based software for assessment and rehabilitation, can serve as reliable biomarkers of attentional processes (chapter 5 and chapter 6). It also examined their effectiveness for both diagnostic and prognostic purposes in patients with acquired brain injuries (chapter 7 and chapter 8). Following evidence showing a coupling between cognitive workload (i.e., the alertness level required by the

current task) and HRV under laboratory conditions (Forte & Casagrande, 2025; Thayer & Lane, 2009; Wei et al., 2024), the study presented in chapter 5 examined whether, in iVR-based activities, HRV can be defined as modulated only by cognitive effort and whether it predicts cognitive performance and subjective ratings. To this aim, HRV was recorded in neurologically healthy participants during iVR-based activities with high and low levels of cognitive and physical workload. Indeed, the results converge with evidence that cardiac measures collected in immersive contexts more closely approximate those elicited by real-life experiences, reinforcing the increased objectivity of these methods (Marín-Morales et al., 2021; Slater and Sanchez-Vives, 2016). Going beyond, the study clarified the feasibility and limits of using HRV as a unique index of cognitive workload. In contrast to evidence from 2D laboratory settings (e.g., Delliaux et al., 2019; Lusque-Casado et al., 2016), iVR activities deployed in chapter 5 required simultaneous integration of motor, perceptual and attentional processes (Marucci et al., 2021). In this setting, decreases in mean RR indicating parasympathetic deactivation and increases mean HR reflecting sympathetic disinhibition (Forte & Casagrande, 2025; Thayer et al., 2009; Thayer & Lane, 2009; Wei et al., 2024), resulted as modulated by a combined influence of different sources of load. Under high-load conditions, the overall HRV pattern was consistent with the well-established "flight or fight" response (LeDoux, 1996) that upregulated alertness to meet increasing demands; however, it resulted mainly driven by physical strain and only partly mitigated by cognitive effort. Collectively, the evidence provided in chapter 5 highlights that investigation of HRV in ecological scenarios can reveal effects often overlooked in laboratory settings, ultimately suggests caution against interpreting HRV as unique biomarker of cognitive workload within iVR environments.

Consistent with chapter 5's results, chapters 6, 7 and 8 provide strong evidence of both feasibility and clinical utility of tools combining oculomotor metrics and iVR. Firstly, chapter 6 explored whether oculomotor metrics collected in iVR tasks can reliably index individual abilities in attention processes, adopting a multi-parameter approach. With this aim, to a large cohort of healthy adults, three iVR tasks specifically developed to evaluate alertness (*iVR-Burst Alertness*), selective attention *(iVR-Burst SpatialSelective)* and spatial attention *(iVR Free Viewing Exploration task, IVR-FVE)* were administered. From each task, oculomotor metrics, well defined in literature to index the respectively attentional components, were extracted and machine learning models were trained to investigate their capacities in predicting performance in each attentional domain. Subsequently, in chapter 7 the same iVR tasks were employed to assess whether the identified eye parameters can be able to distinguish patients with and without deficits in alertness and spatial attention. The same machine-learning approach, used in chapter 6, was employed here to evaluate and identify the best set of performance metrics for the diagnosis. Moreover, chapter 7 investigated whether eye parameters that best detected these deficits align the sites of brain damage, using parcel damage and tract disconnection analyses. Finally, chapter 8 tested the feasibility of the new iVR software for rehabilitation of attention disorders in acquired brain injuries and whether deploying the same set of oculomotor metrics could predict improvements after iVR training.

The findings from these three studies, whether using iVR-based assessment tasks or iVR-based rehabilitation activities either in healthy and brain damaged patients, consistently showed that less efficiency in regulating alertness level, operationalized as slower reaction time in responding to external stimuli, was associated with an erratic exploration pattern, characterized by higher number of fixations, shorter fixation duration and greater instability of fixations, combined with higher blink rate and durations.

Based on previous study, it can be hypothesized that these patterns reflect an overall weakness in top-down regulation mechanisms (Stefani & Sauter, 2023; Unsworth, Miller, & Robison, 2020; Unsworth & Robison, 2017). In fact, fixations are moments when exploration pauses to acquire and process task-relevant information (Marandi & Gazerani, 2019; Salvucci & Golberg, 2000; Skaramagkas et al., 2023). Whether top-down control is less efficient, gaze exploration become more strongly driven by bottom-up salience, resulting, as shown in our results, in a more erratic and ustable fixation pattern Moreover, consistent with prior evidence linking blinks to transient surges in arousal supporting wakefulness and alertness (Demiral et al., 2023; Demiral & Volkow, 2024), the resulted increased in blink metrics can be viewed as a coping strategy that boost top-down control processes to elicit a surge of arousal among the system. The same oculomotor pattern proved to be clinically meaningful: not only distinguishing patient with and without alertness deficit, as shown in chapter 7, but patients who exhibited stronger version of this oculomotor pattern improved the least, suggesting that these patients may have a deeper baseline alertness deficit and they necessitate for a personalized rehabilitation pathway to achieve a better recovery. In addition, this pool of oculomotor metrics was shown in chapter 7 as associated with damage in the right posterior visual regions part of the DAN, area among the most innervating by NE pathways (Morrison & Foote, 1986; Posner & Petersen, 1990; Petersen & Posner, 2012). The fact that the locus coeruleus-norepinephrine system (LC-NE) is the primary source of NE in the brain and a central substrate of alertness, many studies (Aston-Jones & Cohen, 2005; Petersen & Posner, 2012; Joshi, Kalwani, & Gold, 2016) provide further foundation for their implementation as reliable clinical biomarker of alertness abilities. Similarly, studies in chapters 6, 7 and 8 were consistent in defining oculomotor metrics that in immersive environment can serve as biomarker of spatial attention capacities. Consistent with previous evidence, a biased spatial exploration towards the right hemifield, (Bagattini et al., 2022; Chiffi et al., 2021; Guidali et al., 2023; Nardo et al., 2019; Strauch et al., 2024) indexed a weakness in spatial attention allocation strategies

(Franceschiello; Kaufmann et al., 2020; Nardo et al., 2019). Particularly, showing a first fixation directed toward the right hemispace, less percentage of fixation on the left (i.e., gaze laterality), total fixation duration biased on the right (i.e., positive gaze index values), associated with an oculomotor pattern mimicking the productive positive symptoms often described at behavioral level in patients with spatial attention alterations (Rusconi et al., 2002), such as higher number of right refixation and right perseverative refixation (Coz & Davies, 2020; Paladini et al., 2019) were associated in chapter 6 with higher imbalance between the time needed to respond to lateralized targets. This oculomotor pattern were also able to correctly detect patients with and without USN diagnosis (chapter 7), and to determine which patients could improve the most whether engaged in iVR rehabilitation.

In addition, in line with evidence that spatial attention emerges from the interaction between VAN and DAN regions and the white matter tracts connecting these distributed hubs (Alves et al., 2022; Favaretto et al., 2022; Doricchi et al., 2008; Thiebaut de Schotten et al., 2014; Kaufmann et al., 2023; Wiesen et al., 2022), the identified oculomotor pattern was associated with right-lateralized brain damage across the two attentional networks, converging with the well-known right-hemispheric specialization for spatial attention (Heilman & Van Den Abell, 1980). Within the DAN, lesions involved the dorsolateral prefrontal cortex and frontal eye field/dorsal premotor complex, known as core hubs for top-down attention allocation and oculomotor control (Corbetta et al., 1998; Corbetta & Shulman, 2012). Whitin the VAN, alteration in insular/opercular regions and the inferior frontal gyrus, well established brain areas linked with bottom-up attention allocation, resulted as related to the retained oculomotor pattern. Consistently, disconnection of right hemispheric white matter pathways supporting spatial attention abilities such as the inferior frontal occipital fasciculus (IFOF), (Hattori et al., 2018; Rojkova et al., 2016; Sarubbo et al., 2013; Umarova et al., 2010; Weiller et al., 2021), the Frontal Aslant Tracts (Corbetta & Shulman, 2002; Doricchi et al., 2008; Karnath et al., 2011; Vossel, Geng, & Fink, 2014; Bartolomeo & Seidel-Malkinson, 2019), and the Uncinate Fasciculus (UF), (Alves et al., 2022; Thiebaut de Schotten et al., 2012; Von der Heide et al., 2013)) was likewise associated with the derived oculomotor pattern.

Collectively, the results from the studies presented in this thesis strongly support the value of investigating biomarker metrics in iVR tasks. As demonstrated by the findings, assessing oculomotor and cardiac biomarkers under task demands that more closely resemble those required by everyday life activities provides a better understanding of how these measures are associated with attention. Results from chapter 5, showing that HRV modulations are influenced by multiple sources of load acting together with attentional effort, from one side suggests caution in treating HRV as only related to cognitive workload; on the other, represent an important step forward in the direction of having tools allowing to collect measures with greater ecological validity and reliability in tracking cognitive processes. The finding on oculomotor parameters further reinforce this reasoning. In environments that reproduce the complexity of real life, the analysis of single oculomotor parameters resulted as reductionist, instead combining multiple metrics provides a more comprehensive and realist characterization of distinct attentional components. Specifically, fixations number, duration, instability and blink frequency appears most informative for describing alertness, while fixation count and length together better indexes selective attention. Likewise, the direction of first fixation along with the right-left differences in fixation number, duration and refixations accurately capture spatial attention abilities. When considered together, these parameters provide a more reliable representation of attentional abilities, a result made possible by the immersive and naturalistic characteristics of virtual reality environments, which better reproduce the complexity of attention as it operates in everyday life. Crucially, the studies presented in this thesis also greatly support the translation potential of collecting biomarkers within iVR tasks for integration into current neuropsychological procedures. As demonstrated, the same set of oculomotor parameters identified in iVR represents a reliable and objective tool in detecting attention impairments within their correspondent attention domain following acquired brain injuries. The good diagnostic sensitivity associated with the iVR multimodal, dynamic scenarios that more closely represent everyday life attentional demands while maintaining a high level of experimental control over stimulus administration and performance scoring, make this approach valuables in overcoming the often reported limited ecological validity of the current assessment tools and may help in detecting subtle but functionally relevant impairments frequently go unnoticed when measures by standardized evaluation methods.

Similarly, the results underpin using iVR for attention rehabilitation, demonstrating its feasibility in promoting improvements across multiple attention components. Moreover, through the same set of oculomotor biomarkers it also showed the capacity to predict individual recovery trajectories, allowing for more personalized and adaptive rehabilitation strategies. These findings hint at the potential of these methods to also complement current rehabilitation protocol. iVR scenarios favoring training of attention abilities in highly ecological environments, with continuous feedback and adaptive task difficulties, ensures that intervention remains optimally challenging and tailored to individual performance. The added value of the embedded biomarker metrics further enhances this process by objectively informing clinicians about the better strategies to be implemented for each patient, ultimately advancing the personalization of rehabilitation pathways.

Importantly, the results from lesion analysis confirm that these biomarkers are associated with well-known cortical and subcortical networks subserving attention and oculomotor control, further strengthening their clinical validity.

Extending these translational results to practice, the potential of iVR tools to be deployed at home or directly at the bedside, along with the value of oculomotor and cardiac measures to index attention processes without the need for intact language or motor output, could promote earlier detection of attention deficits, favor timely entry into rehabilitation, and thereby mitigate the functional impact of these disorders. In addition, the presented results about the feasibility of iVR tools, combined with the possibility of home use with partially unsupervised sessions, can increase therapy intensity and duration while preserving objective monitoring. This can reinforce not only the continuity of care even in chronic stage but also broadening the access to treatment while reducing regional barriers and differences.

The framework established from these results also suggests the potential for broader clinical applicability. The same iVR paradigms integrating eye-tracking and cardiac measures may be implemented for the detection and rehabilitation of high order cognitive functions, including working memory and executive functions, which are closely intertwined with attentional control and frequently impaired following ABIs (Diamond 2013; Stuss & Knight, 2013). In this perspective, growing body of evidence indicates that oculomotor metrics, including fixation patterns and saccadic behavior are sensitive to executive and memory related cognitive processes, further supporting their use as objective markers into iVR tools (Unsworth et al., 2014; Dalmaso et al., 2020).

Beyond acquired brain injury, the proposed iVR and eye-tracking–based approach may be particularly relevant for clinical populations in which attentional dysfunction represents a core or prominent feature, such as attention-deficit/hyperactivity disorder (ADHD). ADHD has been consistently associated with atypical oculomotor behavior, including altered fixation stability, increased saccadic variability, and differences in blink rate, as well as with dysregulated autonomic responses during attention-demanding tasks (Munoz et al., 2003; Groen et al., 2011; Fried et al., 2014). Importantly, virtual reality–based continuous performance tasks combined with eye-tracking have demonstrated enhanced ecological validity and improved sensitivity to attentional deficits compared to traditional laboratory paradigms, suggesting that multimodal iVR frameworks may offer added clinical value in this population (Neguț et al., 2016; Parsons et al., 2019).

The applicability of the proposed framework may also extend to populations affected by cognitive decline and neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, even though attentional impairment is not typically the primary cognitive deficit in these conditions. In Alzheimer's disease and mild cognitive impairment, alterations in eye movement behavior, including prolonged fixation duration, reduced saccadic efficiency, and abnormal visual exploration patterns, have been shown to reflect deficits in memory, executive control, and visuospatial processing, and have been proposed as sensitive, non-invasive markers of disease-related cognitive decline (Crawford et al., 2005; Molitor et al., 2015; Wolf et al., 2023). Similarly, in Parkinson's disease, oculomotor abnormalities such as increased saccadic latency, reduced saccade amplitude, impaired inhibitory control, and altered fixation stability are well documented and are thought to reflect dysfunctions within fronto-striatal and brainstem circuits rather than isolated attentional deficits, while nonetheless showing sensitivity to disease severity, cognitive status, and medication effects (Brien et al., 2023; Terao et al., 2013).

Importantly, extending iVR-based oculomotor and autonomic biomarkers to diverse clinical populations requires careful consideration of disorder-specific assumptions and limitations. Differences in baseline autonomic regulation, pharmacological treatments, motor and sensory impairments, and fatigue may influence physiological responses and task performance, complicating the interpretation of multimodal biomarkers (Thayer et al., 2012). In addition, the tolerability and usability of immersive virtual reality systems may vary across populations, particularly in individuals with advanced cognitive decline or heightened sensory sensitivity, highlighting the need for adaptive task design and systematic population-specific validation (Weech et al., 2019; Caporusso et al., 2025).

In conclusion, the studies presented in this dissertation converge in enlightening the relevance of investigating biomarkers within immersive virtual reality environments both to deepen understanding of their association with cognitive functioning and to provide more ecologically valid and reliable methods for assessing, monitoring and rehabilitating cognitive impairments following brain damage.

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