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EYE MOVEMENTS IN STROKE

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RINGRAZIAMENTI

ABSTRACT

Background

Stroke is one of the most common diseases and has a wide variety of presentations. One of the most impactful, yet incompletely understood, outcomes of stroke is the emergence of attentional deficits. Attentional deficits negatively affect the prognosis, and they are hard to diagnose, especially at the chronic stage. The development of novel and more sensitive ways for diagnosing attention deficits is highly relevant to the recovery from stroke, and may lead to novel interventions.. The neural networks that control eye movements and the allocation of attention are highly correlated; hence, monitoring of eye movements during natural vision may be a way to measure also attention deficits.

Scope of the study

We investigated the feasibility of utilizing eye tracking in the clinical detection of attentional impairments, and we aimed at finding the best experimental setting to predict clinically measurable metrics of inattention.

Materials and methods

Thirty-four patients received a paper-based test of visuospatial neglect (OCS Hearts test), then they viewed a set of images while their eye movements were measured. The eye movements of twenty-eight patients were also recorded during the free viewing of a blank screen. The analysed metrics included both standard eye-movements metrics such as eye fixations, saccades, blinks, and innovative metrics such as indexes of the laterality and direction of gaze. The correlation between the eye movement metrics and the OCS hearts test score were studied. In addition, we studied aspects of the fixations pattern. Eighteen subjects also performed a Posner cueing task and their reaction times were analysed to measure their ability to direct covertly their attention to the contralesional and ipsilesional visual field under higher or lower certainty conditions.

Results

The performance on the visuospatial task (OCS hearts test) was correlated with the centre of mass of the fixation distribution, the blink-rate, and the direction of

saccades. Specifically, higher performance on the OCS hearts correlated with a more centred distribution of fixations while a higher blink rate was correlated with lower performance. Additionally, the execution of more rightward than leftward directed saccades was also correlated with worse OCS scores. The distribution of fixations along the vertical and horizontal axes in stroke patients differed from that of healthy subjects. Finally, in the Posner cueing task, right hemisphere stroke patients were slower during target detection.

Conclusion

The analysis of a broad spectrum of eye movement metrics has yielded preliminary evidence on the potential usefulness of eye tracking for the diagnosis of sub-clinical attentional impairments. Further research is necessary to overcome the limitations of the present study and to strengthen our observations.

RIASSUNTO

Background

L'ictus è una delle malattie più comuni nel mondo occidentale e si presenta con un'ampia varietà di disturbi. Tra i disturbi più impattanti, nonché meno compresi, vi sono i disturbi dell'attenzione che possono far seguito all'evento cerebrovascolare. I disturbi dell'attenzione hanno un grave impatto sulla prognosi dei pazienti, ma, quando non severi, possono essere difficili da diagnosticare. Ne consegue che la ricerca di nuove maniere per diagnosticare tali disturbi, sia quando clinici che subclinici, è di vitale importanza. I network neurali che sottendono al controllo dei movimenti oculari e quelli che governano l'attenzione sono fortemente correlati tra loro, dunque lo studio dei movimenti oculari potrebbe essere la risposta al bisogno clinico appena menzionato.

Scopo dello studio

Abbiamo studiato la fattibilità di utilizzare i movimenti oculari nella diagnosi dei disturbi dell'attenzione clinici e subclinici, e abbiamo cercato il setting sperimentale più appropriato per raggiungere detto scopo.

Materiali e metodi

Trentaquattro (*34*) pazienti hanno ricevuto un test su carta di attenzione visuospaziale (OCS Hearts test), poi sono stati invitati a guardare una serie di immagini mentre i loro movimenti oculari venivano misurati. Inoltre, i movimenti oculari di ventotto (*28*) di questi pazienti sono stati misurati mentre guardavano uno schermo grigio. Le metriche derivanti dai movimenti oculari utilizzate per le analisi comprendevano sia metriche tradizionali (fissazioni, saccadi, ammiccamenti), sia metriche innovative come degli indici della lateralità e direzionalità dello sguardo. La correlazione di dette metriche con i parametri clinici analizzati tramite l'OCS è stata studiata. In aggiunta, abbiamo studiato il pattern di fissazione dei pazienti. Diciotto (*18*) soggetti hanno anche eseguito la "Posner cueing task" e i loro tempi di reazione sono stati analizzati.

Risultati

Le performance nel test di attenzione visuospaziale (OCS) erano correlate con il baricentro delle fissazioni, la frequenza di ammiccamenti e la direzionalità delle saccadi. In particolare, una migliore performance nel test visuospaziale era correlata a una distribuzione delle fissazioni più centralizzata. Al contrario, un aumento della frequenza di ammiccamenti si correlava a una peggior performance. In aggiunta, l'esecuzione di più saccadi verso destra correlava con un punteggio più basso all'OCS.

Inoltre, abbiamo analizzato la distribuzione delle fissazioni nei pazienti con ictus e queste differivano dai controlli sani.

Infine, riguardo la "Posner cueing task", i tempi di reazione dei pazienti con infarti destri erano significativamente aumentati.

Conclusioni

L'analisi di un ampio spettro di metriche oculari in pazienti con deficit dell'attenzione ha fornito delle evidenze preliminari dell'utilità dei movimenti oculari nella diagnosi clinica dei deficit stessi. Ulteriori lavori di ricerca sono necessari per validare i nostri risultati.

INTRODUCTION

The importance of attention and its impairment in stroke patients

Stroke, the second leading cause of death and disability worldwide (1,2), presents a diverse range of symptoms that can affect speech, movement, sensation, as well as cognitive functions. Unfortunately, both patients and neurologists often prioritize sensorimotor symptoms, while cognitive symptoms such as attention and memory deficits are frequently overlooked, despite affecting a significant majority of stroke patients (more than 600,000 patients per year in the US alone, and 12 million worldwide per year).

Attention deficits can impact various aspects of attention, including alertness, vigilance, focused attention, and divided attention. Alertness refers to the state of wakefulness that enables an individual to appropriately respond to stimuli. Vigilance, on the other hand, involves maintaining a consistent level of alertness over a specific duration. Selective attention involves the ability to enhance behaviorally relevant stimuli while suppressing irrelevant ones, whereas divided attention involves simultaneously attending to different stimuli within the same sensory modality (e.g., two visual stimuli) or across modalities (e.g., one visual and one auditory stimulus) (3).

Defining and subdividing attention poses challenges due to its semantic and biological complexity, further complicating the diagnostic and therapeutic processes for attentional deficits. Despite this complexity, there is a pressing need to explore new approaches for diagnosing and treating attentional impairments, given their high prevalence and substantial impact on patients' prognosis.

In the existing medical literature, attentional impairments have predominantly been studied in severe and conspicuous forms, neglecting the milder and more nuanced presentations often encountered in clinical practice.

Inattention is not only neglect

One of the most well-known forms of attentional impairment is hemispatial neglect, also known as unilateral spatial neglect or hemineglect. This debilitating condition is characterized by difficulties in orienting, responding, or attending to stimuli

presented in the hemifield opposite to a focal brain lesion, without being explained by sensorimotor abnormalities (4).

Hemineglect is a significant contributor to illness, particularly in stroke cases, as it affects up to one third of acute stroke patients (5,6). Moreover, it is strongly associated with a high burden of disability, prolonged hospitalization, poor motor skill recovery, and slow and incomplete response to rehabilitation (7,8).

Importantly, even among stroke patients who do not receive a formal diagnosis of neglect, up to 80% exhibit various attentional deficits (9). These deficits may manifest as impairments in selective attentional processes, sustained attention, or both. These non-spatial attentional impairments alone have a profound impact on patient outcomes, particularly in terms of activities of daily living (ADL) impairments and the frequency of falls (10).

While lesions in the right hemisphere are most commonly associated with unilateral spatial neglect and sustained attentional deficits (11), it is worth noting that lesions in the left hemisphere can also give rise to these impairments, albeit usually with less severity (12). This evidence supports the argument that the left and right hemispheres play distinct roles in governing different aspects of attention.

The neurobiology of attention

The mechanisms underlying attention are only partially understood. Early theories posited that parietal and frontal areas in each hemisphere direct attention to the contralateral side, following a right-to-left and a left-to-right linear gradient for left and right hemisphere respectively (1,2) or, similarly, that the two hemispheres generate a bell-shaped gradient of saliency (3).

With progress in the technical capability to study brain activity through neuroimaging (PET first, then fMRI), different forms of attention have been localized to different brain areas and networks (fig. 1). A right dominant hemisphere network (ventral attention network, VAN) comprising the temporo-parietal junction (TPJ) and ventral frontal cortex (VFC) mediates re-orienting of attention or task sets based on sensory stimuli as well as sustained attention. A bilateral dorsal fronto-parietal network (dorsal attention network, DAN) comprising the frontal eye fields (FEF), intra-parietal sulcus (IPS) and superior parietal lobule (SPL) is concerned with goal-driven and predictive selection (4,5).

Under conditions of divided attention or target selection, anterior frontal regions like the anterior cingulate come into play (6,7).

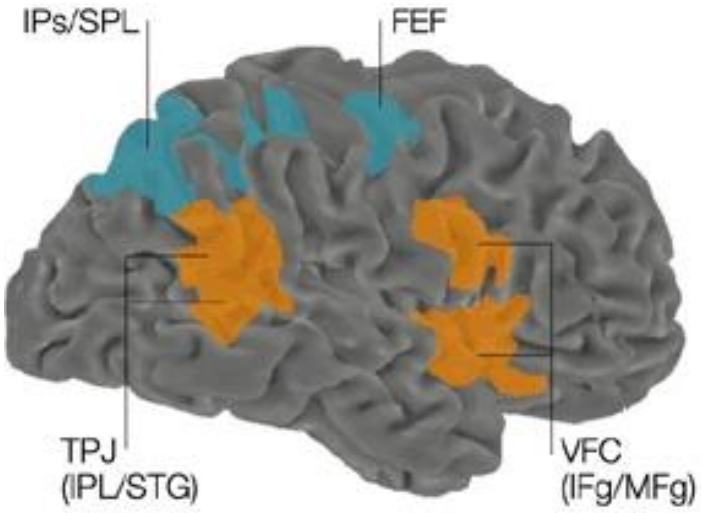

Figure 1, from Corbetta et al., 2002. The dorsal attention network in blue, the ventral attention network in orange.

In agreement with this scheme the current anatomical-functional model of unilateral neglect posits that damage to right hemisphere perisylvian regions cause direct damage to the VAN with secondary deficits in sustained attention (vigilance) and an indirect functional imbalance between left and right DAN causing the rightward visuospatial bias characteristic of hemispatial neglect. However, it should be noted that hemineglect is not a binary (present vs absent) condition, rather different patients can show different grades of inattention. Moreover, beyond the classical hemineglect syndrome caused by right hemisphere lesions, patients with stroke even in the left hemisphere can show attentional impairment for the contralateral visual field (8–10).

Eye movements: a novel clinical tool to screen for inattention?

Clinically, neglect is clinically measured through pencil-and-paper neuropsychological tasks and evaluation of this syndrome in activities of daily living (11). These tests typically include drawing a clock face, cancelling targets among distractors, bisecting horizontal lines, reading, or observing a patient when he/she eats or dress him/herself.

These tests are very sensitive at the acute stage but much less at the chronic stage where computerized reaction time tasks remain highly sensitive (12).

However, these assessments take time and instructions for computer assessment can be difficult in patients with aphasia. Given the importance of attentional impairments and neglect in the outcome of stroke patients, there is an unmet clinical need for a quick, sensitive test to screen stroke patients for the presence of hemispatial neglect or milder forms of attentional impairment that are usually neglected by pencil-and-paper tests.

We reasoned that a simple ecological test of visuospatial attention would be to measure eye movements during the vision of natural stimuli given the strong functional relationship between attention and eye movements, both psychologically and neurally (13–16)

THE INTERPLAY BETWEEN ATTENTION AND EYE MOVEMENTS

A closer look at the way we look

Although our personal experience may suggest that our eyes steadily fixate on a spot just to move slowly and briefly under our conscious control, this couldn't be further from the truth. The eyes are constantly engaged in a plethora of jerky movements that aim to bring objects of interest on the locus of maximal visual acuity: the fovea.

Subtypes of eye movements

Prior to further discussing attention and eye movements, it is useful to give some definitions regarding five subtypes of oculo-motor behaviour (17,18):

- Saccades are fast eye movements that redirect the fovea to new visual targets;
- Smooth pursuit movements keep the image of a moving target on the fovea;
- Vergence movements move the eyes in opposite directions, these are employed when an object is moving closer to us *(convergence)* or further from us (*divergence*). Vergence positions the image on both foveae;
- The vestibulo-ocular reflex (VOR) holds images still on the retina during brief head movements;
- Optokinetic reflex (OKR), an involuntary compensatory eye movement that allows the eyes to maintain fixation on a visual target as it moves by an observer (19).

Saccades

As previously mentioned, saccades are ballistic, stereotyped movements that point the fovea to a region of interest. They are preprogrammed according to the position of the target. Saccades can be voluntary or reflexive: in the former case they are directed to a target according to the goal of the observer (*top-down modulation)*, in the latter, saccades are induced by a visual stimulus that attracts the eyes of the observer (*bottom-up signal*). Many different metrics of saccades (20) can be recorded and studied via eye tracking such as:

- Amplitude (the angular distance the eye travels during the movement);
- Duration (the time taken to complete the saccade), usually around 50-200 ms for the higher amplitudes;
- Velocity (the amplitude of the saccade divided by the duration, commonly reported in degrees per second);
- The main sequence (21), defined as the relationship between the three aforementioned metrics;
- Saccade latency, the time between the target's appearance and the following eye movement, or the intersaccadic interval in a saccade sequence (*scan path*). On average saccade latency is around 200-250 ms.

Fixations

Each saccade is followed by a fixation: in this phase the eyes are relatively stationary and visual information is processed. In the previous paragraph VOR and OKR have been presented, these reflexes allow stabilization movements that represent necessary strategies to hold the target on the fovea. In actuality, the eyes are never completely still but they make microscopic fixational movements that prevent the image from fading away. This phenomenon, known as Troxler effect, is due to a mechanism of neural adaptation: to save energy, a continuous static stimulus stops signal transmission.

Attention and eye movements are not synonyms, the Posner cueing task

As briefly introduced by the Troxler effect, the human brain is an incredibly complex organ, but it still has energetical boundaries that limit its capability to analyse sensory cues. When exploring a natural environment, the brain is bombarded with information that may simply overstock it if they were not filtered. One of the most potent filters that the brain applies to the world before sensory processing is attention. By directing attention to a specific feature or subset of features the brain can enhance its capability to analyse the properties under scrutiny while also ignoring unwanted noise, thus optimizing energy allocation.

There is strong evidence supporting the power of attention in enhancing sensory processing. A paradigm often exploited when studying attentional processes is the Posner paradigm (22). In this paradigm subjects are asked to sit in front of a computer screen that presents two boxes (left and right) and look at its centre (see fig. 2). Subjects are then cued to direct their attention to one of two boxes, but not move their eyes towards it. Whenever a target stimulus appears in one of the boxes subjects are asked to press a key on the computer and reaction time is measured. The standard result is that subjects are faster in detecting objects at the cued location (*valid cue trial*) and slower at the uncude location (*invalid cue trial*). The interpretation is that attention shift spatial attention to the cued location prior to the appearance of the target, hence facilitating its detection, but need to re-orient attention to the uncued location once the target appears, hence slowing down response times.

Other studies showed that moving the eyes necessarily forces a shift of spatial attention, which suggested the theory that ‘covert’ (without eye movements) shifts of attention reflect motor plans for overt saccades (16). More recently neuroimaging showed common mechanisms for visuospatial (covert) attention and saccadic eye movements.

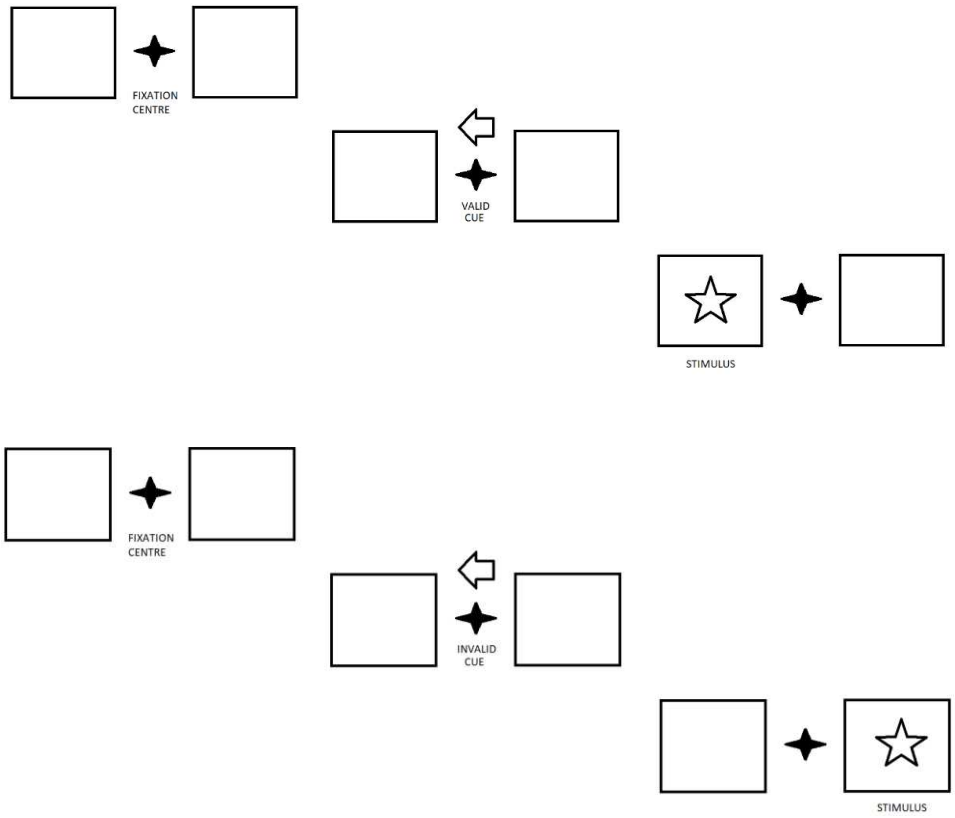

Figure 2 the Posner task

Functional anatomy of attention and eye movements

Anatomically, areas responsible for attention shifts are located within a fronto-parietal network. More specifically, areas specialized in redirecting attention are located near the postcentral and intraparietal sulcus within the parietal lobe, and the precentral sulcus within the frontal lobe (23). Within this network, based on both PET and fMRI data, there is significant overlap with areas active for eye movements (fig. 3,4), in particular in the intraparietal sulcus and postcentral regions of the parietal lobe and, frontally, in the precentral region and superior frontal sulcus region (15). The most important areas comprised in this network will be discussed in the following paragraphs.

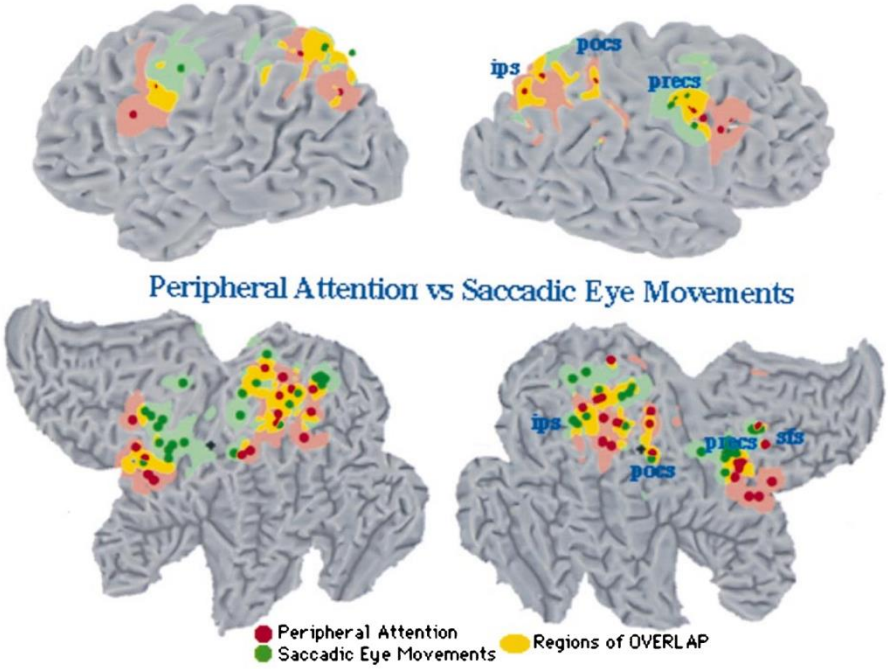

Figure 3 from Corbetta M. (1998): IPS=intraparietal sulcus, PRECS=precentral sulcus, POCS=postcentral sulcus

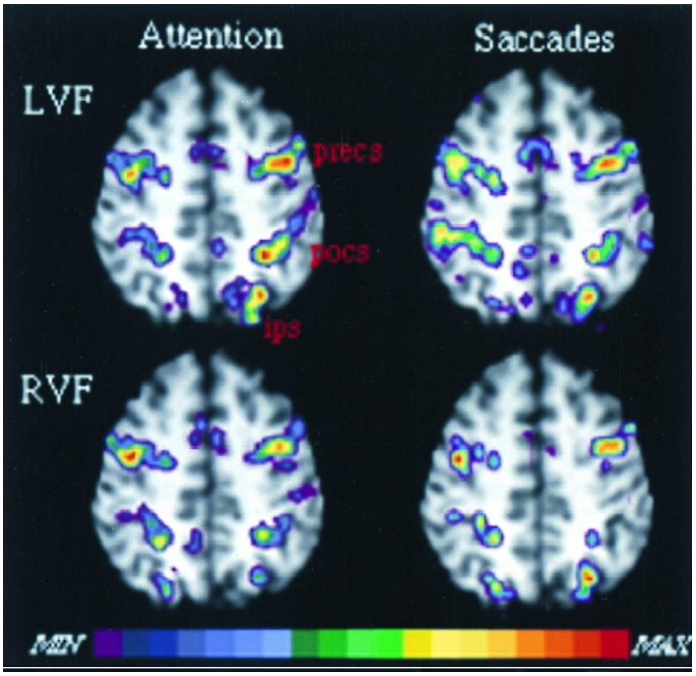

Figure 4 from Corbetta M. (1998), left side: fMRI areas of activation during switching of attention, right side: fMRI areas of activation during saccadic eye movements.

The dimorphous role of the Frontal Eye Fields: attentional and oculomotor

Neurons in the Frontal Eye Fields (FEFs) seem to play a significant role in regulating both attention and saccades. FEFs are equipped with both neurons that respond to a specific visual receptive field and saccade related neurons. Notably, FEF neurons can switch their receptive field prior to a saccade. In doing so, FEF neurons redirect attention to visual areas that will be attended visually once the saccade is completed (see fig. 5).

Experiments in monkeys have shown that FEF inactivation causes both an increased saccade latency and a disruption in spatial attention (24). Similarly, neurostimulation experiments have proven an enhancement of visual processing at receptive fields of FEF neurons upon microstimulation (25).

Of note, consistent with the interplay between primary motor cortex and supplementary motor areas, while FEFs are directly concerned with the voluntary, executive role in saccade initiation, another frontal area termed Supplementary Eye Field (SEF) improves saccadic execution. Neurons in the SEFs have been shown to fire in relation to the learning phase of saccades sequences and cognitive aspects of saccade execution such as intention to move (26–28).

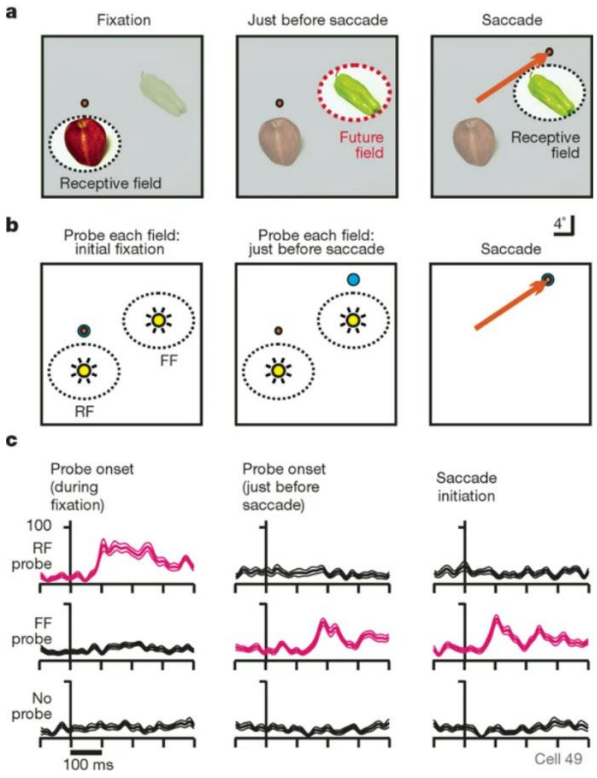

*Fig. 5 from Sommer and Wurtz, (2006): **a**, Just prior to a saccade, visual responsiveness moves from the receptive field (RF) to the future field (FF). **b**, Monkeys stared at (orange dot) a fixation spot (blue dot, left) and made a saccade to a target (blue dot, middle). A probe (yellow circle) was flashed in one of two locations. **c**, FEF neuron. The firing rate is aligned with the events happening in a and b. The sensory response shifts from the RF (fuchsia, left) to the FF (fuchsia, middle) just before the saccade.*

The role of the Posterior Parietal Cortex in spatial attention and eye movements

Less is known about the role of the parietal cortex in the control of attention and saccades. Microstimulation of the monkey lateral intraparietal area (LIP), biases saccades toward the receptive field of parietal neurons (29). In humans, the Posterior Parietal Cortex (PPC) is active during a variety of visuospatial and cognitive tasks including eye movements, visuo-spatial attention and spatial memory (30–32).

Stimulation experiments in humans (33,34) have yielded similar results to those in monkeys, where low threshold stimulations only yield shifts of visual attention and stronger stimulations trigger actual eye movements (35). The parietal area concerned with eye movements is termed Parietal Eye Field (PEF) and appears to be located along and within the IPS. While FEF activation seems to be correlated with voluntary saccades, the PEFs trigger reflexive saccades (36).

These experimental results corroborate the fMRI findings supporting the existence of a dorsal attention network including parietal, frontal and subcortical areas (detailed in the following paragraph), dedicated to the allocation of attention and the generation of eye movements.

Subcortical and peripheral structures

The Superior Colliculi

The Superior Colliculi (SC) are three-layered visuomotor integration regions located on the dorsal surface of the midbrain. The superficial layer is mainly involved in sensory responses to visual stimuli. The intermediate and deep layers are primarily related to oculomotor actions. These two layers contain polymodal spatial maps (retinotopic, tonotopic, somatotopic) derived from the convergence of information from the prestriate, middle temporal and parietal cortices, and motor information from the FEF (24). The SC also receive projections from the basal ganglia, brainstem and cerebellum. Thus, the SC have a central role in the control of the oculomotor system, receiving information about both stimulus' features (*saliency map*) and individual goals (*priority map*). The role of the SC goes beyond eye movements themselves, the SC are also involved in visual attention. The SC is suggested to modulate attentional signals from higher cortical areas as part of a greater top-down network of attention. Similarly to the experimental evidence of the FEF role in spatial attention, experiments in monkeys have uncovered a disruption in attentional tasks upon SC inactivation (24).

The signals gathered by the SC, are, in turn, relayed to the Paramedian Pontine Reticular Formation (PPRF) and the Mesencephalic Reticular Formation (MRF).

The Paramedian Pontine Reticular Formation and the Mesencephalic Reticular Formation

Saccades are generated by a pulse-step mechanism. For horizontal gaze, the pulse phase is triggered by high frequency neuronal firing in the burst neurons of the PPRF. The burst is expected to overcome the viscosity and inertia of the orbital soft tissue. For vertical gaze, the same role is exerted by the MRF.

Step phase is determined by a baseline firing level, and it counteracts the elastic forces that would bring the eyeball back to its starting position. To achieve the appropriate firing rate a complex integration of the velocity signal is performed by the medial vestibular nucleus, the flocculus of the cerebellum, tonic neurons in the nucleus prepositus hypoglossi (nPH) and in the interstitial nucleus of Cajal (INC).

For horizontal gaze, the appropriate pulse and step components, via the PPRF, nPH and medial vestibular nucleus, project to the ipsilateral abducens (VI) nucleus. One group of neurons in this nucleus, the motor neurons, innervate the ipsilateral lateral rectus muscle, other neurons, the interneurons, generate fibers that cross the midline, ascend in the medial longitudinal fasciculus (MLF) and reach the motor neurons of the contralateral medial rectus, thus making conjugate gaze possible. Communication between the two sides of the MRF is achieved through the posterior commissure (18).

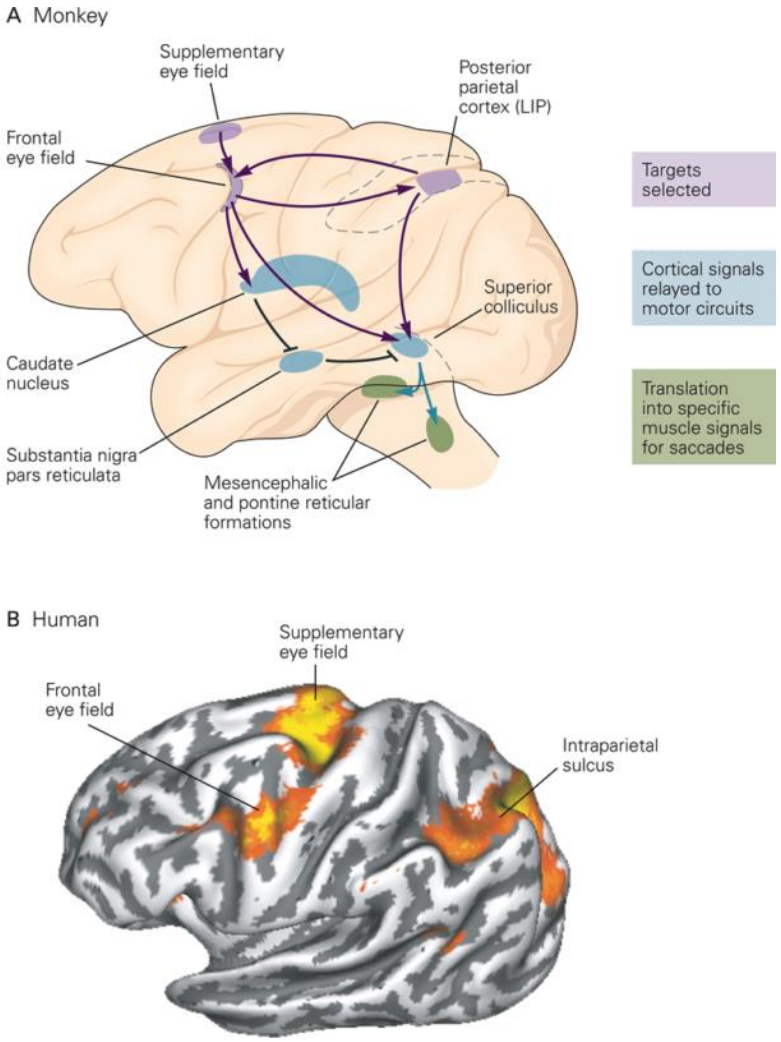

Figure 6 from Principles of Neural Sciences, 5th edition: a) The monkey saccade network b) the cortical human homologues of the monkey FEF, SEF and LIP

The extraocular muscles and cranial nerves

There are six extraocular muscles organized in three antagonistic pairs: the lateral and medial rectus muscles, the superior and inferior rectus muscles and the superior and inferior oblique muscles. Each pair rotates the eye about one principal axis (37):

- Horizontal: either toward the midline (*adduction*) or away from it (*abduction*);
- Vertical: either elevation or depression;
- Torsional: either intorsion or extorsion. In the former the top of the eye moves toward the midline; in the latter it moves away from the nose.

Medial and lateral rectus muscles are responsible for adduction and abduction respectively. Elevation and depression are guaranteed by the coordinated activity of the remaining muscles. In the primary position elevation depends on the contraction of the superior rectus and the inferior oblique muscles. Conversely, the inferior rectus and superior oblique muscles act as depressors. When the eyeballs are adducted, oblique muscles exert their maximal vertical action; however, when they are abducted, rectus muscles act as the vertical movers. Locations of the extraocular muscles are illustrated in Figure 7 (38).

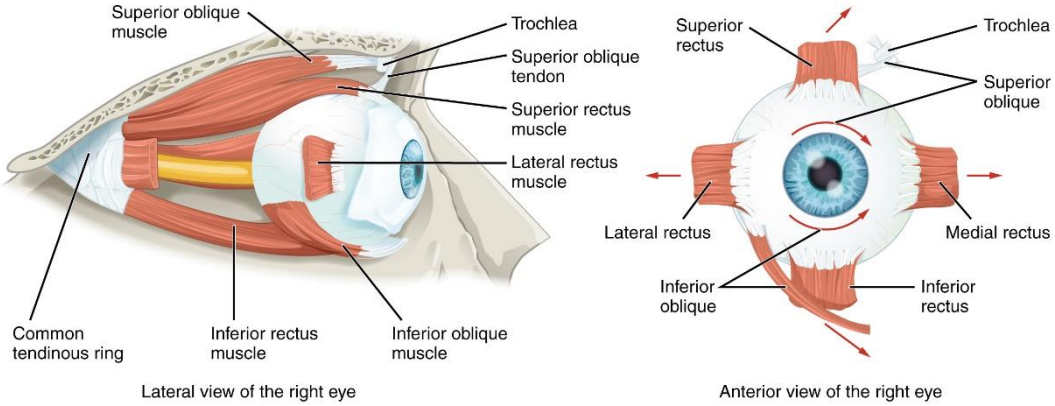

Figure 7 from Lecturio.com: the extraocular muscles

Three cranial nerves are responsible for the extraocular muscles' innervation:

- The oculomotor nerve (III cranial nerve): its somatic motor fibers emerge from the oculomotor nucleus at the level of the SC. Its fibers remain ipsilateral and reach their effectors inside the orbital cavity: every

extraocular muscle except for the lateral rectus and superior oblique. This nerve also contains visceral motor fibers for the intrinsic eye muscles and sensory trigeminal fibers, which carry proprioceptive information and sympathetic postganglionic fibers;

- The trochlear nerve (IV cranial nerve): it exits from the dorsal surface of the caudal midbrain (inferior colliculus). It is the only one whose fibers cross the midline. It innervates the superior oblique muscle;
- The abducens nerve (VI cranial nerve), whose nucleus is located in the pons in the floor of the IV ventricle. Its fibers, emerging from the pons-medullary junction, remain ipsilateral until they reach the lateral rectus muscle.

Other cortico-subcortical areas working in parallel with the saccade network

The oculomotor system is influenced by other important brain areas through a complex network of excitatory and inhibitory signals (39,40). These structures are here outlined:

- Prefrontal cortex (PFC): it modulates oculomotor function during specific tasks. It is involved in working memory, response suppression and with the flexible control of eye movements. Its role has been studied through many experimental paradigms such as the antisaccade test and it is believed to maintain memorized information for ongoing intentional saccades and facilitate anticipatory saccades (prediction), depending upon current external environmental and internal circumstances (37,41);
- Anterior Cingulate Cortex (ACC), it coordinates the activity of the saccade network during complex tasks (37);
- Visual occipital cortex (primary and associative areas): it serves the elaboration of visual inputs (42);
- Basal ganglia: they are associated with the inhibitory control of saccades. The cortical intention to make a saccade follows a path where the FEF excites the caudate nucleus which in turn suppresses the Substantia Nigra pars reticulata (SNr), thus eliminating its inhibition on the descendent pathways;
- Cerebellum: cerebellar fastigial nuclei (CFN) modulate the kinetics of saccades, by regulating metrics such as amplitude and duration, and

effectively preventing wrong responses thanks to a feedback loop mechanism. That is, the cerebellum accelerates and decelerates saccades "online", while they are being executed (43).

In regard to smooth pursuit movements, FEF has a less significant role compared to the Middle Temporal cortex (MT) and the Medial Superior Temporal area (MST). These regions are connected with pontine nuclei and with the cerebellum in order to coordinate ocular and head movements.

What stems thus far from the sole analysis of the networks involved, is that eye movements are neither driven by a trivial, purely motor goal, nor are they mere consequences of sensory inputs. Rather, they are the result of complex network interactions. Eye movements seem to reflect the complexity of these networks and perhaps the cognitive and attentional load that can be associated with scene exploration. Thusly, the neural basis of eye movements provides strong insight in favour of the application of their metrics as a proxy to study complex faculties of the human mind.

Behavioural overlap between attention and eye movements

Having highlighted the anatomical overlap between eye movements and attention, a key question to answer is whether said overlap is purely spatial or it serves a biological purpose.

Under a behavioural perspective, attention cooperates with saccades by means of "pre-saccadic shifts". A pre-saccadic shift is essentially the covert allocating of attention to the saccadic goal, which captures perceptual priors (e.g., extrafoveal information) and thusly helps identifying object that fall on the fovea once the saccade actually happens (44). There is strong evidence supporting the behavioural importance of pre-saccadic shift of attention. As highlighted by the Posner task, the correct allocation of attention speeds up sensitive tasks, so a lack of this boost in sensory processing may be at the basis of the poor outcomes of stroke patients with attentional deficits.

The premotor theory of attention goes even further in stressing this overlap. According to it, attention and actual eye movements are subtended by the same

neural substrates and represent a continuum where spatial attention reallocation is seen as a premotor process functionally equivalent to planning goal directed actions such as eye movements. The evidence supporting this theory is conflicting (16,45–47).

Clinical and experimental detection of eye movements

Neurologists clinically examine smooth pursuit by asking a patient to follow their finger or a pen as it moves back and forth horizontally and vertically. Pursuit is easy to capture and can be assessed relatively reliably at the bedside. Disturbances of smooth pursuit, in the form of saccadic pursuit, are a rather nonspecific finding during this test. To assess saccades, neurologists face the patient with their hands in front of him/her, and alternately extend one finger and ask the patients to look quickly at the extended finger. This test is used to see whether the saccades are normally initiated in response to the finger movements. In contrast to pursuit, saccadic eye movements are so fast, that they are extremely challenging to evaluate accurately with the naked eye. Hence, we need a tool to record saccades reliably, assess their speed, and the latency with which they are initiated.

The gold standard for eye movements detection nowadays is based on the use of a search coil, implanted in a modified contact lens and inserted into one eye, while the subjects' head is positioned in a graded magnetic field (39,48). When the eye with the device moves, it induces a current in the coil, which flows into the electric wire connected to it (Faraday-Neumann-Lenz law) and this in turn can be measured to detect the direction of gaze. Even though this is the most precise method for eye movements detection, with a spatial resolution down to 0.1 degrees, the method is also irritating to the eye and quite painful. Thusly, the recording can only be performed for short amounts of time, even when the subject has received a topical anaesthetic, plus the hygiene of the cornea must be maintained. Additionally, recording can become inaccurate when the contact lens containing the search coil slips over the cornea.

The invasiveness of a search coil is not feasible in healthy humans where the gold standard is eye tracking based on infrared (IR) light. In infrared-light based eye tracking devices, an IR light is projected onto the cornea. The cornea reflects the

infrared light, and its point of reflection (glint) is recorded by a charge-coupled device camera. While the head is still, the bright corneal point of reflection can be assumed static. Conversely, when illuminated by the IR light, the pupil is dark (see figure 8). The pupil and cornea can thusly be precisely detected and the relative movements of the pupil in respect to the fixed cornea, be measured (49).

Subjects are first instructed to look at a few set locations for calibration. The current gaze direction is then recorded and calculated relative to the set calibration locations. This method allows the examiner to record the direction of gaze both horizontally and vertically with a spatial resolution of 0.25-0.5 degrees (39).

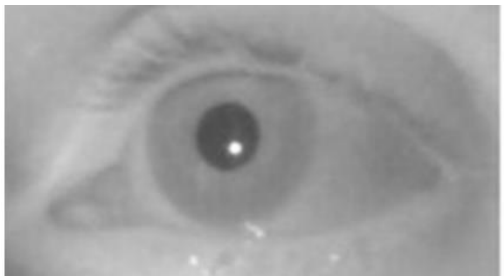

Figure 8 from Gneo M., D'Alessio T. et. Al 2012, the dark pupil and the bright corneal reflection spot

STROKE AND EYE MOVEMENTS

Having discussed the physiological presentation of eye movements and the networks that govern them, it is now time to tackle the anomalies that affect eye movements during stroke.

What is stroke?

According to the American Heart Association and the American Stroke Association: "Central nervous system infarction (stroke) is defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury. Central nervous system infarction occurs over a clinical spectrum: Ischemic stroke specifically refers to central nervous system infarction accompanied by overt symptoms, while silent infarction by definition causes no known symptoms. Stroke also broadly includes intracerebral haemorrhage and subarachnoid haemorrhage." (50)

In the neurological ward, stroke arguably ranks first in importance due to its high frequency and often sudden and severe presentation that requires a quick recognition and treatment (51).

Stroke presents itself as an abrupt presentation of a neurological deficit, ranging from a mild disorder that goes unnoticed by the patient to hemiplegia and coma, and, relevant to this dissertation, it may present as an affection of both ocular movements and attention.

Being a cerebrovascular disease, the aetiologies of stroke have typically been split into *ischemic* and *haemorrhagic.*

Ischemic stroke

The two major causes of ischemic stroke are atherosclerotic-thrombotic disease and cerebral embolism.

The latter is the most common cause of ischemic stroke, it typically develops rapidly, reaching its peak almost at once and prodromal symptoms are usually lacking. The manifestations may vary from this temporality, in which case one can suspect a propagating thrombotic process in the occluded vessels. Usually, the embolic material consists of fragments from a thrombus adhering to the endocardial surface of the cardiac chambers or valves. Similarly, the thrombotic

material can derive from infectious processes of the aortic or mitral heart valves in the context of an endocarditis. In some cases, in a severely stenotic vertebral or carotid artery, the distal portion of a thrombus may detach giving rise to artery-to-artery embolism. Furthermore, a clot that originates in the venous system can bypass the lungs and reach the systemic circulation if a cardiac wall is open, e.g., patent foramen ovale (PFO). Lastly, embolism may be caused by fat, tumor cells, amniotic fluid or air bubbles in rare circumstances.

The embolus usually stops at the bifurcation or natural narrowing of the lumen of an intracranial vessel (see vascular anatomy of stroke, discussed later). Given this mechanism, when it comes to the risk factors of cerebral embolism, they share the common thread of somehow favouring the deposition and later embolization of thrombotic material, and these are (52):

- atrial fibrillation (AF), it appears as the most prominent cause of the condition, with patients affected by chronic AF being five to six times more liable to stroke (53). The risk conferred by AF increases with age;
- sinus arrhythmia;
- valvulopathies (mitral valve stenosis, prosthetic valves, marantic and infectious endocarditis);
- ischemic heart disease (particularly recent infarction, hypokinetic portions of the muscle, mural aneurysms and thrombi);
- dilated cardiomyopathy;
- intracardiac tumors;
- septal anomalies.

Atherothrombosis has a more variable presentation than that of embolism, it can affect both large intracranial vessels, large extracranial vessels and small vessels (lacunes). The ensuing stroke can stem from the reduced blood flow of the affected vessel and from a mechanism of embolization (artery-to-artery). In the first case, the damage may stem from the occlusion and reduced blood flow of the affected artery, or, when affecting proximal vessels, it may lead to an infarction in the territory between arterial branches that are susceptible to reduced blood flow – “borderzone infarction”.

In contrast with the abrupt presentation of cerebral embolism, atherothrombosis may be preceded by prodromal, minor signs of focal neurological disfunction,

transient ischemic attacks (TIAs). Even though cerebral embolism may rarely manifest as a TIA, when the TIAs are recurring and stereotyped, one should suspect an atherothrombotic aetiology (51).

The risk factors for cerebral atherothrombosis are the same as the ubiquitous vascular disease (atherosclerosis) itself:

- hypertension;
- age;
- hypercholesterolemia;
- cigarette smoke;
- *asian origin* (*only for the intracerebral variety, not for the extracranial disease*);
- diabetes.

Pathophysiology of ischemic stroke

Cerebral blood flow (CBF) shows self-regulatory properties, remaining constant for an average arterial pressure between 60 and 150 mmHg. Self-regulation is due to the variation of PaCO2, myogenic factors that mediate vasoconstriction/vasodilation, and nervous modulation of vascular tone (54). The cerebral metabolism is highly specialized and critically dependent on oxygen and glucose supply. Regardless of the aetiology of ischemic stroke, whenever there is an unreversed drop in the CBF, this leads first to an increase in the oxygen extraction fraction (OEF), but eventually the lack of oxygenation unleashes a series of catastrophic events. The cell switches to the anaerobic glycolysis, a rapid disfunction in the energy supply system ensues and this ultimately leads to a failure to maintain membrane ion gradients and also to an increased release of excitatory amino acids, which causes excitotoxicity (55). Early activation of the AMPA receptor determines an accumulation of intracellular water and Na+, neuronal swelling and cytotoxic oedema. While NMDA receptor activation, through an increased cytosolic calcium concentration, results in the release of lipases, nucleases, proteases, production of NO and free radicals. Free radicals in turn lead to peroxidation of the membrane lipids, destruction of the membranes, protein oxidation and further DNA damage. Cerebral ischemia is also a potent inducer of the gene expression of apoptosis related proteins such as Bcl-2, various heat shock proteins and caspases.

Recent studies show that oligodendrocytes, due to their large size and low levels of antioxidants, are extremely susceptible to the damages of oxidative stress, Their disfunction leads to damage of the myelinated bundles and functional disconnections in regions far from the ischemic area, a concept known as *diaschisis* (52).

Additionally, increasing evidence suggests that the activation of microglia has a dual function in ischemic stroke: it can promote neural degeneration but also neurogenesis and synaptic recovery (56).

The central, necrotic, part of the ischemic area is called “the core" and is composed of non-recoverable tissue. Around the lesion, however, it is possible to identify a region termed “*the ischemic penumbra*", made up of tissue that is potentially salvageable by re-establishing an adequate blood flow as soon as possible (Time = Brain) (57).

Haemorrhagic stroke

Intracerebral haemorrhage is the third most frequent cause of stroke. This type of stroke is mostly caused by hypertensive primary intracerebral haemorrhage, ruptured saccular aneurysms and vascular malformations, or use of anticoagulants. The clinical presentation of intracerebral haemorrhage is often that of an unbearable headache, acute reactive hypertension, hemiparesis, vomiting. Seizures can ensue in the first few days, coma appears with massive ventricular bleeding or if there is substantial distortion of the midbrain (51).

The initial brain damage is related to mass effect from the initial hematoma and hydrocephalus, it occurs immediately after the haemorrhage through the first few days. Subsequently, over days to weeks, the activation of injurious pathways (including inflammation, iron and blood-related toxicity) and oxidative stress further the damage (58).

Vascular anatomy of stroke

To understand the clinical manifestations of stroke, it is crucial to keep in mind the normal neurovascular anatomy. Vascular anatomy is highly variable, but in most brains, it is organized as follows.

The anterior circulation represents the territory belonging to the carotid arteries and vascularizes most of the brain parenchyma. The two common carotid arteries, originating from the aortic arch, branch into external and internal carotids. The internal carotid enters the skull and penetrates the cavernous sinus. Just outside the cavernous sinus, the ophthalmic artery originates from it and, subsequently, so do the other four terminal branches: anterior cerebral artery (ACA), middle cerebral artery (MCA), anterior choroidal, and posterior communicating artery.

The posterior circulation, vascularized by the vertebrobasilar system, on the other hand, supplies a small portion of the brain parenchyma, but it is critical for this discussion, since it supplies many of final relay structures dedicated to eye movements. The vertebral artery (VA) originates bilaterally from the subclavian arteries, passes the foramen magnum, and terminates as the two VAs join to form the basilar artery (BA) at the bulbo-pontine level. The posterior-inferior cerebellar arteries (PICA) are collateral branches of the intracranial tract of the VAs.

The basilar artery runs along the midline, forms the two superior cerebellar (SCA) and anteroinferior cerebellar (AICA) arteries, and then bifurcates into the two posterior cerebral arteries (PCA). The circle of Willis consists of the two ACAs, the anterior communicating artery, the two posterior communicating arteries, and the two PCAs. The arteries and their territory of vascularization can be seen in figures 9-11.

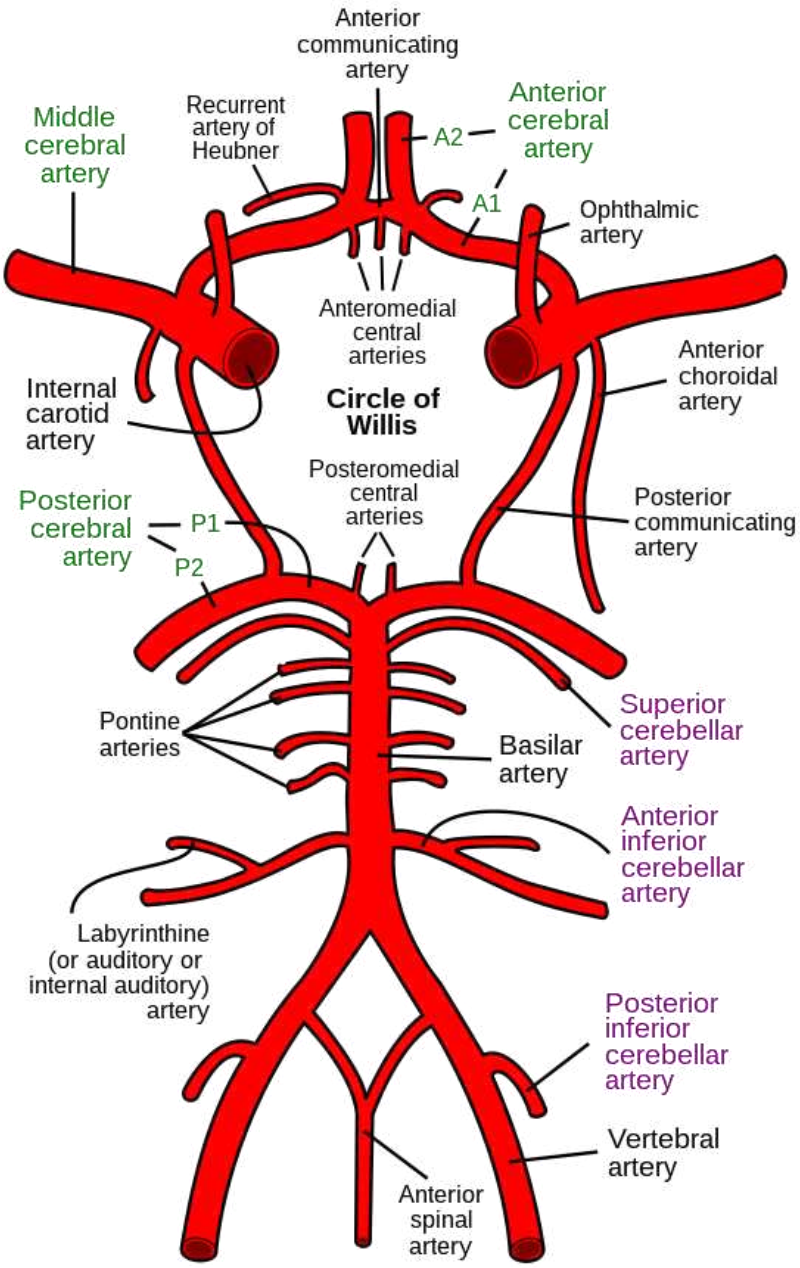

Figure 9, the circle of Willis

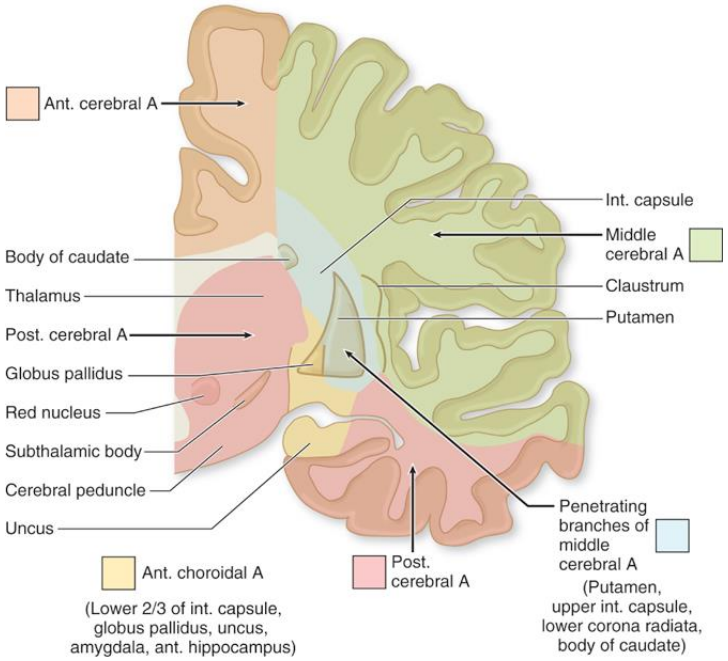

Figure 10 from Adam and Victor's principles of neurology 11th ed., vascular territories of the major cerebral vessels;

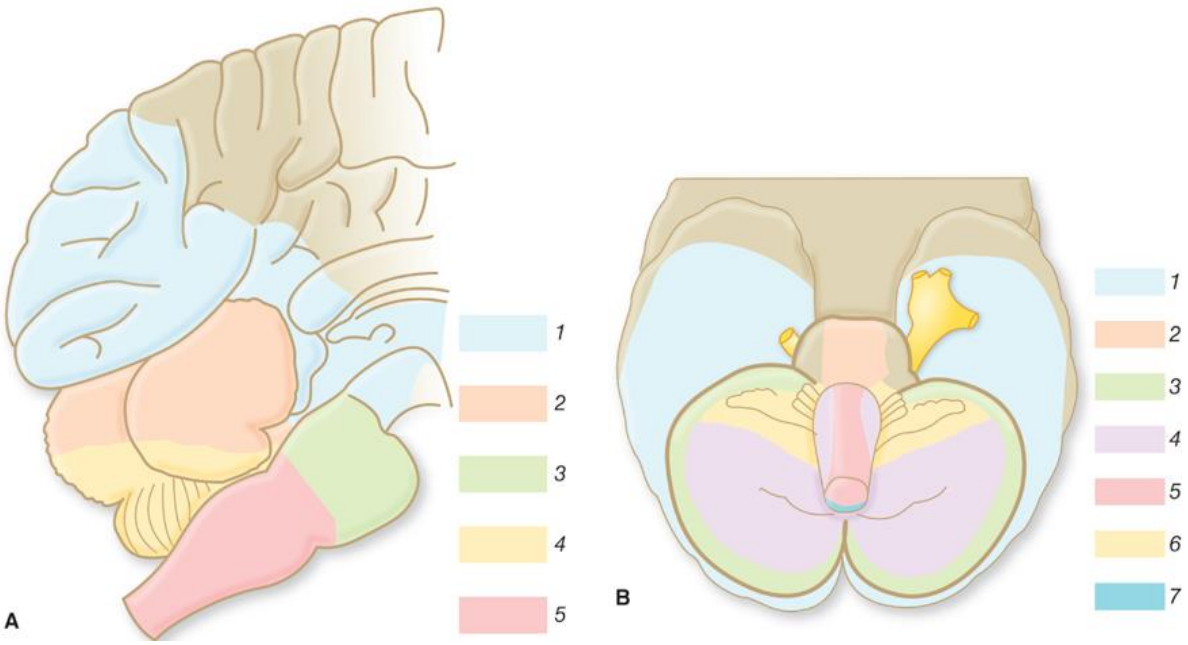

Figure 11 from Adam and Victor's principles of neurology 11th ed., vascular territories of the vertebrobasilar system arteries; ***a)*** *1=PCA, 2=SCA, 3=BA, 4=PICA, 5=VA;* ***b)*** *1=PCA, 2=SCA, 3=paramedian branches of the BA and spinal artery, 4=PICA, 5=VA, 6= AICA, 7= dorsal spinal artery*

As previously highlighted, much of our brain is dedicated to the fine regulation of eye movements; it should not come as a surprise, then, that infarctions and haemorrhages in many different brain areas can result in ocular dysmotility. Some of the typical stroke related syndromes affecting ocular motility will be discussed first, secondly, the discussion will focus on newly discovered stroke related impairments of ocular motility and inattention that are still under study. Obviously, ocular dysmotility may stem from other conditions affecting the nerves and brain, such as demyelinating diseases, masses and infections, but that is beyond the scope of this dissertation and the focus will solely be on syndromes arising from central sites of vascular injury.

Stroke syndromes affecting ocular motility

Brainstem syndromes

A summary of the discussed syndromes is given in Table I.

Eponym	*Site*	*CN*	*Tracts involved*	*Signs*	*Usual cause*	*Artery*
Weber syndrome	Base of midbrain	III	Corticospinal tract	Oculomotor palsy with crossed hemiplegia	Vascular occlusion, tumor, aneurysm	PCA
Claude syndrome	Tegmentum of midbrain	III	Red nucleus, superior cerebellar peduncles after decussation	Oculomotor palsy with contralateral cerebellar ataxia and tremor	Vascular occlusion, tumor, aneurysm	PCA
Benedikt syndrome	Tegmentum of midbrain	III	Red nucleus, corticospinal tract, and superior cerebellar peduncles after decussation	Oculomotor palsy with contralateral cerebellar ataxia, tremor, and corticospinal signs, may have choreoathetosis	Infarct, haemorrhage, tubercoloma, tumor	PCA

Millard-Gubler syndrome and Raymond-Foville syndrome	Base of pons	VII and often VI	Corticospinal tract	Facial and abducens palsy and contralateral hemiplegia, sometimes gaze palsy to side of lesion	Infarct or tumor	BA
INO	MLF	VI, III indirectly	MLF	Loss of adduction of the ipsilesional eye on conjugate gaze in the contralateral direction	Demyelinating, ischemic, neoplastic, inflammatory lesions	BA
One and a half syndrome	MLF and PPRF	VI, III indirectly	MLF	Ipsilateral conjugate gaze palsy and paralysis of adduction of the ipsilateral eye on conjugate gaze to the opposite side	Pontine haemorrhage	BA

Table I readapted from Principles of Neurology 11th edition (51)*and Neurologia clinica 3rd edition*

Weber, Claude and Benedikt syndrome

An infarction of the interpeduncular branches of the posterior cerebral arteries, can lead to Weber syndrome, Claude syndrome and Benedikt syndrome. These syndromes arise from an infarction of the midbrain, which hosts many important structures such as the nucleus for the III cranial nerve, the corticospinal tract, the red nucleus and the superior cerebellar peduncles. Due to damage at the nucleus or fascicles of the III nerve, the three share the common feature of an ipsilateral III nerve palsy, which, when complete, manifests as diplopia, ptosis, iridoplegia, inability to rotate the eye upward, inward or downward, cycloplegia, and a "down and out" position due to the remaining action of the spared nerves (IV & VI). The oculomotor palsy is often incomplete though, and the pupils may be spared if only the lower midbrain is affected by the inciting insult.

In Weber syndrome, a concomitant damage at the corticospinal tract before the decussation of the pyramids leads to contralateral hemiparesis/hemiplegia with upper motor neuron signs (59). In Claude syndrome, the red nucleus, superior

cerebellar peduncles after decussation, and dentatorubro fibers are involved (60). This gives rise to contralateral cerebellar hemiataxia and tremor. Patients may also have a dissociated horizontal nystagmus of the abducting eye due to internuclear ophthalmoplegia (INO) if the medial longitudinal fasciculus (MLF) is involved.
Lastly, Benedikt syndrome is caused by a large damage that combines the features of the aforementioned syndromes and also includes choreoathetotic movements.

Millard-Gubler and Raymond-Foville syndrome

Millard-Gubler syndrome is due to a low, ventral pontine lesion, clinically manifest as an ipsilateral facial and/or abducens palsy (leads to diplopia, internal strabismus or esotropia, and loss of power to rotate the affected eye outward). The cranial nerve disturbances are combined with a contralateral hemiparesis or hemiplegia, due to the damage at the corticospinal tract (61). Raymond-Foville syndrome is virtually indistinguishable from Millard-Gubler, except for a more dorsally extended damage. The more dorsal extent of Raymond-Foville Syndrome involves the adjacent parapontine reticular formation (PPRF). Thus, the disease can present with conjugate lateral gaze palsy, adding to the abducens palsy the inability to adduct the contralateral eye towards the lesion (62).

Internuclear ophthalmoplegia

A small paramedian pontine infarction can lead to internuclear ophthalmoplegia (INO). As previously highlighted, conjugate gaze is guaranteed by the activity of the MLF, which pairs the excitation of one VI nucleus with the activation of the contralateral III nucleus (see fig. 12). Infarctions in the region traversed by the MLF, lead to an impairment or loss of the adduction of the eye ipsilateral to the lesion. For instance, with a lesion of the left MLF, the left eye will fail to adduct while a patient is looking to the right. Nystagmus of the abducting eye might be present. The MLF also contains axons that originate in the vestibular nuclei and regulate vertical eye position, thusly INO may also lead to a vertical deviation of the eye (51).

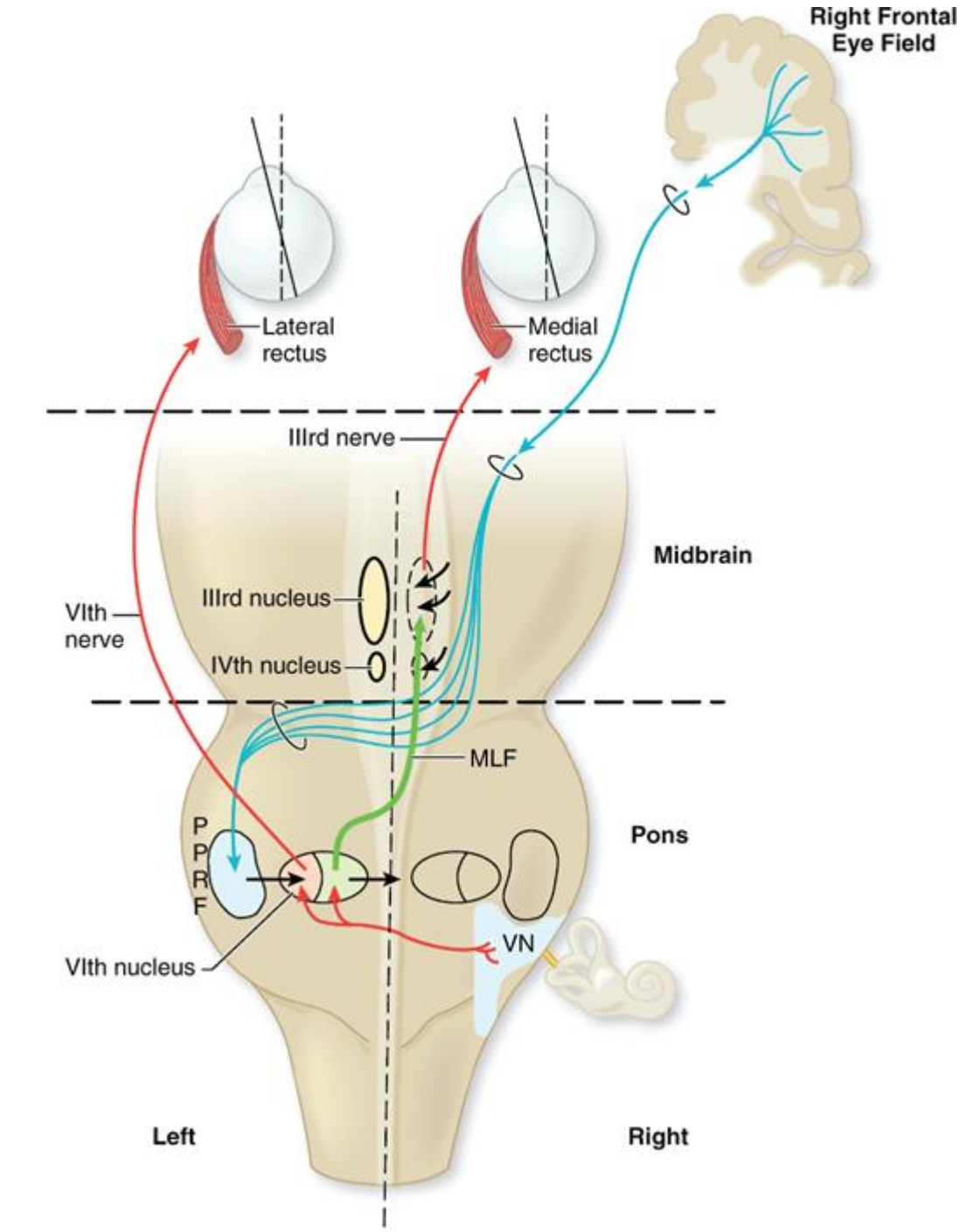

Figure 12 from Adam and Victor's Principles of neurology 11th ed.

One and a half syndrome

Pontine haemorrhage and ischemia may simultaneously damage many of the structures previously mentioned, when the lesion involves the PPRF and the adjacent MLF, the patient presents with "one and a half syndrome" (63). Clinically, the syndrome is characterized by both an ipsilateral conjugate gaze palsy and

paralysis of adduction of the ipsilateral eye on conjugate gaze to the opposite side (INO). One eye remains fixed in the midline, while the other can only make abducting movements.

Vertical gaze disturbances

Vertical gaze disturbances are only rarely caused by stroke. When the dorsal midbrain is infarcted, lesions may involve the vertical gaze center (rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and the interstitial nucleus of Cajal (INC) and its connections. The patient presents with Parinaud syndrome, characterized by paralysis of upward gaze, light-near dissociation (pseudo-Argyll Robertson pupils), bilateral lid retraction (Collier's sign) and convergence retraction nystagmus (64).

Cortical Strokes

Frontal eye field damage

An acute, destructive lesion involving the frontal lobe will cause a contralateral hemiparesis and a gaze palsy in the contralateral direction. The eyes, governed by the remaining normal hemisphere, will be deviated to the affected side. The patient will at first be unable to generate saccades to the contralesional side. Because the pursuit pathways originating in the occipitoparietal region may not be involved with a small frontal lesion, a patient might be able to follow slowly moving targets in either horizontal direction. Furthermore, appropriate tonic ocular deviations may be produced by caloric irrigation. When the lesion is confined to one frontal lobe, the paralysis of horizontal saccades is transient, regressing in a matter of days, usually before any improvement is noticed in the hemiparetic extremities (60).

Parietal eye field damage

The eye movements' disruption following PEF damage is usually subtle. A lesion involving the parietal cortex is manifest mainly for reflexive saccades and may lead hypometria (reduced saccade amplitude) and increased saccade latency (65).

Evidence for common attention and eye movement deficits in stroke

The literature concerning both inattention and eye movements in stroke patients is quite limited. Patients affected by unilateral spatial neglect also show contralesional and directional hypokinesia (66). That is, patients are slower in generating saccades to the contralesional side that tend to be hypo metric, most commonly toward the left visual field for right hemisphere lesions.

In addition, when following multiple moving targets, patients with right-hemisphere (RH) lesions with or without neglect, tend to make more fixations than healthy controls, suggesting an impairment in visual search and processing (67).

Moreover, when engaged in a free viewing task, patients with neglect tend to show a shift of their mean gaze position toward the side of the lesion. Importantly, using the mean gaze position to predict the presence/absence of neglect yields better results in terms of sensitivity and specificity when compared to many paper-based tests currently used clinically (68).

Finally, there is strong evidence supporting the role of saliency in mediating the amount of asymmetry in the mean gaze position of inattentive patients (69). During a free viewing task of pairs of flipped images, neglect patients showed a rightward bias that was somewhat mediated when a salient element was localized to the left side of the picture (70).

THE EXPERIMENTAL STUDY

Introduction

The aim of this study was to see if measures of eye movements, which are free of linguistic limitations and are highly ecological, can provide a measure of attention function in patients with stroke. Specifically, we correlated several neuropsychological measures of attention impairment and metrics extracted from eye-tracking during spontaneous behaviour. Patients were tested in two conditions: free viewing of natural pictures, and free viewing of a blank screen. In line with other studies (66–68) , we report that eye movements during visual exploration are correlated with attention deficits; in addition, we found that the correlation was stronger when looking at a blank screen, a condition in which spontaneous (intrinsic) activity is predominant. Finally, we related these measures to the side of the stroke to study possible hemispheric asymmetries.

Materials and methods

The eye tracker

The Eye Tracker records the eyes' position and their movements. In this study the screen-based Eye Tracker EyeLink 1000 Plus (SR Research®) was employed. The device has a sampling-rate of up to 2000 Hz, an accuracy of 0,25°-0,50° and a saccade resolution of 0,25°. The Remote Mode without head support and chin-rest was used in our experiment (sampling-rate: 1000 Hz). This mode makes the participant's set-up simple and comfortable: the individual sits in front of the device while looking at the computer screen immediately above. An infrared light source is directed toward the cornea and the camera tracks its reflection. In addition, the machinery records slight head movements by keeping track of an adhesive target temporarily placed between the participant's eyebrows. A rapid session of calibration and validation precedes the test to separate eye and head movements and to adjust the device to the individual.

The computer screen had a resolution of 1920x1080 pixels, thusly, by dividing the screen in two spaces on the vertical and horizontal axis, we were able to define left-sided fixations as fixations happening in the 960 pixels on the left of the midline (after normalizing the data, we defined the x of those fixations as $x<0$,

with the midline being x=0) and the right-sided fixations as the ones happening on pixels greater than 960 (here the x was set as >0). Similarly, the upper 540 pixels identified the upper quadrant (y<0) and the lower 540 pixels identified the lower quadrant (y>0).

The OCS hearts test

The OCS (Oxford Cognitive Screen) is a first-line, paper-based, stroke-specific test developed at the university of Oxford (71). The complete OCS tests manu domains of function including language, praxis, numerical cognition, memory, spatial and controlled attention. For our topic of interest, we only extracted the scores from the Hearts cancellation task that measures visuospatial attention. During the Hearts task, the patient is asked to cross out hearts that are made of a closed shape and leave out broken hearts in a printed picture (see fig. 13). In the subsequent statistical analyses, we employed several metrics extracted from the hearts cancellation task of the OCS. Specifically:
OCS_Hearts.overall.accuracy defined as the total number of hearts the patient was able to correctly cross, *Hits_Right* was defined as the number of hearts correctly crossed in the right hemispace; *Hits_Left* was defined as the number of hearts crossed in the left hemispace. Lastly, *R-L* was defined as the subtraction: Hits_Right - Hits_Left that measures biases in visuospatial attention.

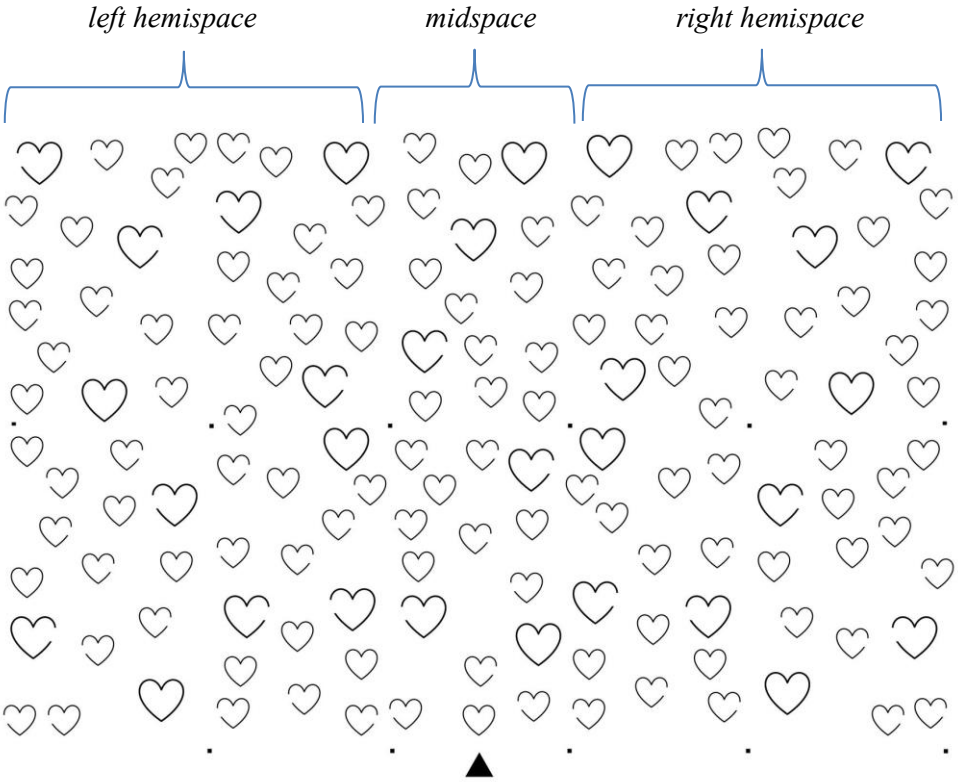

Fig 13 the hearts cancellation task of the OCS

The Posner task

We previously introduced the Posner cueing task (22). The classical experiment introduced by Posner himself has been modified and employed in many different versions throughout the years (72,73); here, the Posner cueing task employed was in line with the original version proposed by the author. Subjects sat in front of a desk, centered 60 cm from a computer screen, holding a button that they were instructed to press whenever they saw a target stimulus (i.e., a red dot) appearing either on the left or on the right of a fixation cross at the center of the screen. During the task, subjects were instructed to keep their eyes on the central cross that served as the fixation center. Before the presentation of each trial, a cue appeared at the fixation center for a time interval ranging between

1000 and 2000 milliseconds. The cue was an arrow that could point either to the left or right side. Subjects were instructed to covertly direct their attention to the side pointed by the arrow, that is, subjects should not move their eyes to that side but just attend to that location, try to be more aware of it. On 75% of the trials (*valid cue trials*), after the cue appearance, a stimulus appeared on the side pointed by the arrow. Conversely, on 25% of the trials (*invalid cue trials*), the stimulus appeared contralaterally. Subjects were aware of this and, given the two percentages, they learned the association between the cue and the appearance of the stimulus and tended to direct their attention to the side pointed by the arrow in the majority of cases. Subjects then pressed the button they were holding as quickly as possible after seeing the stimulus and their reaction times (RTs) were measured.

The experimental session

The recordings were collected at the University Hospital of Padua and all the patients collected gave their informed consent prior to their participation to the experimental session, that consisted in two phases: the free visual exploration of a blank screen ("*blank viewing*") and the free visual exploration of a set of 20 images ("*free viewing task*").

Specifically, patients were asked to look at a blank screen (the whole screen was grey) for 3 minutes first, this blank viewing condition is thought to mirror the resting state dynamics of our brain. Then, subjects had to look at 20 pictures presented on the screen for 10 seconds each. Subjects were told to look at images as if they were watching TV. Neither specific tasks nor questions were prepared so as to guarantee the most spontaneous and ecological conditions achievable.

Preliminarily to the start of the eyetracking session, the participant was asked to sit in front of a desk where the computer screen and the Eye Tracker had been positioned and to find a comfortable position. He/she was centred on the display at a distance of ~60 cm. In spite of the target put on the forehead, whose function has been already described, subjects were asked to maintain a stable posture and head position, contributing to a more accurate and precise recording. With the exception of the computer screen, the room was almost in utter darkness. Otherwise, the lights would have interfered with the device, creating artefacts (e.g., impacting pupil dilation). Once the viewer was correctly positioned, the experimenters adjusted the pupil detection and the corneal reflection thresholds to maximize the quality of data acquisition.

Both eyes were sampled, except cases where visual disorders or diseases like cataract affected one of the eyes. The viewers were allowed to put on their glasses if it was necessary for an optimal visual acuity. The subject was then asked to fixate thirteen calibration points on the screen to set-up the Eye Tracker. This process was carried out twice (calibration and validation) to validate the calibration accuracy and get an estimate of the calibration error. At this point the real experimental session, which consisted of the blank viewing and free image viewing tasks, started.

Images were real-world scenes derived from the Place365-Standard dataset (74), a database used in a previous work on 120 young healthy participants (75).

For our following analysis, the subset of 20 images was selected based on the gaze entropy calculated on the free-exploration patterns of young healthy people. Images with the highest and lowest values were used for the present study, to maximize the possibility of identifying oculomotor abnormalities affecting the whole fixations pattern. The whole session was exceptionally brief to foster clinical suitability of this approach: it only took around 10 minutes per subject, including the explanation of the procedure, the calibration/validation procedure and the actual tests.

Participants

A total of n=60 first time stroke patients were recruited as part of a larger ongoing project on stroke (see inclusion and exclusion criteria in table II). A summary of the patients' clinical findings, brain lesion characteristics and eye-movements metrics is given in table III. The subjects were studied with fMRI/MRI, hdEEG, they were administered neuropsychological assessments including the OCS, and their eye tracking data was collected within 2 weeks after stroke onset. Of the 60 patients recruited, at the time of the present analysis, a total of n=34 had completed both the eye tracking and the OCS testing. All of the 34 patients completed the free viewing task during the eye tracking acquisition. Due to data loss, only 28 of those 34 also completed the blank viewing task. In addition to the stroke patients, 14 age-matched healthy subjects underwent the same eye tracking procedure to serve as controls.

Patients	*Inclusion criteria*	*Exclusion criteria*
-60 patients from Clinica Neurologica and Stroke Unit AOPD	-Age 18 or higher; -First symptomatic stroke, ischemic or hemorrhagic in etiology; -Time of enrollment: < 2 weeks from stroke onset; -Awake, alert, and capable of participating in research.	-Previous stroke based on clinical imaging; -Stroke in multiple vascular territories; -mRS pre-event >2; -Fazekas score >/= 2; -Bedridden during hospitalization; -Presence of central nervous system tumors; -History of dementia; -Previous central nervous system surgeries; -Schizophrenia, bipolar disorder, major depression, or other severe psychiatric conditions;

		-Other medical conditions that preclude active participation in research and may alter the interpretation of the behavioural/imaging studies; -Inability to provide consent; for aphasic patients informed next-of-kin provide consent.

Table II: inclusion criteria

Patient's ID	*Cm_X during blank viewing*	*Lesion site*	*OCS scores (overall, R, L, R-L)*	*Age, sex*
s_01	missing	right striatum and internal capsule	48, 19, 19, 0	80 f
s_02	missing	right striatum and internal capsule	42, 17, 18, -1	55 f
s_03	missing	left temporal lobe, striatum and internal capsule	50, 20, 20, 0	70 m
s_04	missing	left cerebellum	42, 13, 19, -6	81 m
s_06	-0.29, left	left frontobasal and temporal lobes	45, 18, 19, -1	72 f
s_07	-0.23, left	left corona radiata	49, 19, 20, -1	80 m
s_08	-0.04, left	left striatum and internal capsule	44, 16, 18, -2	69 m
s_09	-0.27, left	left striatum and internal capsule	24, 8, 11, -3	58 m
s_10	-0.23, left	left pons and medulla oblungata	36, 14, 17,-3	78 f
s_11	-0.22, left	left striatum and internal capsule	49, 20, 19, 1	63 f
s_14	-0.26, left	left frontal and temporal lobes, striatum and internal capsule	46, 18, 19, -1	57 m
s_15	-0.10, left	left frontal and parietal lobes	48, 20, 19, 1	72 f
s_16	-0.48 left	left frontal and parietal lobes, insula, striatum and internal capsule	0, 0, 0, 0	81 f
s_17	-0.09, left	right corona radiata	48, 19, 19	58 m
s_18	-0.01, left	right parietal lobe and insula	42, 14, 19, -5	68 f
s_19	missing	left centrum semiovale	48, 19, 19, 0	72 m
s_20	0.01, right	right occipital cortex and hippocampus	48, 20, 19, 1	52 m
s_21	-0.07, left	left temporal and occipital lobes	50, 20, 20, 0	63 m
s_22	-0.14, left	right temporal and occipital lobes	49, 19, 20, -1	48 m
s_23	-0.31, left	right frontal and parietal lobes, insula	48, 18, 20, -2	54 m
s_24	-0.23, left	left striatum and internal capsule	47, 20, 18, 2	68 m
s_26	0.02, right	left occipital cortex and thalamus	49, 20, 19, 1	57 m
s_28	0.03, right	right striatum, internal capsule and insula	44, 18, 17, 1	61 f
s_29	-0.32, left	right occipital lobe	41, 17, 16, 1	49 m

s_35	-0.42, left	right frontal, temporal and parietal lobes, striatum and internal capsule	44, 19, 18, 1	77 m
s_38	-0.22, left	left frontal and parietal lobes	48, 18, 20, -2	39 m
s_39	0.01, right	left occipital cortex and thalamus	44, 17, 18, -1	81 m
s_41	0.029, right	left temporal lobe, striatum and internal capsule	0, 0, 0, 0	78 f
s_42	-0.04, left	left cerebellum	48, 20, 19, 1	40 f
s_43	-0.12, left	right pons	40, 14, 18, -4	66 m
s_45	-0.12, left	right frontal lobe, striatum and internal capsule	10, 10, 0, 10	80 f
s_50	-0.16, left	left frontal, temporal and parietal lobe	50, 20, 20, 0	40 f
s_51	-0.20, left	left parietal and temporal lobe	29, 0, 19, -19	71 m
s_54	missing	right frontal lobe	50, 20, 20, 0	35 f

Table III a summary of the patients' characteristics

Data collection

As previously mentioned, a total of n=34 patients had completed both the OCS hearts cancellation task and the free viewing task, and n=28 completed both the OCS and blank viewing. Eye movements data from a total of 14 healthy subjects were also collected to serve as controls.

Regarding eye movement metrics, both standard and innovative metrics were employed in this study. As for the new metrics employed in this study, *fix_LI* (fixation laterality index) is defined as the number of fixations on the right side minus the fixations on the left side divided by their sum.

$$fix_{LI} = \frac{fix_{dx} - fix_{sx}}{fix_{dx} + fix_{sx}}$$

Sac_LI (saccadic laterality index) is defined as the difference between rightward saccades and leftward saccades, divided by the total number of saccades. Of note: the direction of saccades is independent of the starting side, that is, a leftward saccade can happen both in the left and right visual hemifield. Hence the fix_LI is concerned with the amount of fixations in one hemifield (*a metric of spatial representation asymmetry*), whilst the sac_LI takes into account the directionality of gaze (*a metric of directional hypokinesia*).

$$sac_{LI} = \frac{sac_{dx} - sac_{sx}}{sac_{dx} + sac_{sx}}$$

The center of mass (*cm*) is defined as the barycentre of the fixation density map, and it has a horizontal (*cm_x*) and a vertical component (*cm_y*).

The saccade main sequence (*sac_mainSeq*) is defined as the linear relationship between the amplitude and the velocity of a saccade.
A summary of the metrics employed, and their shortened aliases is given in table IV.

Fixations' metrics	-Total number of fixations -Average number of fixations during image viewing -Standard deviation of the number of fixations for image viewing -Average fixation duration -Standard deviation of fixation duration -Fixation rate -Fixation laterality index -Center of mass (X and Y axis)	-fix_Ntot -fix_NtriM -fix_NtriSD -fix_durM -fix_durSD -fix-rate -fix_LI -cm_X & cm_Y
Saccades' metrics	-Saccade laterality index -Total number of saccades -Average saccade amplitude -Standard deviation of saccade amplitude -Average saccade velocity -Standard deviation of saccade velocity -Saccade main sequence -Number of square wave jerks	-sac_LI -sac_N -sac_amplM -sac_amplSD -sac_velM -sac_velSD -sac_mainSeq -N_swj
Blinks' metrics	-Total number of blinks -Blink rate -Average number of blinks during image viewing -Standard deviation of the number of blinks for each image -Average blink duration -Standard deviation of blink duration	-bli_N -blink_rate -bli_NtriM -bli_NtriSD -bli_durM -bli_durSD

Table IV the metrics utilized for the statistical analysis

Statistical analysis

All the subsequent statistical analyses were performed by means of R software (R Core Team, 2019).

Results

As a first step, we computed a correlation matrix (see fig. 14) between the eye movements' metrics and the OCS test scores, for both the free image viewing and blank viewing tasks. We measured an overall higher correlation in the blank viewing condition as compared to the image viewing condition (see fig. 14 top, bottom).

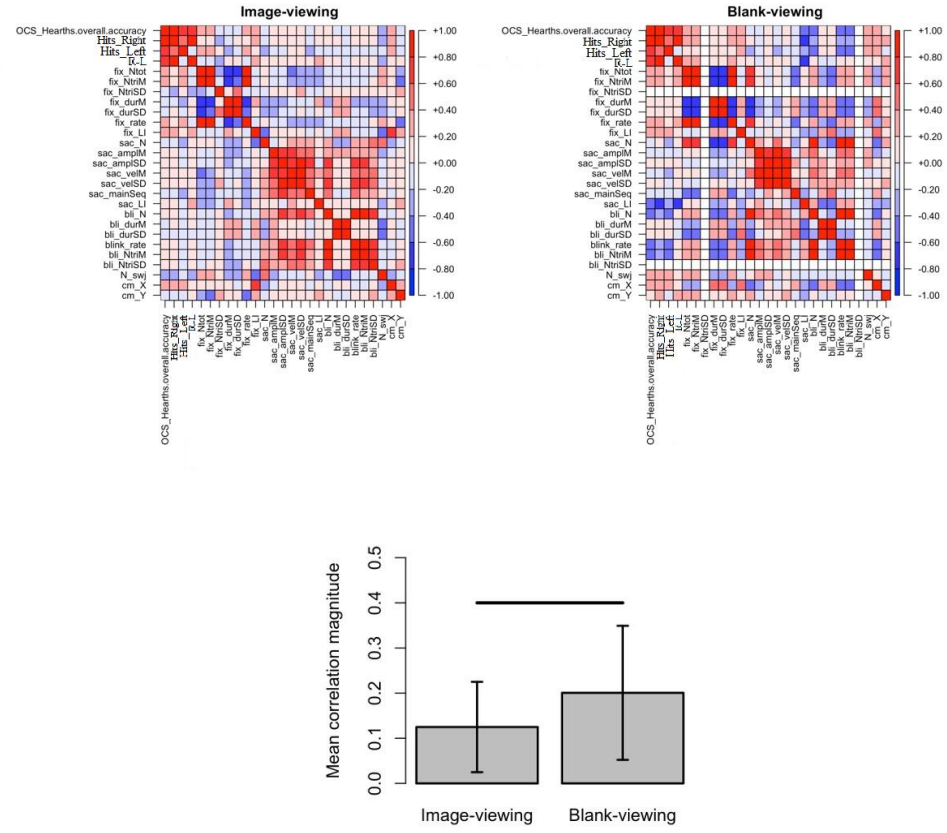

Fig.14. Top: group-averaged correlation matrix between neuropsychological measures and eye movement metrics; Bottom: mean correlation magnitude for free viewing and blank condition.

Blink rate and visuospatial attention (OCS)

Figure 15 shows a negative non-significant linear relationship between the z-scored blink rate during blank viewing and the overall performance during the OCS hearts task (r=-0.35, p=0.12). This is also true for the performances in the two visual hemispaces, as evidenced by the correlations between blink rate and Hits Left (r=-0.36, p=0.11), and blink rate and Hits Right (r=-0.29, p=0.19). This is consistent with other works of literature linking a higher amount of blinks to an increased cognitive load, cognitive impairment, fatigue and poor performances in sustained attention tasks (76–78). The curious, new finding, though, is that the resting state "blank viewing" blink rate showed a stronger correlation with the neuropsychological assessment than the free viewing task.

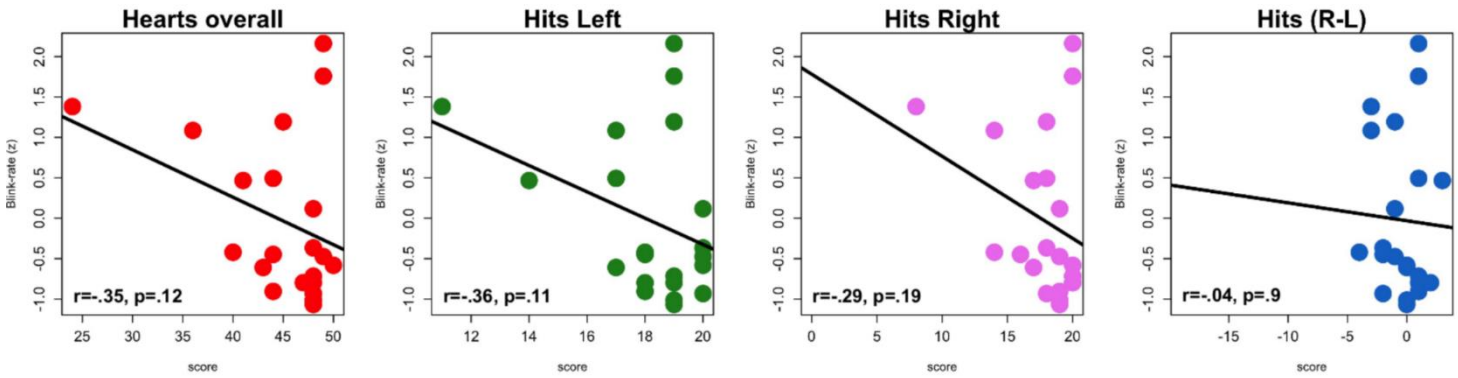

Figure 15, correlations between the z-scored blink rate and the z-scored OCS parameters

Center of mass and visuospatial attention (OCS)

The density distributions of the cm_x in stroke patients and healthy controls (see fig. 16) showed a tendency in stroke patients to have a left lateralization of the center of mass (pseudoneglect), which is consistent with evidence in literature about healthy controls (86,87), and with the control group of the present study (see fig. 16 bottom row). Stroke patients, however, tended to have a greater left shift of the cm_x when compared to healthy subjects, especially in the blank viewing task (see fig.18). Additionally, we studied the correlation between cm_x and OCS_Hearts performance (see fig. 18).

As for the correlation between cm_x and OCS_Hearts.Overall performance, the line's slope shows that a "centralisation" of the cm_x, that is, a tendency for the center of mass to approach the midline (cm_x=0), was correlated with a better

OCS_Hearts.Overall score. This was also true for the lateralized scores of visuospatial attention (see fig. 19).

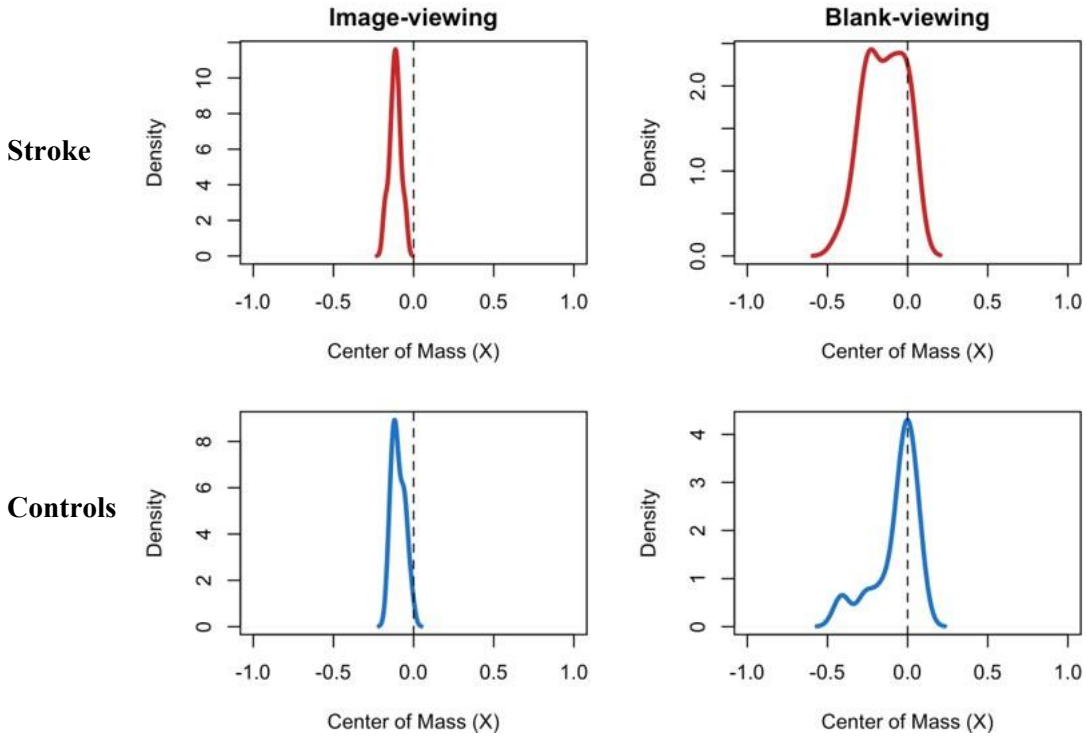

Figure 16 showing the density distribution of cm_x in stroke patients, top row, red and healthy subjects bottom row, blue

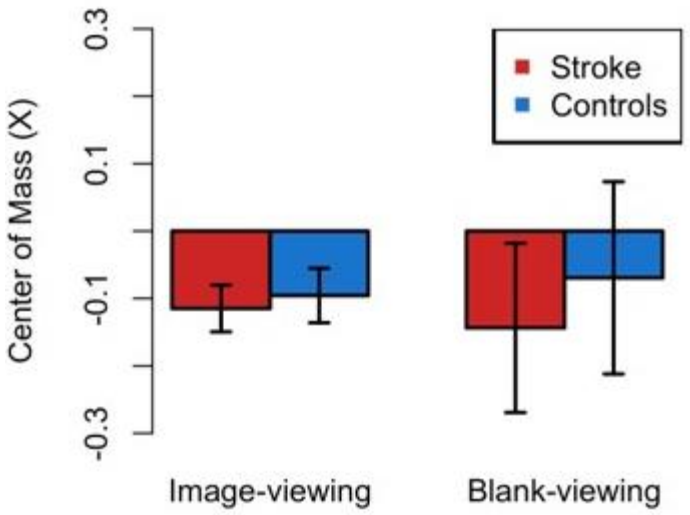

Figure 17 comparison between the stroke patients' cm_x and the controls' cm_x

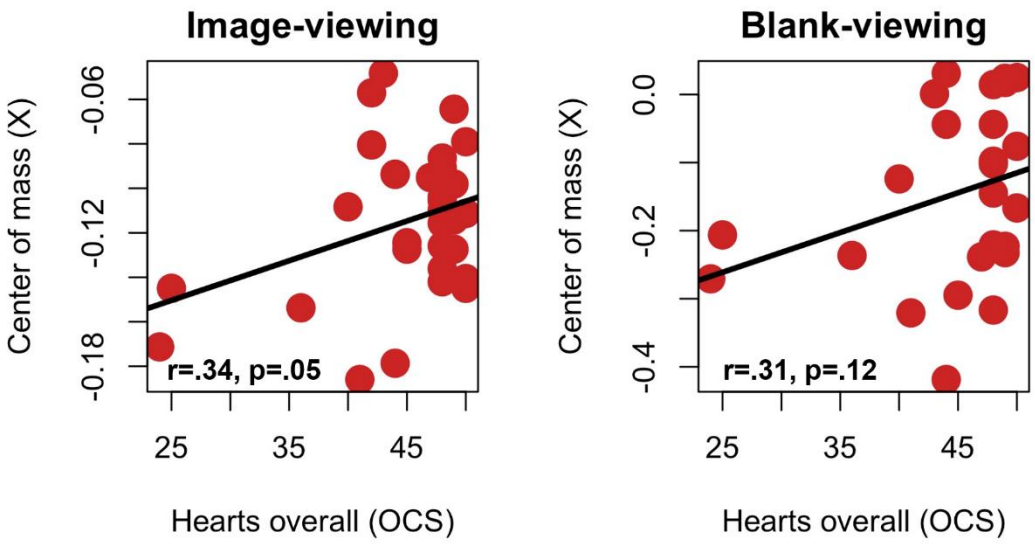

Figure 18 the correlation between cm_x centralisation and OCS hearts overall scores

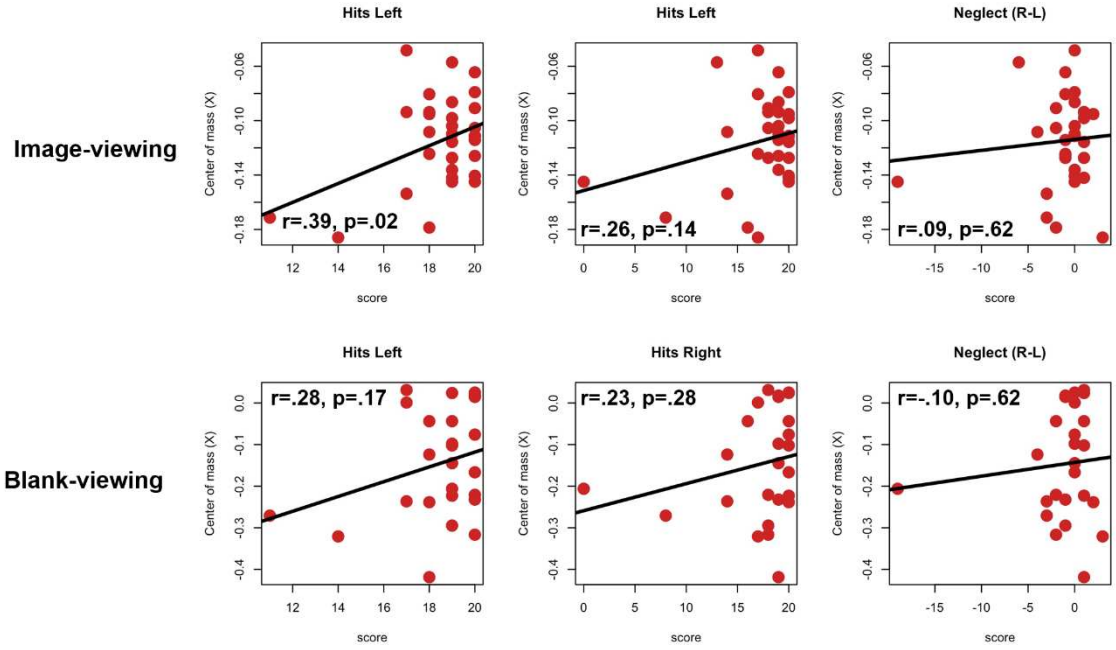

Figure 19 the correlation between the lateralized metrics of visuospatial attention and cm_x

Saccades Laterality Index and visuospatial attention (OCS)

We previously defined the saccade laterality index (Sac_LI). Sac_LI increased as patients made more *rightward* saccades or made less *leftward* saccades. Patients who made more rightward than leftward saccades during blank viewing performed worse at the OCS test. This was once again particularly evident in the blank viewing task, while the same effect was attenuated in the free image viewing task (see fig 20).

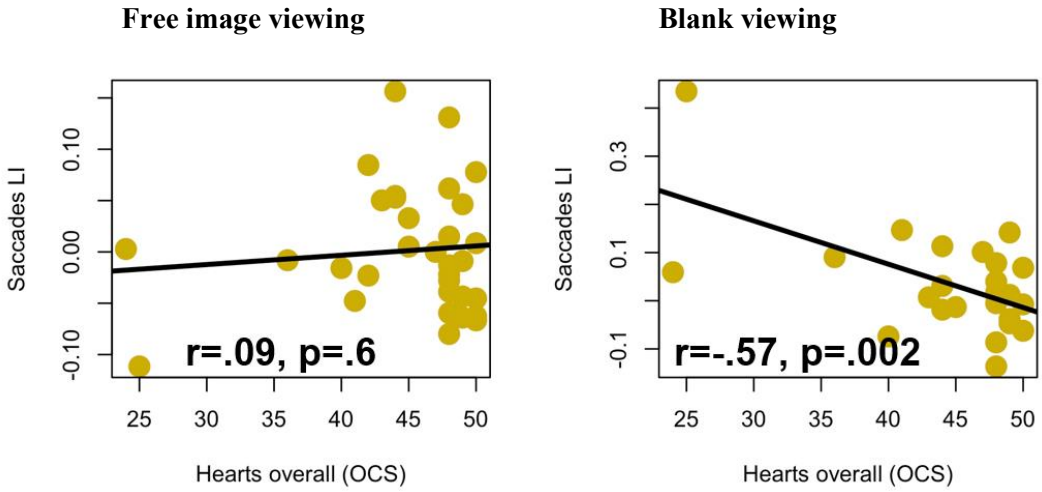

Figure 20 the correlation between OCS_hearts.overall performance and Sac_LI

Cm_Y in stroke patients vs controls

In addition to the correlation analyses, we also performed further investigations on the stroke patients' eye movements metrics themselves. In particular, even though cm_Y showed no correlations with the neuropsychological tests, it still varied between healthy subjects and patients. Stroke patients had a significant upward shift of the vertical center of mass (see fig. 21, 22).

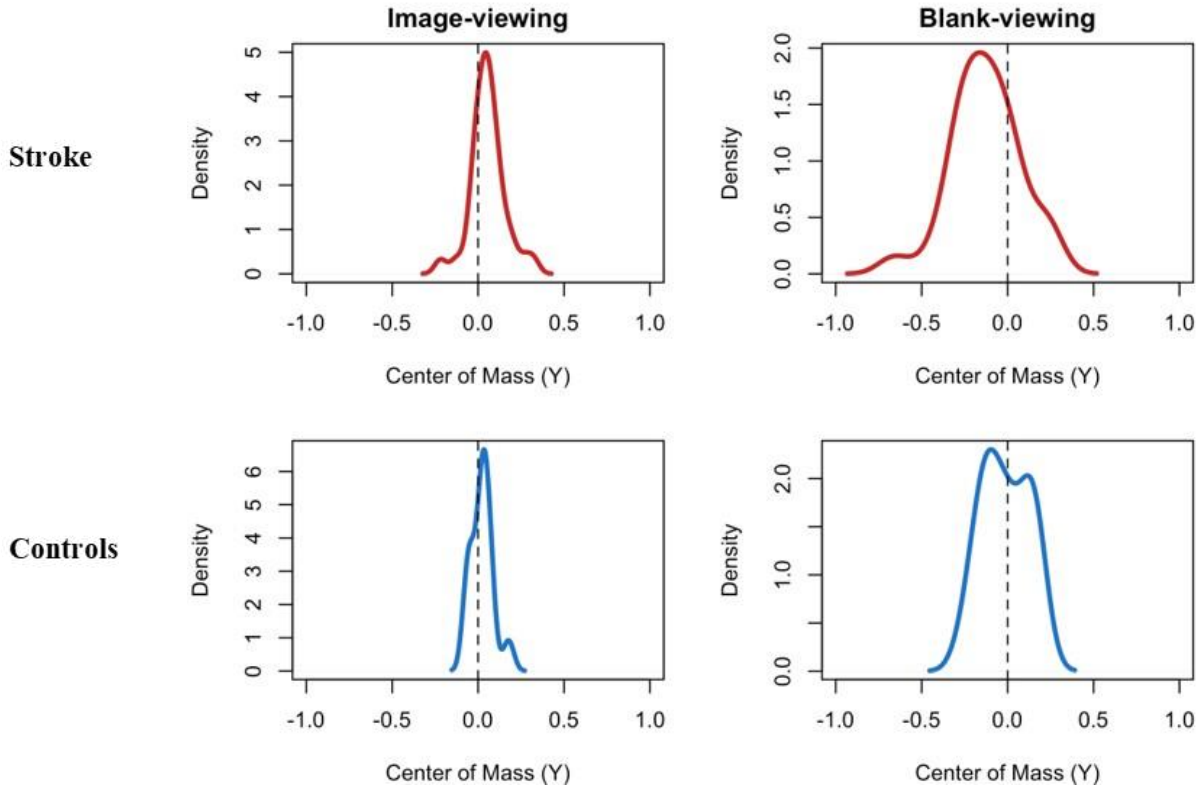

Figure 21 the density distribution of cm_y in stroke patients (top row, red) and healthy subjects (bottom row, blue)

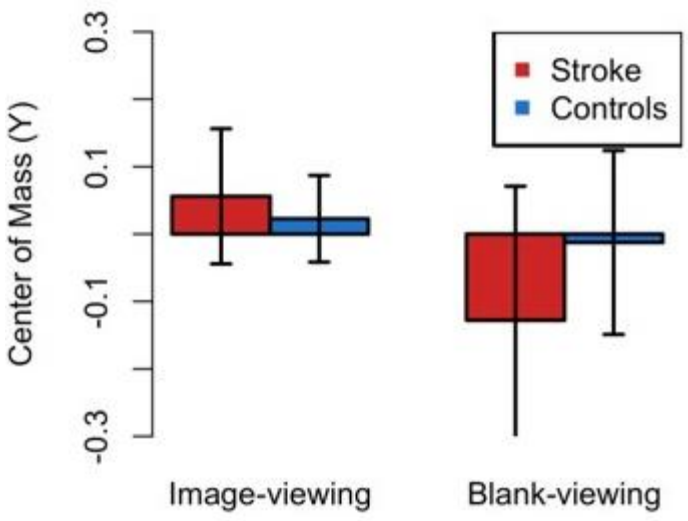

Figure 23 comparison between the stroke patients' cm_y and the controls' cm_y

Cm_x in left vs right strokes

Furthermore, we split stroke patients in two groups: those with a left-sided lesion, and those with either a right-sided lesion or left-sided cerebellar lesion. We decided to group the patients with left-sided cerebellar lesions with the right-sided damage group because of the cerebellar connectivity to the contralateral hemisphere. We then compared the cm_x of the two groups (see fig. 23).
During blank viewing, the patients with a left stroke had a significant left-sided shift in the mean gaze position (t[26.045]=-7.4, p<.001). Right stroke patients, conversely, had a distribution of the cm_x that approached the midline, that is, they did not show the typical pseudoneglect seen in either left stroke or healthy subjects during blank viewing. This is consistent with other works of literature finding an homolesional lateralization of gaze in both right and left stroke patients (79).

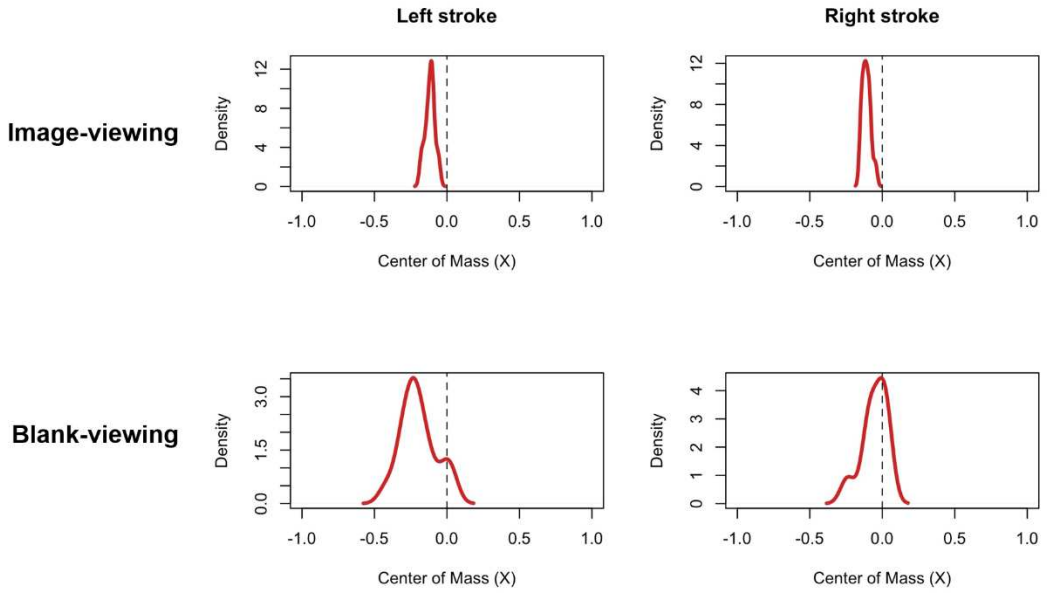

Figure 23 the density distribution of cm_x in left and right stroke patients

Posner task in left and right strokes

The two stroke groups also behaved differently during the Posner task (see fig. 24). In our sample of patients, right-hemisphere damaged patients had longer reaction times to items presented in the left hemispace than to items presented homolesionally. The difference reached significance in the t-test (t[36.3]=2.22, p=0.03). This was true for both validly and invalidly cued stimuli.

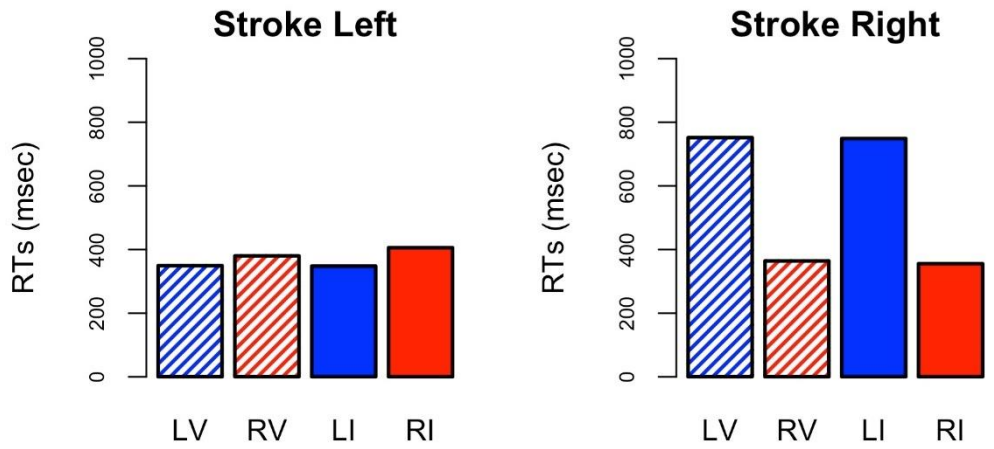

Figure 24, the Posner task. LV = left valid, RV = right valid, LI = left invalid, RI = right invalid

Stepwise regression model

Lastly, we computed a stepwise regression model using metrics from the free viewing and blank viewing task to explain the variance of the OCS performances. The regression model performed better (larger R^2) when using variables from the blank viewing task at predicting the R-L parameter of the OCS, while it performed better by using metrics from the free viewing task when predicting the other scores of the OCS (fig. 25).

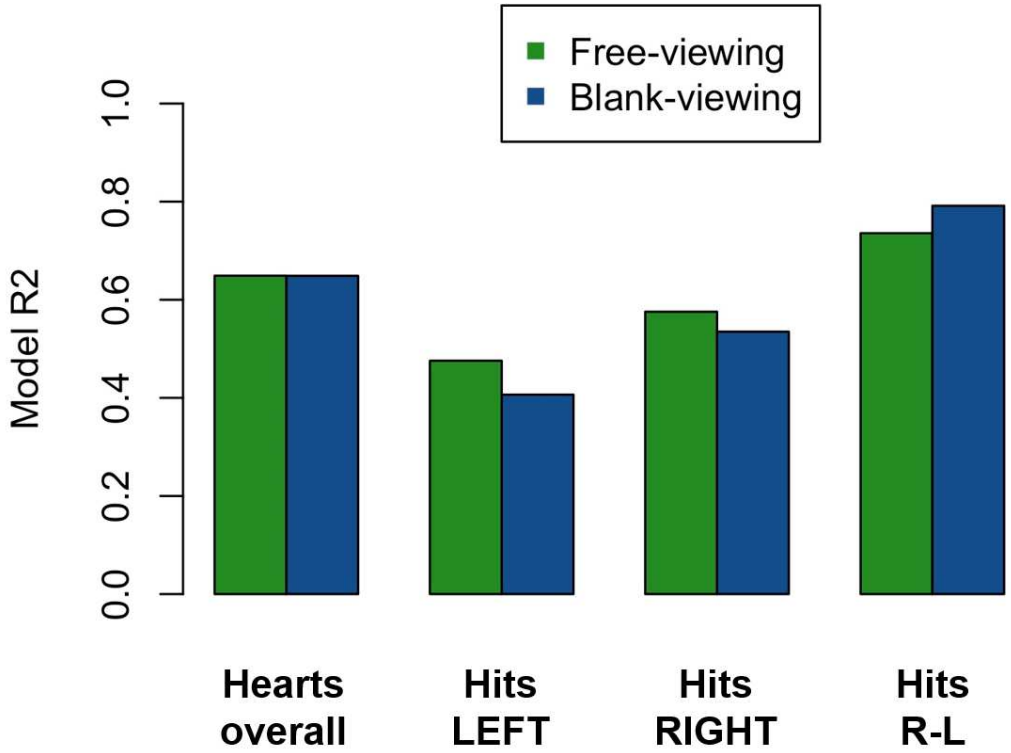

Figure 25, performance of the stepwise regression model across the different scores in the OCS_hearts task

A case of severe hemispatial neglect: s_51

Finally, we wish to report the case of a severe neglect patient, patient s_51. S_51 suffered from an ischemic lesion involving the left middle cerebral artery, which in turn severely affected the left temporal and parietal lobes (see fig. 26).

This patient scored 29 in the OCS_Hearts.Overall, crossing 19 hearts on the left hemispace, 10 in the mid-space and none on the right hemispace (see fig. 27). The patient was hence clinically classified as having right hemispatial neglect (80). By measuring the patient's eye movements and by plotting the fixation density map (heatmap, see fig. 28), we found a left-sided shift of the fixation density.

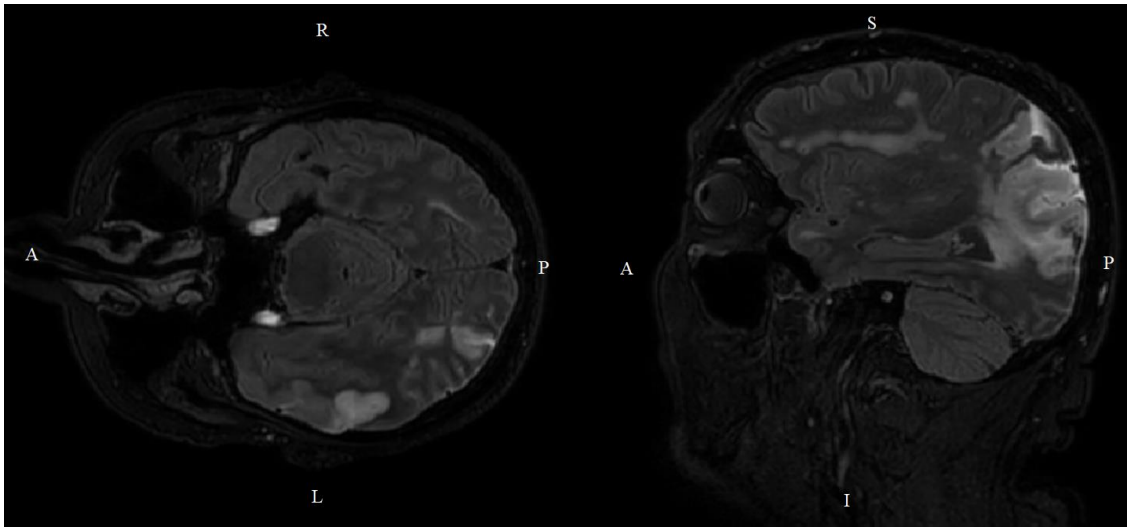

Figure 26, s_51's flair-MRI showing the left-sided temporo-parietal lesion

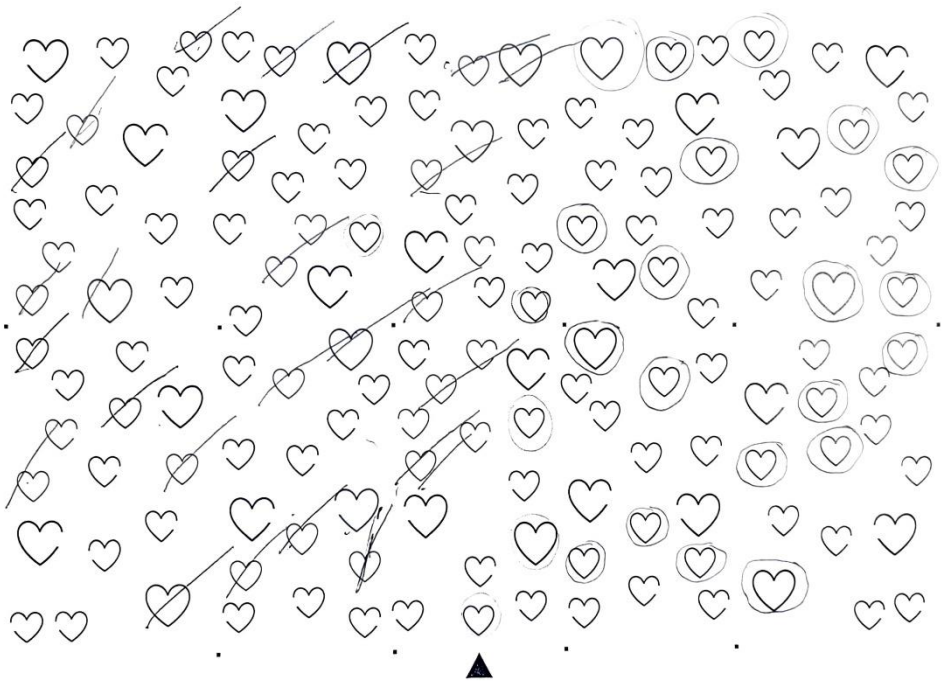

Figure 27: s_51's OCS_Hearts performance, here the strikes were made by the patient, while the circles around the hearts were drawn by the neuropsychologist while counting them

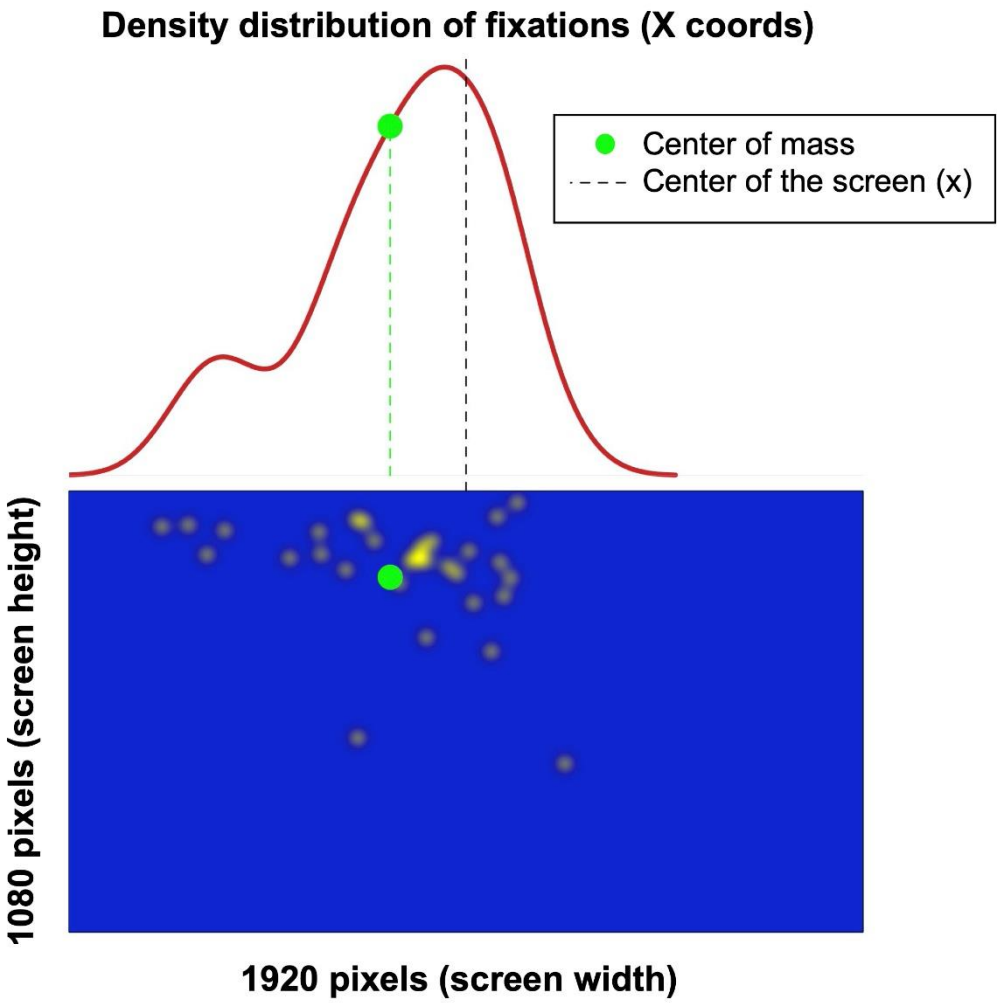

Figure 28 s_51's fixation pattern, on the top the density distribution of fixations, on the bottom the green dot represents the center of mass of fixations

Stroke patient 51 hence provides a strong example of the link between attention bias and eye movement position.

Discussion

This experimental thesis provides evidence that eye movement metrics collected during an ecological, culture-free task can track attentional deficits. The visuospatial attentional performance of stroke patients as indexed by the OCS hearts test scores was correlated with metrics easily computable from an image-viewing and a blank-viewing task. Our main finding is that the eye movement metrics that correlated most with the clinically measured deficits, were extracted while viewing a blank screen as compared to free viewing of real-world images. We think that this attention bias is expression of an indwelling asymmetry in functional activity and hemispheric balance that is responsible for neglect (81) and that is also present in the absence of any task. Apparently, the visual information presented on both sides of the visual field tend to decrease the attention bias. This echoes findings in the neglect literature indicating that the automatic, rather than task-triggered, allocation of attention is the most sensitive clinical measure of neglect (82,83); those findings may, in theory, generalize to subtler forms of attentional impairment as well.

The eye movement metrics that correlated with the OCS scores were the blink rate, the lateralization of saccades direction, and the lateralization of the center of mass of the fixation pattern.

As previously mentioned, the correlation between an increasing blink-rate and worse attentional performances (despite not fully reaching significance) may be due to an increased cognitive load and fatigue in stroke patients (76,77). The augmented blink-rate is thought to reflect an higher engagement of the default mode network and a reciprocal decrease of activity in the dorsal attention network (84). An increased blink rate hence may reflect a relative deactivation of the dorsal attention network with worsening of attention performance.

The saccadic lateralization index (sac_LI) underlies a decreased number of leftward saccades that in turn, increases the sac_LI. This effect corresponds to what has been referred to as “directional hypokinesia” in the neglect literature. We posit that our right-hemisphere patients even though showed a nearly normal performance on the OCS did show subtle signs of eye movement planning to the left.

Furthermore, we found a significant correlation between the horizontal center of mass (cm_x) and the OCS performance. Patients with an enhanced lateralization of their center of mass are likely to explore the visual space in an asymmetrical, incomplete way. Conversely, patients with a more central center of mass

approaching the midline probably had a more balanced distribution of fixations, hence they explored the entire paper when looking for hearts to cross and scored better at the OCS test.

Importantly, the center of mass of the fixation pattern was computed during a free-viewing task (both employing images and a blank screen), not in the same session of the administration of the OCS.

Interestingly, the cm_x also showed differences between the various groups. When comparing healthy subjects with stroke, we observed an enhanced left side bias as compared to the small left side bias present in healthy subjects. This is likely due to a leftward shift caused by the more numerous left hemisphere damaged patients. When left and right hemisphere damaged patients were divided it was apparent that the leftward shift belongs to left hemisphere patients whereas right hemisphere patients tend to have a more central (rightward) shift. These effects are related to the relative hyperactivation observed in the normal hemisphere in the case of neglect pushing attention contraversive to the activated hemisphere (81). An increased lateralization of the mean gaze position following stroke has been reported elsewhere (79).

Another interesting finding is the upward shift in mean gaze position (negative cm_y) in stroke patients. Given that the OCS performance across visual quadrants correlates with the tactics of visual exploration employed during blank and image viewing, then by looking at the OCS performance we can justify the finding.

Notably, one of our patients (s_09) omitted all the hearts in the lower quadrant during the OCS test, a sign of altitudinal neglect (85,86). At the group level, stroke patients bisected similarly in the upper quadrant (average number of crossed hearts: 23) than in the lower quadrant (average: 22). Some authors argue that the lower quadrant, especially the lower left quadrant is commonly left unattended when the attentional resources are limited (87). Thusly, in our sample, sub-clinical inattentive patients might have contributed to the mean cm_y shift by leaving the lower quadrant generally more unattended during the viewing tasks.

Finally, we measured the performance of patients in the Posner task. We found that patients who had a stroke in the right hemisphere were significantly impaired in reacting to objects presented to the left hemispace. Interestingly, as in prevous work, invalid trials especially in the left visual field were slower than valid trials. This finding is consistent with a wealth of literature on the role of right-sided

networks in switching attention to the contralateral side (5,15), and with the high sensitivity of the Posner task for attention impairment.

Conclusion

We showed an analysis of the correlation between (sub-)clinical attentional deficits and metrics extracted from eye-tracking. Eye tracking has several advantages over more traditional ways to measure attentional deficits, such as its quick and simple execution, and its feasibility in almost any patient regardless of language comprehension and cognition. Interestingly, we provided evidence of the overall better correlation between clinical deficits and metrics extracted from a spontaneous, stimulus-free task rather than an image viewing task. We believe that screening the brain in its most unbound status might provide relevant information on how it will behave during tasks.

In conclusion, we argue that further research in the feasibility of utilizing eye tracking for the clinical detection of attentional impairments might lead to a quicker detection of subtle deficits, which in turn, might positively affect the outcome of stroke patients.

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